Rol de la condición física sobre la salud durante el envejecimiento

TESIS DOCTORAL

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Role of fitness on health during aging

DOCTORAL THESIS

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Índice

Índice de tablas **6**

Índice de figuras **7**

Listado de abreviaturas **8**

Declaración **9**

Resumen en castellano **10**

Resumen en inglés **12**

Principales aportaciones **14**

Coherencia e importancia unitaria de la tesis doctoral **16**

PRIMERA PARTE **18**

Introducción general y objetivos **18**

1. Envejecimiento: un problema global de salud ***19***

1.1 Retos para una sociedad envejecida **19**

1.2 Problemas de salud asociados al envejecimiento **21**

1.3 Deterioro cognitivo y envejecimiento **23**

1.4 Capacidad intrínseca y envejecimiento **24**

2. Envejecimiento y función muscular ***25***

2.1 Cambios en el sistema muscular asociados al envejecimiento: **26**

Cambios en el tamaño, tipo de fibra y características contráctil **26**

2.2. Sarcopenia **28**

3. Actividad física, condición física y sus efectos sobre la salud ***30***

3.1 Actividad Física y sus beneficios para la Salud **30**

3.2 Condición física relacionada con la salud **31**

3.3 Condición física relacionada con la salud y resultados **32**

4. Encuesta Nacional de Salud, Envejecimiento y Vejez, SABE Colombia ***33***

5. Objetivos ***35***

6. Descripción estadística ***36***

6.1 Definición y ejemplo de análisis de mediación 36

6.2 Definición y ejemplo de análisis de moderación 38

7. Referencias 41

SEGUNDA PARTE 57

Artículos de investigación 57

Artículo 1 58

Artículo 2 76

Artículo 3 96

Artículo 4 116

Artículo 5 136

TERCERA PARTE 157

Discusión general 157

CUARTA PARTE 176

Conclusiones 176

QUINTA PARTE 180

Perspectivas de futuro y recomendaciones 180

ANEXOS 183

Índice de tablas

Tabla 1……29

Índice de figuras

Figura 1……...*17*

Figura 2……...*20*

Figura 3……...*22*

Figura 4……...*25*

Figura 5……...*28*

Figura 6……...*37*

Figura 7……...*38*

Figura 8……...*39*

Figura 9……...*40*

Listado de abreviaturas

AF: Actividad Física

AFC: Aptitud Física Cardiorrespiratoria

ATP: Adenosine Trifosfato

BDNF: Brain Derived Neurotrophic Facto

CFRS: Condición Física Relacionada con la Salud

CRP: proteína C-reactiva

EE. UU.: Estados Unidos

EWGSOP: European Working Group on Sarcopenia in Older People

GLUT4: Glucose Transporter Type 4

IC: Intervalo de Confianza

IGF-1: Insulin-like growth factor-1

IL-6: Interleucina 6

IMC: Índice de Masa Corporal

JCR: Journal Citation Reports

mTOR: mammalian Target of Rapamycin

SABE: Estudio Nacional de Salud, Bienestar y Envejecimiento

OMS: Organización Mundial de la Salud

OR: Odds Ratio

ROM: Range of Movement

TNF- α: Factor de necrosis tumoral

VO2max: Volumen Máximo de Oxígeno

Declaración

Miguel Ángel Pérez Sousa expresa que:

- La Tesis Doctoral que presenta es por compendio de publicaciones por lo que su estructura está sujeta a las directrices de la Universidad de Sevilla.
- La Tesis Doctoral está basada en cuatro artículos de investigación, los cuales ya han sido publicados en revistas internacionales.
- Los artículos no han sido incluidos en otras Tesis Doctorales.
- La participación en los artículos que componen esta Tesis Doctoral ha sido la de exploración y análisis de datos, establecimiento de hipótesis, interpretación de resultados y escritura de los manuscritos.

Agradecimientos

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A mi pareja, a mi familia, a “Darro” y a “Misifú”. A todos y cada uno, por su compañía y paciencia en este largo proceso.

Resumen en castellano

Introducción: Durante el envejecimiento concurren una serie de cambios bioquímicos y físicos afectando las principales funciones del cuerpo humano. Existe suficiente evidencia científica de que la inactividad física agrava el aumento de peso, tejido graso y la pérdida de masa muscular y que esto a su vez empeora la salud de los adultos mayores y por ende las funciones en la vida diaria. Sin embargo, se desconoce cuál es el papel que juega la condición física entre las comorbilidades comunes de los adultos mayores. Los trabajos presentados en esta Tesis Doctoral se basan en resultados obtenidos del análisis de la base de datos del Estudio Nacional de Salud, Bienestar y Envejecimiento, SABE Colombia 2015

Estudio 1: el objetivo fue conocer la prevalencia de probable sarcopenia de acuerdo a las actualizaciones del European Working Group on Sarcopenia in Older People 2 así como explorar los factores asociados. En los análisis se incluyeron 5237 hombres y mujeres colombianos de 60 años o más de edad. La prevalencia de probable sarcopenia fue de 46,5% (95% IC: 45,1 ─ 47,8). La inactividad física (OR = 1,35, 95% IC = 1,14 ─ 1,59), diabetes (OR = 1,32, 95% IC = 1,11 ─ 1,56) y artritis (OR = 1,44, 95% IC = 1,25 ─ 1,67), estaban estrechamente relacionadas con la probable sarcopenia.

Estudio 2: el objetivo consistió en determinar si la velocidad de la marcha moderaba la asociación entre obesidad y dependencia funcional. Además, es examinó los umbrales de moderación de acuerdo con la técnica estadística de Johnson-Neyman. Participaron un total de 20,507 de adultos mayores colombianos. Los resultados indicaron que la velocidad de la marcha moderaba (β=0.081; 95% IC: 0,045 ─ 0,117) la asociación entre obesidad y dependencia funcional. Los umbrales por debajo del cual la velocidad de la marcha moderaba negativamente la asociación era de <0,77 m/s, por el contrario, el segundo umbral a partir del cual la velocidad de la marcha moderaba positivamente la asociación era de >1,06 m/s.

Estudio 3: el objetivo fue determinar si el exceso de adiposidad central se relacionada con la dependencia funcional y también si esta asociación es moderada por la fuerza de prensión manual. Participaron en este estudio 4169 individuos mayores de 59 años. Los resultados destacaron el rol mediador de la fuerza de prensión manual sobre la relación

inversa exceso de adiposidad y dependencia funcional. Los umbrales arrojados por la técnica de Johnson-Neyman fueron de 0,35 kg/kg^2 y de 0,62 kg/kg^2.

Estudio 4: el estudio tenía como objetivo conocer si la pérdida de fuerza muscular asociada al exceso de adiposidad central podría ser mediado por el nivel de glucosa en sangre. Participaron en el estudio un total de 1571 adultos mayores colombianos. Los resultados indicaron que la glucosa en sangre mediaba el efecto perjudicial de un exceso de adiposidad central sobre la fuerza muscular (β = -0.069, 95%IC = -0.082 − -0.057).

Estudio 5: el objetivo de este estudio fue conocer si la velocidad de la marcha y la fuerza de prensión manual se asociaban con el deterioro cognitivo. Además, se examinó el posible rol mediador de la velocidad de la marcha y la fuerza de prensión manual sobre el deterioro cognitivo asociado al envejecimiento. Participaron 4416 colombianos con una edad igual o mayor a 60 años. Los resultados destacaron la estrecha relación entre la velocidad de la marcha y fuerza muscular sobre la cognición. También, los análisis de mediación arrojaron que estos dos componentes de la condición física mediaban el deterioro cognitivo asociado al envejecimiento.

Resumen en inglés

Introduction: During aging, a series of biochemical and physical changes occur, affecting the main functions of the human body. There is sufficient scientific evidence that physical inactivity aggravates weight gain, fat tissue, and muscle mass loss. So, physical inactivity worsens older adults' health and, therefore, the functions in daily life. However, the role that physical fitness plays among common comorbidities in older adults is unknown. The papers presented in this Doctoral Thesis are based on results obtained from the analysis of the database of the National Study of Health, Well-being and Aging, SABE Colombia 2015

Study 1: The aim was to know the prevalence of probable sarcopenia according to the European Working Group's updates on Sarcopenia in Older People 2 and explore the associated factors. The analysis included 5237 Colombian men and women aged 60 years or older. The prevalence of probable sarcopenia was 46.5% (95% CI: 45.1 ─ 47.8). Physical inactivity (OR = 1.35, 95% CI = 1.14 ─ 1.59), diabetes (OR = 1.32, 95% CI = 1.11 ─ 1.56) and arthritis (OR = 1, 44, 95% CI = 1.25 ─ 1.67), were closely related to probable sarcopenia.

Study 2: This study aimed to determine if the speed of the gait moderated the association between obesity and functional dependence. Also, the thresholds for moderation were examined according to the Johnson-Neyman statistical technique. A total of 20,507 Colombian older adults participated. The results indicated that gait speed moderated (β = 0.081; 95% CI: 0.045 ─ 0.117) the association between obesity and functional dependence. The thresholds below which the gait speed negatively moderated the association were <0.77 m / s. On the contrary, the second threshold above which the gait speed positively moderated the association was> 1. 06 m / s.

Study 3: The aim was to determine whether excess central adiposity is related to functional dependence and whether this association was moderated by handgrip strength. Four thousand one hundred sixty-nine individuals older than 59 years participated in this study. The results highlighted the mediating role of manual grip strength on the inverse relationship between excess adiposity and functional dependence. The thresholds obtained by the Johnson-Neyman technique were 0.35 kg / kg2 and 0.62 kg / kg2.

Study 4: The study aimed to know if the loss of muscle strength associated with excess central adiposity could be mediated by glucose level in the blood. A total of 1571 Colombian older adults participated in the study. The results indicated that blood glucose mediated the detrimental effect of excess central adiposity on muscle strength (β = -0.069, 95% CI = -0.082 - -0.057).

Study 5: This study's objective was to find out if gait speed and handgrip strength were associated with cognitive impairment. Besides, the possible mediating role of gait speed and handgrip strength on cognitive impairment associated with aging was examined. 4416 Colombians with age equal to or greater than 60 years participated. The results highlighted the close relationship between gait speed and muscle strength on cognition. Also, the mediation analyzes showed that these two components of physical condition mediated the cognitive deterioration associated with aging

Principales aportaciones

1. Miguel Ángel Pérez-Sousa, Jesús del Pozo, Carlos A. Cano-Gutiérrez, Mikel Izquierdo, Robinson Ramírez-Vélez. **High prevalence of probable sarcopenia in a representative sample from Colombia: Implications for geriatrics in Latin America**. JAMDA, 2020. DOI: 10.1016/j.jamda.2020.10.021 Impact Factor: 4.36 (Q1); 8/51 Medicine, General & Internal – Science Edition **–** Journal Citation Reports

2. Robinson Ramírez-Vélez, Miguel A. Pérez-Sousa, Luis C. Venegas-Sanabria, Diego A. Chavarro Carvajal, Carlos A. Cano-Gutierrez, Jorge E. Correa-Bautista, Katherine González-Ruíz, Mikel Izquierdo. **Gait speed moderates the adverse effect of obesity on dependency in older Colombian adult**. Experimental Gerontology, 2019. DOI: 10.1016/j.exger.2019.110732 Impact Factor: 3.37 (Q2); 19/51 Geriatrics & Gerontology – Science Edition – Journal Citation Reports

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4. Miguel Ángel Pérez-Sousa, Jesús del Pozo, Carlos A. Cano-Gutiérrez, Atilio J. Ferrebuz, Carolina Sandoval-Cuellar, Mikel Izquierdo, Paula A. Hernández-Quiñonez, Robinson Ramírez-Vélez. **Glucose Levels as a Mediator of the Detrimental Effect of Abdominal Obesity on Relative Handgrip Strength in Older Adults**. Journal Clinical Medicine, 2020. DOI:10.3390/jcm9082323. Impact Factor: 3.30 (Q1); 36/165 Medicine, General & Internal – Science Edition – Journal Citation Reports

5. Miguel Ángel Pérez-Sousa, Jesús del Pozo, Pedro R. Olivares, Carlos A. Cano-Gutiérrez, Mikel Izquierdo, Robinson Ramírez-Vélez. **Role for Physical Fitness in the Association between Age and Cognitive Function in Older Adults: A Mediation Analysis of the SABE Colombia Study.** International Journal of Environmental Research and Public Health, 2021. DOI: 10.3390/ijerph18020751. Impact Factor: 2.84 (Q1); 32/171 Public, Environmental & Occupational Health – Social Science Edition – Journal Citation Reports

Coherencia e importancia unitaria de la tesis doctoral

Esta tesis doctoral presenta 5 artículos indexados en JCR en los que el candidato es primer autor en 3 de ellos y segundo autor de dos. Todos ellos responden a un proceso de interacción entre hipótesis y resolución en el que los resultados aportados por los análisis estadísticos y su interpretación ofrecen novedosos hallazgos. El objeto de estudio común que queda reflejado en el título de este documento es la relación entre la condición física y el envejecimiento y como interacciona esta en la salud de los adultos mayores. Se enuncian, por tanto, una serie de resultados plasmados en artículos de investigación publicados en revistas de primer nivel. Estos responden a una coherencia interna que puede verse dibujada en la Figura 1. El **primer** estudio presenta la prevalencia existente de un común denominador entre los adultos mayores como es la sarcopenia. En nuestro caso estudiamos la presencia de probable sarcopenia, término de reciente actualización por el grupo de expertos del European Working Group on Sarcopenia in Older People (EWGSOP). En el **segundo** de ellos estudiamos la relación existente entre la obesidad y la dependencia funcional y como la velocidad de la marcha (componente de la condición física en adultos mayores) modera dicha relación. El **tercer** estudio, en línea del anterior, se estudia la asociación entre la adiposidad central y la dependencia funcional y el efecto moderador de la fuerza de prensión manual. En el **cuarto** estudio, quisimos explorar cual era el rol perjudicial del nivel de glucosa entre la relación obesidad abdominal y la pérdida de fuerza muscular. Y finalmente, en el **quinto** artículo nos propusimos estudiar como el nivel de condición física mediaba el deterioro cognitivo fruto del envejecimiento. Por tanto, con este último cerramos el círculo en el que hemos estudiado no sólo los efectos de la condición física sobre el funcionamiento motor sino también sobre aspectos neurocognitivos.

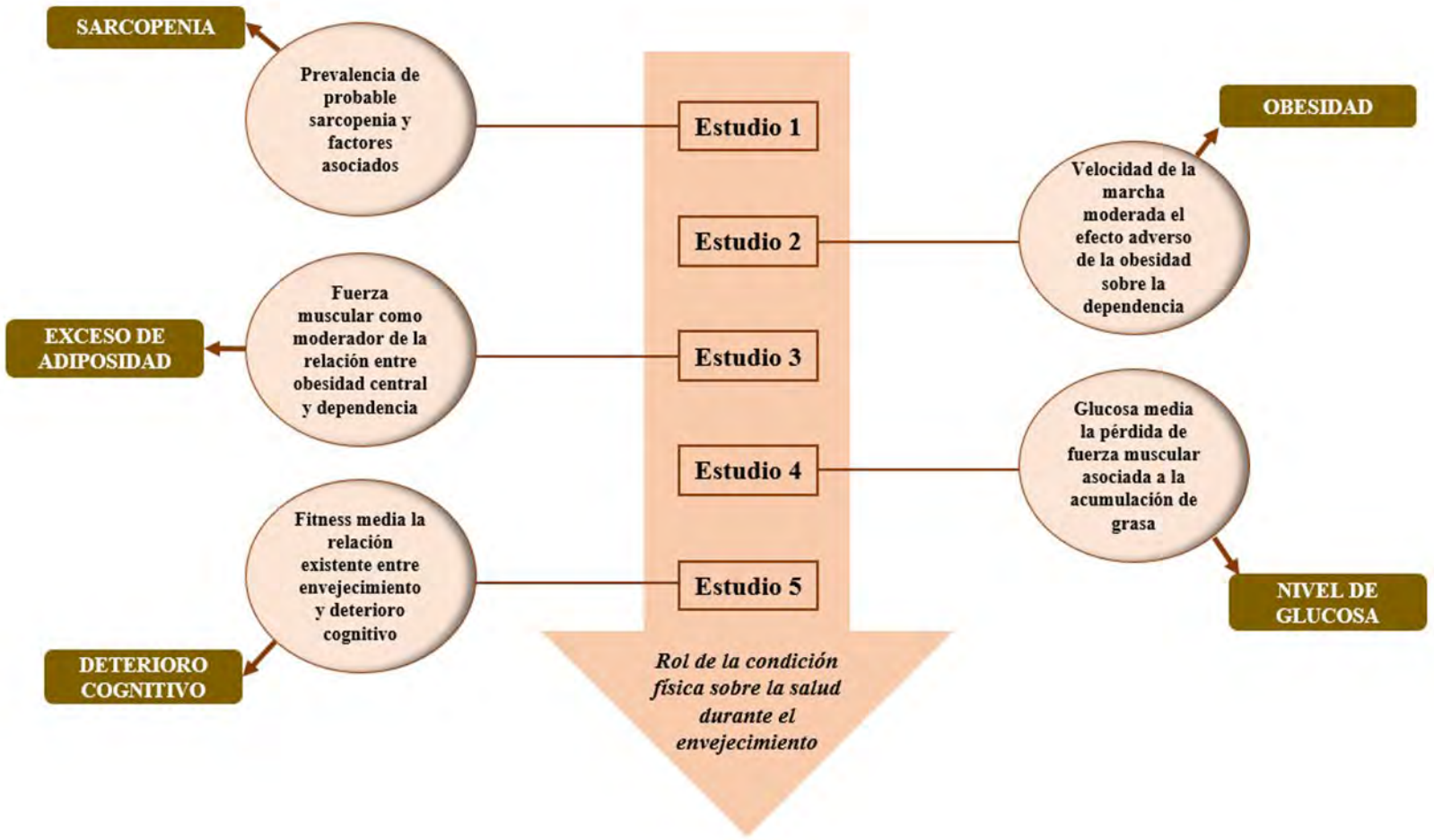

Figura 1. Coherencia interna entre estudios presentados en este documento de tesis doctoral. Puede observarse la evolución entre objetos de estudio contenidos en los círculos teniendo como objetivo último conocer el rol de la condición física sobre los efectos adversos (contenido en los rectángulos) asociados al envejecimiento.

PRIMERA PARTE

Introducción general y objetivos

1. Envejecimiento: un problema global de salud

Durante las últimas décadas, la Organización Mundial de la Salud, ha establecido como objetivos prioritarios de desarrollo sostenible la mejora del estado de bienestar. Para ello, los planes políticos se han centrado en la inversión económica en recursos tecnológicos y asistenciales para la mejora de la salud. La mejora de las condiciones de salubridad, la adopción de estilos de vida saludable, una detección temprana de enfermedades y la efectividad de tratamientos médicos, están propiciando una menor tasa de mortandad y un aumento de la longevidad a nivel mundial. Recientes estudios demográficos estimaron para el año 2017 que la población global de adultos-mayores con 60 años o más era de 962 millones (1), y se estima que para el año 2050, la cifra se duplique, llegando a los 2.1 billones aproximadamente (2). En lo que respecta a los países latinoamericanos, las estimaciones indican que para el año 2030 la población de 60 años alcanzará el 17% del total de la población, y para el 2050 uno de cada cuatro habitantes de América latina serán adulto-mayor (3).

Estas cifras y tendencias no son cambiantes en Colombia. La encuesta censal de 2018 arrojó datos similares, donde la población total era de 48 millones de personas, siendo un 13.4% el porcentaje de población en edad adulto-mayor (>60 años) (4). Además se espera que para el año 2050 este porcentaje aumente hasta situarse cercano al 30% (3).

Así pues, dichas predicciones de longevidad para los próximos años, supondrá un incremento de los recursos en materia de salud para el mantenimiento del estado de bienestar, ya que como explicaremos en los siguientes apartados, el envejecimiento lleva asociado la aparición de enfermedades Este hecho nos lleva a profundizar en el papel que la condición física puede jugar para un envejecimiento saludable.

1.1 Retos para una sociedad envejecida

Aunque el aumento de la esperanza de vida sea un resultado excelente de la mejora del estado de bienestar, tener una sociedad envejecida supone un reto para la economía de los países implicados. El envejecimiento lleva asociado la aparición de problemas de salud. Estos problemas originados por anormalidades bioquímicas o fisiológicas, desencadenan en enfermedades, dolencias o desarrollo de condiciones de salud desfavorables (5). Los adultos-mayores tienen más probabilidad de desarrollar enfermedades crónicas de tipo cardiovascular, respiratorias, endocrinas, metabólicas, desordenes musculoesqueléticos o problemas mentales

(6). La aparición de estas enfermedades junto con su agravamiento en el tiempo tiene como consecuencia la aparición de discapacidad y por tanto de dependencia funcional, entendida esta como la incapacidad de realizar satisfactoriamente y de manera autónoma las actividades de la vida diaria (7). El desarrollo de dependencia funcional conlleva a un aumento del gasto sanitario, tanto en los tratamientos como en los recursos asistenciales. Además se proyecta que para el 2050 las regiones con mayor crecimiento de adulto-mayor en dependencia serán Asia y Latino-América (7).

Por tanto, el fin último que debería perseguirse sería el retraso de esta dependencia funcional. Dicho esto, nos surge una pregunta, ¿por qué? Para dar una respuesta adecuada debemos contextualizar el reto del que estamos hablando. Si el número de personas mayores de 65 años, considerados estos como personas no activas laboralmente, es cada vez mayor, y el número de personas de entre 16 y 64 años, considerados como activos, es menor, la ratio entre trabajadores y pensionistas tiende a reducirse. Por lo que cada vez serán menos personas activas los que deberán mantener a los pensionistas. Esto provoca una mayor presión económica en nuestro estado del bienestar. Ahora bien, si la salud de los pensionistas se agrava partir de los 65 años tornándose en personas dependientes, tendremos un alto porcentaje de población entre 65 y +80 años con necesidades costosas. Por el contrario, si tratamos de mantener las condiciones físicas de nuestros mayores haciendo cada vez más tardía la aparición de síndromes geriátricos que limiten su independencia funcional conservando la condición física, tendremos adultos-mayores saludables, reduciéndose así la presión sobre el sistema de salud.

Figura 2. Ratio trabajadores / pensionistas. Adaptado *de United Nation of Economic and Social Affairs. Population division. World Population Prospects. The 2004 revision.*

Esta tesis se centrará fundamentalmente en como determinadas enfermedades crónicas y síndromes geriátricos comunes en el adulto mayor influyen sobre la salud y como la condición física (fuerza y velocidad) pueden interactuar entre ambas.

1.2 Problemas de salud asociados al envejecimiento

Es común la creencia de que el envejecimiento es el factor de riesgo predominante para la mayoría de las enfermedades y condiciones que limitan la salud, relacionando espuriamente envejecimiento con enfermedad. Si bien es cierto que el envejecimiento es consecuencia de diversos daños moleculares y celulares a lo largo del tiempo conllevando al deterioro de las capacidades físicas y mentales, al aumento de la aparición de enfermedades y finalmente a la muerte. Pero, ahora bien, estos cambios no son ni lineales ni genéricos. Podemos observar octogenarios con una excelente salud y capaces de desenvolverse de manera autónoma y sin embargo septuagenarios frágiles y dependientes. Por tanto, esto nos hace pensar que la relación envejecimiento-enfermedad sea mucho más compleja.

El grupo de expertos en *Geroscience* del Instituto Nacional de Salud de los EEUU, identificó los 7 principales factores que impulsan el envejecimiento, los cuales se asocian a la aparición de enfermedades crónicas y síndromes geriátricos. Además, se concluyó que estos factores no actúan de manera independiente sino que están relacionados entre sí. Estos 7 factores son: la inadaptación al estrés, la pérdida de proteostasis (biogénesis, plegamiento, tráfico y degradación de las proteínas), el agotamiento de las células madre, la alteración del metabolismo, daño macromolecular, modificaciones epigenéticas y la inflamación (Figura 4) (8). Muchas enfermedades crónicas y condiciones patológicas están determinadas, al menos en parte, por algunos de estos mecanismos. Siguiendo la hipótesis de los autores de este estudio, la aparición de enfermedades dependería de la velocidad e intensidad de los procesos celulares y moleculares del envejecimiento los cuales están influenciados por la predisposición genética y por el estilo de vida (8).

Figura 3. Los 7 factores del envejecimiento.

Las enfermedades crónicas y síndromes geriátricos más comunes relacionados cos con el envejecimiento son:

1. Enfermedad cardiovascular: número 1 de enfermedades con mayor tasa de mortandad en la mayoría de los países (9)
2. Accidente cerebrovascular: dependiendo en que área del cerebro puede causar la muerte. Esta enfermedad en el adulto-mayor suele tener efectos a largo plazo como la limitación funcional llegando a la dependencia (9).
3. Hipertensión: la presión arterial elevada de forma crónica puede causar problemas de corazón, en vasos sanguíneos y riñones. Además es un factor de riesgo importante para un mal desenlace del virus COVID-19 (10)
4. Cáncer: de acuerdo con la American Cancer Society, el 77% de los canceres son diagnosticados en personas con más de 55 años (11).
5. Diabetes mellitus tipo 2: su prevalencia va en aumento, aunque parece ser que la tendencia es a establecerse en meseta. Antes o después de la aparición de la diabetes, adoptar hábitos más saludables como el ejercicio regular y una dieta bien equilibrada puede mantener los niveles de glucosa en sangre en un rango

normal y prevenir el deterioro de la salud (12). También es uno de los factores determinantes del virus COVID-19 (10).

6. Parkinson: tres cuartas partes de los casos comienzan después de los 60 años siendo los varones más propensos a padecerla (13).
7. Demencia: son varios tipos de demencia como la frontotemporal, vascular o Alzheimer, siendo este el más común de todos (14).
8. Enfermedad pulmonar obstructiva crónica: la principal causa de esta enfermedad es la exposición a contaminantes como la polución o tabaco (15).
9. Osteoartritis: principalmente en mujeres tiene como factores asociados la predisposición genética, obesidad y sobrepeso y lesiones previas de rodilla (16)
10. Desórdenes sensitivos: específicamente visuales y auditivos son los principales desordenes sensitivos en el adulto mayor, los cuales son factores limitantes de su independencia funcional (17).

Hasta aquí hemos resumido las principales enfermedades crónicas que padece el adulto-mayor sin entrar a los síndromes geriátricos relacionados con las características neuromusculares como la sarcopenia o fragilidad, los cuales serán tratados más adelante.

1.3 Deterioro cognitivo y envejecimiento

Una de las adversidades principales asociadas al envejecimiento es el deterioro cognitivo (18). Esto es la pérdida de funciones cognitivas tales como la memoria, la atención, y la velocidad en el procesamiento de la información. A veces el deterioro cognitivo cursa con demencia a edades avanzadas dificultando aún más si cabe la independencia funcional del adulto mayor (19). No existe una causa única del deterioro cognitivo. Los síntomas pueden permanecer estables por muchos años progresando a otro tipo de demencia severa o Alzheimer (20). La evidencia actual señala que el deterioro cognitivo leve ya existe cambios menores en cuanto a las características y funcionamiento del cerebro. Por ejemplo, en estudios de autopsias con deterioro cognitivo leve se ha informado de acumulaciones anormales de proteína beta amiloide y proteínas de tau, estas muy relacionadas con la enfermedad de Alzheimer (21). También se ha señalado como existe una mayor presencia de cuerpos de Lewy, proteína relacionada a la enfermedad de Parkinson (22). Por último, parece ser que micro accidentes vasculares y un flujo sanguíneo reducido también pueden causar dicho deterioro(23). Estudios

por imágenes destacan un encogimiento del hipocampo y uso reducido de glucosa (24). Los factores de riesgo asociados al deterioro cognitivo son entre otros Diabetes, tabaquismo, hipertensión, colesterol elevado, obesidad, depresión, baja actividad física y un pobre rendimiento físico (25–27). La prevalencia de deterioro cognitivo continúa aumento, situándose en Colombia en un 5.6%(18). Existen muchos estudios donde reflejan la asociación entre deterioro cognitivo y bajos niveles de fuerza muscular y resistencia cardiorrespiratoria(28,29).

1.4 Capacidad intrínseca y envejecimiento

Recientemente, la OMS publicó su *World Report on Ageing and Health* (2) en el cual introduce un nuevo paradigma centrado en la "función" para el estudio y práctica clínica relacionado con el antienvejecimiento. El nuevo concepto denominado capacidad intrínseca es un indicador cuantificable y multidimensional del estado funcional de la persona (2,30) el cual es definido como la suma de las capacidades físicas y mentales (30). La capacidad intrínseca abarcaría cinco dominios: cognición, aspectos psicológicos, locomoción, función de los sentidos y vitalidad (30,31). En la Figura 5 se puede observar los dominios y subdominios de los que está compuesto la capacidad intrínseca. La capacidad intrínseca es un constructo dinámico el cual sufre cambios a lo largo de la vida alcanzando el mejor estado durante la edad adulta y tiende a decaer entre el final de la edad adulta y el inicio de la vejez. El declive es propio de cada individuo en función de las características de este y de su relación con el entorno(31). En esta línea, se han estudiado extensamente las comorbilidades asociadas a la edad, incrementando el deterioro de dicha capacidad intrínseca (32). Por ello, a las clásicas enfermedades hipocinéticas como diabetes, hipertensión, obesidad, o enfermedades cardiovasculares, se le adhieren comorbilidades relacionadas con la edad como sarcopenia, depresión, fragilidad, riesgo de sufrir caídas, inmovilidad y/o deterioro cognitivo (33). Este aumento de las comorbilidades en el adulto-mayor conlleva a un empeoramiento de los resultados en salud. De tal manera que influye negativamente en la eficacia de los tratamientos (34,35), aumenta el riesgo de eventos adversos (35), incrementa el riesgo de hospitalización y prolonga la estancia hospitalaria (36), empeora la calidad de vida de las personas (33), aumenta el riesgo y severidad de dependencia (33,37,38) e incrementa el riesgo de muerte (33).

2. Envejecimiento y función muscular

Más de 500 músculos repartidos por el cuerpo, controlados por el sistema nervioso, conforman nuestro sistema muscular el cuál soporta el sistema esquelético (39). La contracción muscular, posibilita el mantenimiento y la postura del cuerpo, la respiración y el movimiento de los segmentos corporales a diferentes velocidades, precisión y potencia con el fin de intentar resolver las demandas presentadas (39). La función muscular representa la respuesta del sistema muscular a través de una serie de mecanismos neurales, fisiológicos y moleculares.

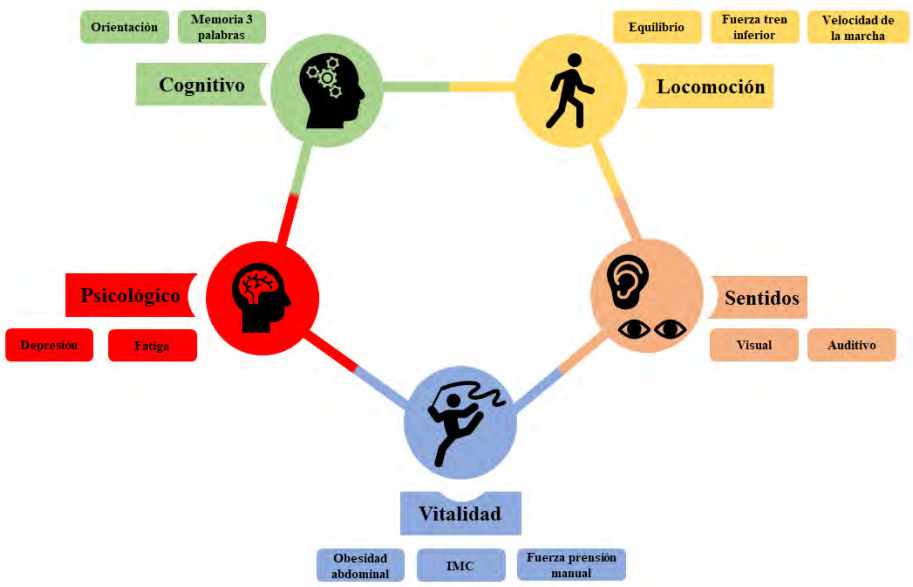

Figura 4. Dominios y subdominios de la capacidad intrínseca según Cesari et al. 2018, *Evidence for The Domains Supporting The Construct of Intrinsic Capacity*.

El envejecimiento es una fenómeno multifactorial de declive progresivo, no lineal e irreversible, de las capacidades físicas y psíquicas a lo largo de la vida (40). Este fenómeno es dependiente de factores biológicos junto con las interacciones del individuo con el entorno, ya sean culturales, sociales o ambientales (41).

En los últimos años, se ha generado un cuerpo extenso de evidencias científicas demostrando que el envejecimiento trae consigo una serie de cambios nocivos de la función muscular (42,43). Para facilitar la evaluación de la función muscular a nivel clínico, se han desarrollado batería de test específicos de la condición física, tales como la batería Eurofit (44)

o la Senior Fitness (45), las cuales están estrechamente relacionadas con el rendimiento motor del adulto-mayor.

Pero el sistema muscular no solo es importante para el rendimiento motor, sino que además actúa como órgano regulador y secretor de diferentes funciones donde una buena salud muscular influirá en el estado general de salud a lo largo de la vida. Por ejemplo, el músculo es el principal almacén y absorción de glucosa (46,47). Además el transportador de glucosa GLUT4, activado ante la contracción muscular, es el principal captador de glucosa en sangre, favoreciendo así una correcta homeostasis (46,47). También los músculos están involucrados en la oxidación de ácidos grasos y síntesis de glucógeno por lo que una alteración de este órgano puede conllevar a la aparición de enfermedades metabólicas como insulino-resistencia, síndrome metabólico u obesidad (48). Por último, el sistema muscular interactúa con otros órganos mediante la secreción de miokinas con autocrinas, endocrinas o paracrinas (49). Estás miokinas generadas por el musculo como respuesta a la contracción conectan con otros órganos como el tejido adiposo, huesos, cerebro, hígado o riñones (49). Por lo tanto, el músculo no es un simple sistema para generar movimiento, sino que además es un órgano vital para una correcta homeostasis del cuerpo.

En la siguiente sección, destacaremos los principales cambios que suceden en este órgano con el paso de los años.

2.1 Cambios en el sistema muscular asociados al envejecimiento:

Cambios en el tamaño, tipo de fibra y características contráctil

El primer cambio que se produce con la edad es la atrofia de masa muscular. Este decremento se origina principalmente a partir de los 50 años a razón de 1─2% de pérdida de masa muscular por año, siendo mayor la pérdida de fuerza muscular de un 1,5% entre los 50─70 años incrementándose esta pérdida a partir de los 70 años a razón de 3% por año (50). Sin embargo, durante períodos de inactividad física estas pérdidas son mayores. En diferentes estudios se ha destacado como con tan sólo dos a tres semanas de inmovilización la masa muscular decrece en 5─10% sumado a una pérdida de fuerza de 10─20% (51–53). También se experimenta una reducción en el tamaño de fibras asociado al envejecimiento. Diferentes estudios señalan una pérdida de 10─40% en el tamaño de las fibras tipo II en ancianos

comparado a adultos jóvenes (54,55). El envejecimiento también cambia el fenotipo de las fibras musculares. En diferentes estudios, se han observado como la fibras rápidas o tipo II adquieren las características de las fibras lentas o tipo I, lo que implica una reducción de la capacidad de producir fuerza máxima (56,57). Si bien, otros estudios indican una adaptación de las tipo I hacia las características de las tipo II (58). Por lo que aún no hay consenso en esta cuestión. Bien es cierto que los resultados de estos estudios dependerán de las características de la población estudiada y más concretamente de los hábitos de actividad física que tengan los sujetos. En este sentido las fibras tipo I son las encargadas de realizar actividades de baja intensidad tales como caminar o hacer las tareas diarias como limpiar o hacer la comida, sim embargo las fibras tipo II son las encargadas de las actividades de alta intensidad como coger peso o correr rápido, tareas éstas poco comunes en personas envejecidas.

Cambios en la arquitectura muscular

Los principales cambios en cuanto a la estructura del músculo en personas con más de 65-70 años son la reducción del tamaño de las fibras (también mencionado anteriormente), una menor longitud de las fibras y una deficiencia en el ángulo de peneación (59,60). Además de esto, numerosos estudios indican un aumento de la infiltración de tejido adiposo en el músculo (61). En este sentido se observan cambios longitudinales en ancianos desde los 70 a los 79 años de un aumento de grasa intramuscular de 30% en mujeres y 50% en hombres (62). La calidad estructural del musculo también se ve perjudicada por un exceso de fibrosis (formación de bandas fibrosas entre fibras musculares) (63).

Cambios en las unidades motoras y activación neuromuscular

A nivel neuromuscular, el envejecimiento induce la pérdida de motoneuronas α y una regeneración incompleta del tejido nervioso en la fibra muscular previamente perdido (64). Además, existe una pérdida de transporte axonal (transporte de proteínas y otras moléculas desde y hacia la neurona), de la velocidad de conducción de la señal (64,65) y de la excitabilidad de las vías espinales y del córtex motor (66).

Cambios intracelulares

Con la senectud se experimentan cambios intracelulares. Principalmente los estudios indican una disminución en el número de mitocondrias y peor funcionamiento, esto afecta a la

disponibilidad de moléculas de ATP por lo que dificulta tanto las actividad muscular tanto aeróbica como anaeróbica (67).

Otros cambios bioquímicos

Además de estos cambios relativamente físicos, también ocurren diversos cambios químicos. Por ejemplo a nivel hormonal, el envejecimiento está relacionado con una descenso de los procesos hormonales anabólicos, teniendo como resultado una menor tasa de producción de la hormona de crecimiento (68). Además se experimenta una menor tasa circulante en plasma del factor IGF-1, el cual está muy involucrado en la síntesis proteica a través de la vía mTOR (69).

El envejecimiento también trae consigo un aumento de factores proinflamatorios como bien se ha indicado en diferentes estudios. Adultos-mayores experimentan una mayor concentración de citokinas como la IL-6 o la TNF- α (70,71).

2.2. Sarcopenia

Los fenómenos neuromusculares acontecidos durante el envejecimiento anteriormente descritos responden al término de “Sarcopenia” definido este como un trastorno progresivo y generalizado caracterizado por una pérdida acelerada de masa muscular y función el cual está asociado a un incremento de problemas de salud incluyendo caídas, dependencia funcional, fragilidad e incluso la muerte (72). En la práctica clínica el diagnóstico de sarcopenia se atribuye a personas con una baja masa y/o fuerza y/o calidad muscular. La sarcopenia es un proceso que responde al envejecimiento comenzando su mayor declive a partir de los 75 años con la pérdida de masa y fuerza muscular, aunque puede observarse también en individuos de mediana edad donde se experimenta un descenso a partir de los 45 años (ver Figura 5) (72).

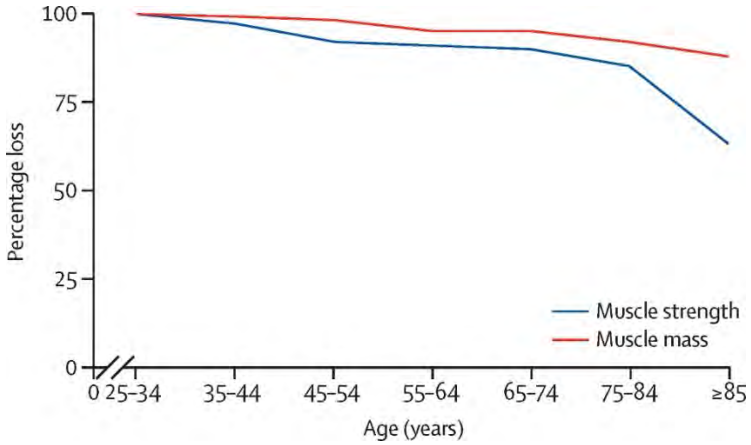

Figura 5. Porcentaje de pérdida de masa y fuerza muscular con la edad en hombres *(Sarcopenia de Alfonso J Cruz-Jentoft, Avan A Sayer 2019)*

De acuerdo con el grupo de expertos del EWGSOP para el diagnóstico de sarcopenia se deben cumplir al menos dos criterios de los propuestos (ver Tabla 1).

Tabla 1. Criterios y valores de referencia para el diagnóstico de sarcopenia según EWGSOP2

Criterio	**Hombres**	**Mujeres**
Fuerza en prensión manual (kg)	<27	<16
Masa muscular apendicular dividido por altura (kg/m^2)	<7	<5,5
Velocidad de la marcha (m/seg)	<0,8	<0,8
Tiempo en Up and Go test (seg)	≥20	≥20

*Nota: kg = kilogramo; m/seg = metro x segundo

Impacto de la sarcopenia sobre la salud

El tejido muscular, supone aproximadamente el 60% del total de la masa corporal (39), un deterioro en sus funciones puede generar afectaciones patológicas determinantes en la salud. Por tanto, la sarcopenia está asociada a numerosos resultados adversos sobre la salud que entre los más comunes podemos encontrar, deterioro cognitivo, pérdida de dependencia funcional, discapacidad y fragilidad (73–75). La sarcopenia también está asociada a enfermedades crónicas como la diabetes tipo 2, afecciones cardiovasculares, renales o pulmonares y obesidad sarcopénica (76–78).

Como argumentábamos en secciones anteriores, los efectos de la pérdida de masa muscular iban más allá de meros cambios estructurales, teniendo la misma o mayor importancia las alteraciones bioquímicas que afectan a la salud. En esta línea, parece ser que existe una inflamación sistémica de bajo grado asociada a la edad (79) y como una buena salud muscular podría moderar sus efectos adversos (49). En concreto, se ha estudiado ampliamente la asociación entre adipoquinas o factores proinflamatorios y mioquinas o factores antinflamatorios y su relación con enfermedades y otras comorbilidades asociadas a la vejez (80,81). Por ejemplo, existe evidencia sobre cómo diferentes factores proinflamatorios como IL-6, TNF-α, IL-1Rα, y la CRP están relacionados con el desarrollo de patologías asociadas a la edad y con el aumento del riesgo de mortalidad (82,83). Concretamente estudios previos indican una fuerte relación entre esta inflamación con la sarcopenia y pérdida de función física (64). También una mayor concentración en plasma de factores proinflamatorios como IL-6 y CRP están asociados a mayor fragilidad en mayores de más de 75 años (84,85), o como esta inflamación sistémica de bajo grado se asocia con un mayor riesgo de discapacidad funcional asociada a la demencia (86). Además, se ha informado sobre la relación entre inflamación a través del factor IL-6 y mayor probabilidad de padecer depresión, deterioro cognitivo y por consiguiente demencia (87). Adicionalmente, eventos asociados a la edad como disfunción mitocondrial, empeoramiento del sistema inmune e inflamación crónica de bajo grado, son características comunes de la sarcopenia, sobrepeso, obesidad, obesidad sarcopénica y estrés oxidativo, por lo que el círculo vicioso se retroalimenta si no actuamos de manera precisa contra esto (88). Incluso, hay suficiente evidencia sobre el descenso en los niveles de NTs durante el envejecimiento y riesgos asociados. Concretamente con respecto al BDNF, diversos estudios relacionan bajos niveles plasmáticos de BDNF con el peso y la edad (89), déficit de memoria o dificultades de aprendizaje (90,91), enfermedad de Alzheimer (92), demencia (93), deterioro cognitivo (94), depresión (95), incluso hay evidencia sobre bajos niveles séricos de BDNF y severidad de la enfermedad de Huntington (96).

3. Actividad física, condición física y sus efectos sobre la salud

3.1 Actividad Física y sus beneficios para la Salud

Diversos estudios han indicado el papel protector de la AF en edades avanzadas, disminuyendo el riesgo de contraer enfermedades crónicas no transmisibles (100). Por ello, la

AF es considerada como una de las inversiones más efectivas en salud pública (101) debido a su eficacia y bajo costo en comparación con tratamientos de enfermedades propias de la edad. Los beneficios de la AF sobre la salud trascienden la dimensión física demostrando efectos positivos en los dominios psicológico y mental en los adultos mayores al reducir la ansiedad y mejorar el estado de ánimo (102). Además, el bienestar subjetivo de los adultos mayores es reforzado debido al cumplimiento de sus actividades de la vida diaria de forma autónoma y por compartir experiencias saludables con la comunidad (103). La práctica de AF moderada y vigorosa en personas mayores de 50 años reduce el riesgo de contraer enfermedades crónicas y de mortalidad prematura, además retrasa la aparición de la dependencia funcional y discapacidad y favorece la autonomía en la vida cotidiana (104–106).

3.2 Condición física relacionada con la salud

La condición física se refiere a un conjunto de atributos o funciones del cuerpo humano como musculoesquelético, cardiorrespiratorio, psiconeurológico o endocrino-metabólico, que están implicados en la realización de la actividad física diaria y / o el ejercicio (107). El término se confunde o distorsiona frecuentemente con ejercicio físico y la actividad física, por lo que es necesaria su definición. "Actividad física" se refiere a cualquier movimiento corporal producido por el músculo esquelético que resulta en un gasto de energía; "Ejercicio" se refiere a la actividad física planificada, estructurada, repetitiva e intencionada con el objetivo de mejorar o mantener uno o más componentes de la actividad física. Por consiguiente, la condición física puede referirse a las aptitudes físicas relacionada con las habilidades motrices o a las relacionadas con la salud. La condición física relacionada con la habilidad motriz se asocia con el rendimiento de la habilidad motora o el deporte, cuyos componentes incluyen velocidad, agilidad, equilibrio, coordinación, potencia y tiempo de reacción. Por otro lado, la condición física relacionada con la salud (CFRS) se refiere a los rasgos y capacidades de la condición física que se asocian con un bajo riesgo de desarrollo prematuro de enfermedades hipocinéticas (es decir, las relacionadas con la inactividad física). En consecuencia, CFRS se compone de la aptitud física cardiorrespiratoria, la fuerza y la resistencia muscular, la velocidad / agilidad y la flexibilidad o el rango de movimiento, algunos autores también incluyen la composición corporal (107–109).

La CFRS se compone de lo siguiente:

a) Aptitud física cardiorrespiratoria (AFC): es la capacidad general de los sistemas cardiovascular y respiratorio y la capacidad de realizar una actividad física continua y extenuante. El biomarcador de la AFC es el consumo máximo de oxígeno (VO2max), que se obtiene mediante una prueba incremental hasta el agotamiento (107). Vo2max se define como la capacidad máxima del organismo de capturar, transportar y usar oxígeno para producir energía en las rutas del metabolismo aeróbico (110).

b) Fuerza muscular: es el resultado de la acción muscular, concéntrica, isométrica o excéntrica (movimiento o deformación de un cuerpo) frente a una resistencia externa, que como tal puede ser el propio peso corporal o cualquier otra resistencia u objeto externo al sujeto (111). Existen varias pruebas para evaluar la fuerza muscular ya que la fuerza máxima generada depende del segmento corporal requerido en la acción, el tamaño y el número de músculos involucrados o la coordinación de los grupos musculares, entre otros. Los componentes principales de la aptitud física relacionada con la salud podrían ser la fuerza de las extremidades superiores, la fuerza de la zona central del cuerpo y la fuerza de las extremidades inferiores.

c) Velocidad / agilidad: la velocidad es la capacidad de mover el cuerpo o parte de él, lo más rápido posible. La agilidad es la capacidad de moverse rápidamente y cambiar de dirección mientras se mantiene el control y el equilibrio. En consecuencia, la agilidad es una combinación de equilibrio, velocidad, potencia y coordinación (107).

d) Flexibilidad o rango de movimiento (ROM): se refiere a la capacidad de mover una articulación o conjunto de articulaciones a través de su rango completo de movimiento (109).

3.3 Condición física relacionada con la salud y resultados

Siguiendo la línea mencionada anteriormente, existe una evidencia sólida y consistente de que el nivel de CFRS está determinado por la cantidad y el tipo de AF realizada. Por lo tanto, un alto nivel de CFRS implica buenos resultados de salud, por el contrario, una baja CFRS puede estar conexa con mayor probabilidad de sufrir enfermedades físicas y psicológicas independientemente del IMC (112,113). Los efectos beneficiosos para la salud son consecuencias de las mejoras de uno o más componentes de la CFRS. En general, son las mejoras del AFC y la fuerza muscular, las responsables de un mejor estado de salud. Los

componentes de flexibilidad y velocidad / agilidad también juegan un papel importante en los resultados de salud. Sin embargo, la mejora de estos, son factores coadyuvantes, junto con la AFC y la fuerza muscular, bien para mejorar el estado de salud o para evitar enfermedades en el futuro.

Nuestros estudios se han fundamentado principalmente en dos dimensiones de la CFRS como son la fuerza del tren inferior evaluada mediante prensión manual y la velocidad de la marcha en 3 metros.

La fuerza de prensión manual está estrechamente relacionada con la movilidad y su deterioro se asocia con una amplia variedad de resultados clínicos adversos (114). Es una evaluación proxy relativamente simple y económica de la cantidad y calidad muscular siendo por ello una de las herramientas de evaluación de la condición física más utilizadas en estudios clínicos y epidemiológicos (114).

La velocidad de la marcha es una medida rápida, económica y confiable de la capacidad funcional con un valor predictivo bien documentado de los principales resultados relacionados con la salud como hospitalizaciones, deterioro funcional y cognitivo, caídas, mala calidad de vida y mortalidad (115,116).

4. Encuesta Nacional de Salud, Envejecimiento y Vejez, SABE Colombia

Colombia, al igual que los demás países de Latinoamérica, se enfrenta al fenómeno poblacional con una sociedad aún más envejecida como vimos en la primera sección de esta tesis. Por ello el Ministerio de Salud y Protección Social estableció el Sistema Nacional de Estudios y Encuestas Poblacionales para la Salud con el objetivo de actualizar los datos epidemiológicos de las personas adultas mayores. Con este interés, dicho Ministerio realizó junto con la Universidad del Valle el diseño de la Encuesta SABE para Colombia. El ejercicio de planificar la SABE Colombia implicó mantener la comparabilidad con la Encuesta SABE Internacional, buscando coherencia con marcos conceptuales y metodológicos identificados en cuanto a la información necesaria para identificar el estado de salud de la población adulta mayor en este país. De este modo el estudio forma parte del proyecto multicéntrico de la Organización Panamericana de Salud ejecutado en 7 capitales de América Latina y el Caribe

(117). La Encuesta SABE Colombia fue ejecutada entre 2014 y 2015 por grupos de investigación de la Universidad del Valle y la Universidad de Caldas (118).

Específicamente, la Encuesta SABE Colombia explora y evalúa interdisciplinariamente y en profundidad, diversos aspectos que intervienen en el fenómeno del envejecimiento y la vejez de la población colombiana. El estudio aporta a la comprensión del envejecimiento y la vejez en las áreas urbanas y rurales de Colombia desde el modelo de los Determinantes Sociales de la Salud y en el marco de la política de los Determinantes del Envejecimiento Activo. Los resultados de la Encuesta SABE Colombia le proporcionan al país información clave sobre la salud, el bienestar, el envejecimiento y la calidad de vida de las personas adultas mayores, hombres y mujeres mayores de 60 años. En consecuencia, la Encuesta aporta información para proyectar necesidades de atención en salud de las personas adultas mayores, para optimizar sus oportunidades de participación, protección y seguridad social y para planificar la respuesta estatal ante eventos asociados al rápido crecimiento de esta población en el país, en la perspectiva de incrementar su calidad de vida (118).

La muestra comprendida en la encuesta era de 24,553 procedentes de 32 departamentos asumiendo una tasa de respuesta del 80% de los 30961 individuos calculados al inicio. Finalmente, a tasa se redujo al 70% estando compuesto el estudio de 23694 adultos mayores procedentes de 244 municipios rurales y urbanos (118).

La encuesta incluye preguntas que arroja información sobre los siguientes apartados: socioeconómico, medio ambiente físico y social, conducta, cognición, funcionalidad, condiciones médicas y de salud, uso y acceso a servicios de salud y antropometría y valoración funcional (118).

5. Objetivos

Los objetivos de esta tesis versan en comprender las asociaciones entre condición física y los resultados de salud y el rol que juega la condición física entre los resultados de salud.

A continuación, los detallamos:

i. Estudiar las asociaciones entre la velocidad de la marcha y los resultados adversos en salud
ii. Examinar las relaciones entre la fuerza de prensión manual y resultados de salud
iii. Examinar si la velocidad de la marcha, la fuerza de prensión manual y el perfil de glucosa son mediadores y/o moderadores entre comorbilidades comunes en adultos mayores.

6. Descripción estadística

Los trabajos contenidos en este documento están basados, en parte, en métodos estadísticos no muy comunes en su uso y de reciente actualización. Por ello, hemos creído conveniente describir las dos técnicas principales empleadas como son la mediación y moderación.

La investigación clínica se caracteriza por intentar responder a los efectos de cierta terapia o tratamiento, o establecer si una terapia es más efectiva que otra sobre ciertas características o circunstancias del sujeto. Tradicionalmente, las inferencias estadísticas basadas en las pruebas de significancia de la hipótesis nula o de la magnitud de los efectos del tratamiento han sido suficientes para establecer una determinada evidencia de los procesos causales. Sin embargo, la evolución de los recursos estadísticos, así como la continua inquietud de los investigadores por responder al cómo y porqué y bajo qué condiciones se producen estos efectos causales, ha complejizado los procesos tanto en estudios experimentales (laboratorio) como correlacionales (transversales y/o longitudinales). Por tanto, no resultaría adecuado desarrollar tratamientos universalmente conocidos y exitosos, sino que sería más efectivo, diseñar tratamientos adecuados para situaciones específicas. Por consiguiente, este tratamiento debería tener en cuenta las siguientes premisas: ¿para quién o bajo qué condiciones un determinado tratamiento será exitoso?, ¿cuáles son los componentes o "ingredientes" activos de un determinado tratamiento?, ¿qué componentes o "ingredientes" del tratamiento son inocuos o repercuten negativamente en el resultado? Para responder a estas cuestiones es necesario utilizar metodologías de mediación y moderación, que permitan conocer como interactúan los factores que intervienen en un tratamiento (119). De esta manera a las ya conocidas variables dependientes, independientes y variables de control, se unen las variables mediadoras y moderadoras.

6.1 Definición y ejemplo de análisis de mediación

El análisis de mediación permite establecer como cada uno de los componentes del tratamiento interactúa con otro y provoca los efectos, es decir, posibilita identificar qué mecanismos de acción, a través de los cuales un tratamiento logra sus efectos. De esta forma los componentes o "ingredientes" identificados como activos pueden intensificarse y/o

refinarse y por el contrario, aquellos que son inocuos o perjudiciales podrían ser descartados. En términos conceptuales la mediación hace referencia a conocer cómo un efecto *X* opera sobre *Y* a través de una posible tercera variable, llamada variable "mediadora". Pongamos el ejemplo de que queremos conocer si la mejora del dolor crónico de espalda (variable dependiente "*Y*"), tras participar en un programa de entrenamiento de fuerza (variable independiente *"X")* es influida por la mejora de la densidad mineral ósea (variable mediadora "M_1") o por la mejora de la fuerza muscular (variable mediadora M_2"). En el ejemplo, X afecta a Y porque X afecta a una de las dos variables mediadoras M_1 o M_2, o a ambas a la vez. Por lo tanto, un modelo de mediación es un conjunto de dos o más eventos causales que actúan de manera encadenada con la secuencia X→ M → Y. De esta manera la variable o variables M, debe ser colocada causalmente entre X e Y, siendo esta afectada por X y esta a su vez afectando a Y. En la figura 4 mostramos de manera gráfica como interactúan las variables según el ejemplo propuesto, donde *X* es la condición de tratamiento (participar en el programa de fuerza Vs no participar), *Y* es la variable resultado (dolor crónico de espalda), M_1 variable mediadora 1 (mejora de la densidad mineral) y M_2 variable mediadora 2 (mejora de la fuerza muscular). El ejemplo propuesto contempla dos variables mediadoras, por lo que hablamos de mediación múltiple, pudiéndose ser paralela o en serie, aunque no entraremos a comparar estos modelos de mediación.

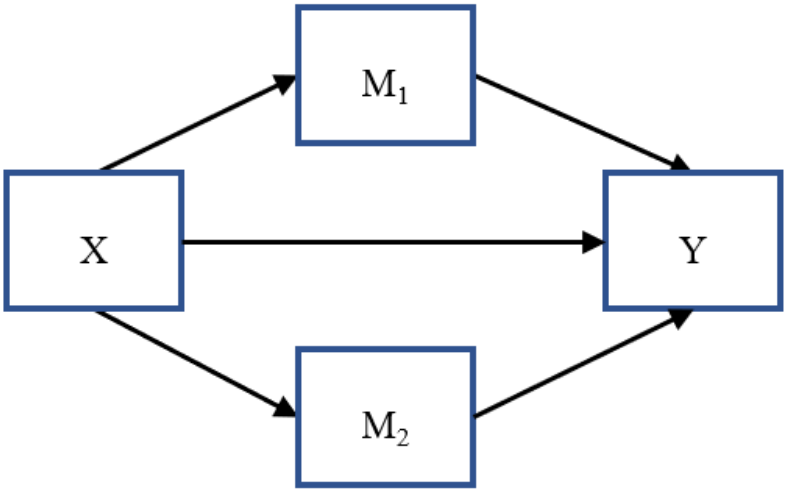

Figura 6. Modelo de mediación paralela con dos variables mediadoras.

No obstante, el modelo más usual que podemos encontrar en el análisis de mediación sólo incluye una variable mediadora, por lo que el resultado estaría basado en describir si existe o no efecto indirecto de la variable mediadora y la magnitud de dicho efecto indirecto. En la figura 5, exponemos el modelo gráfico de mediación simple. Resultados significativos de mediación, serán cuando el valor "0" no pase por el intervalo de confianza, fijado por costumbre al 95%.

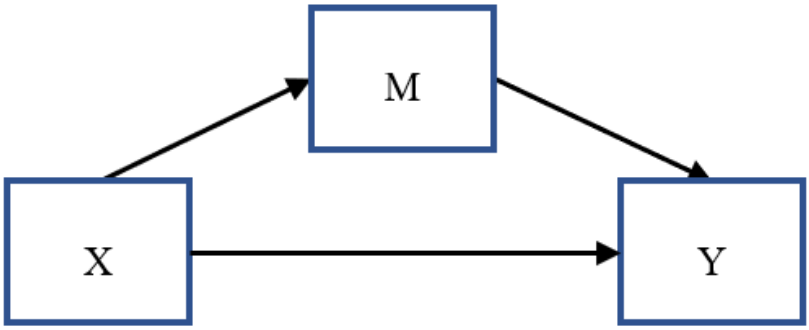

Figura 7. Modelo de mediación simple.

6.2 Definición y ejemplo de análisis de moderación

El análisis de moderación permite conocer que pacientes responden mejor a un determinado tratamiento y para quienes podría ser más apropiado otro tipo de tratamiento. A partir del análisis de moderación podrían asociarse variables como tipo de tratamiento y tipo de paciente (referido a las características de estos como género, rango de edad, presencia o ausencia de una comorbilidad …). El análisis simple de moderación permite conocer los efectos de interacción de la variable moderadora entre la variable independiente y dependiente.

Los moderadores son variables intervinientes que afectan a la dirección y/o fuerza de la relación entre una variable independiente y una variable dependiente, reduciendo, incrementando, anulando o invirtiendo dicha relación (120,121).

Volviendo al ejemplo anterior, imaginemos que ahora queremos conocer si los beneficios del programa de fuerza sobre el dolor de espalda se producen o no en función de una característica especifica de los participantes que llamaremos estado de peso. Para ello hemos

elaboramos una variable *dummy* (normo peso Vs sobrepeso) que será la variable moderadora *W*, *X* es la condición de tratamiento (participar en el programa de fuerza Vs no participar), *Y* es la variable resultado (dolor crónico de espalda). Este modelo con un moderador se ejemplifica en la figura 6.

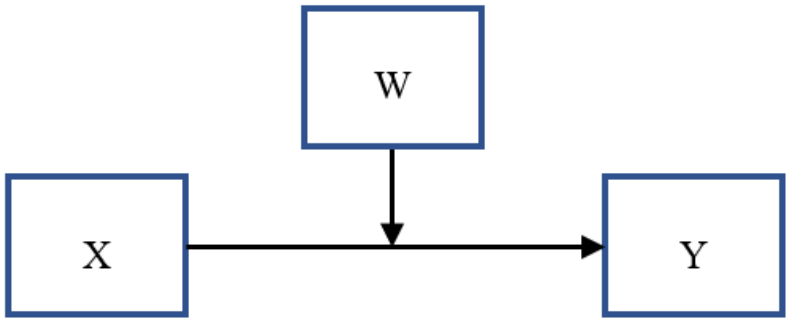

Figura 8. Ejemplo de moderación.

En el ejemplo expuesto, la variable moderadora "W" es *dummy*. Por lo que, si esta variable obtuviera un resultado significativo de interacción, diríamos por ejemplo que tras el programa de fuerza los participantes que mejoraron significativamente su dolor de espalda fueron los de estado de peso normal, no existiendo mejoras significativas en los participantes con sobrepeso.

Cómo decíamos, este ejemplo está basado en una variable moderadora *dummy*, pero también podemos encontrarnos con variables moderadoras continuas. Sigamos el ejemplo anterior, dado que existe evidencia de que participar en el programa de fuerza mejora el dolor de espalda, ahora queremos saber cuál es la mejora que deben experimentar los participantes del programa en su nivel de fuerza para que se genere una mejora significativa del dolor de espalda. Para ello, se aplica la técnica *Johnson-Neyman* incluida en la macro PROCESS (121), la cual encuentra dentro del continuo de los datos de W (mejora de la fuerza) la región de significancia y/o umbral. En la figura 7, exponemos un ejemplo del *plot* de la técnica *Johnson-Neyman*, en la cual la región de significancia o umbral viene determinada por la línea discontinua.

Finalmente, y siguiendo la metodología aportada por Hayes (121), se considera efectos de interacción o variable moderadora cuando el valor "0" no pase por el intervalo de confianza, fijado por costumbre al 95%.

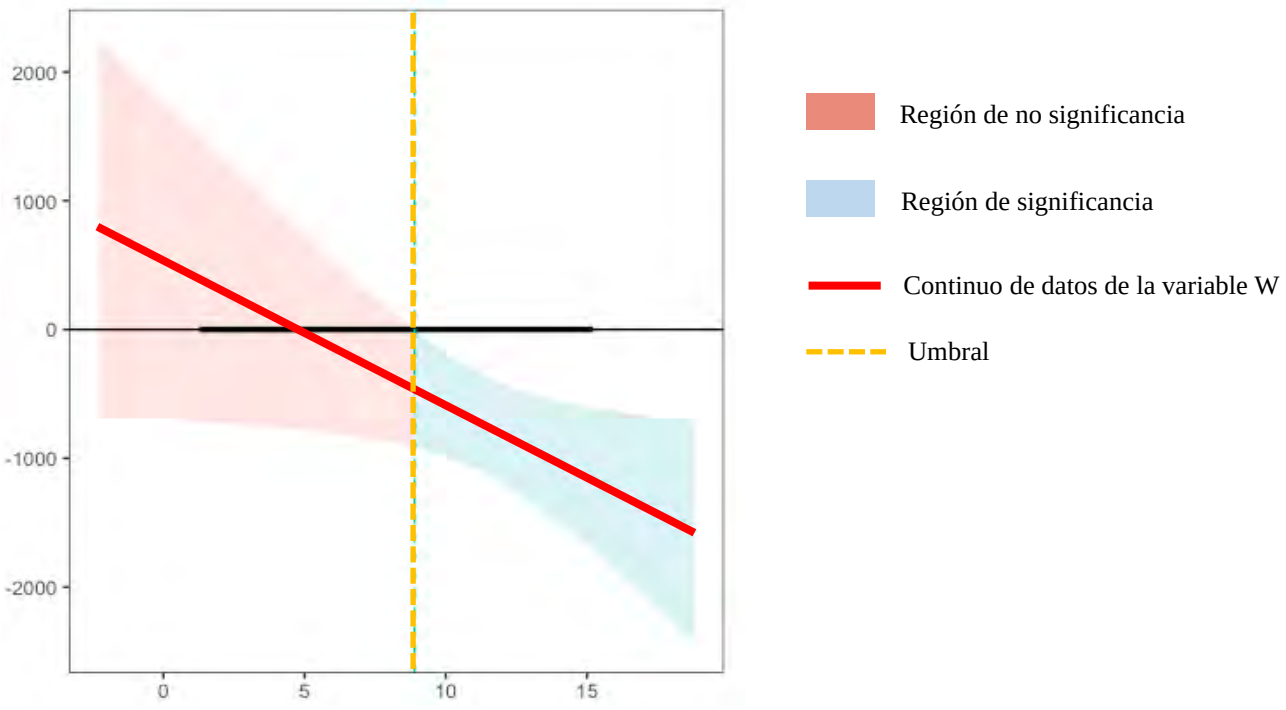

Figura 9. Ejemplo del plot de la técnica Johnson-Neyman

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SEGUNDA PARTE

Artículos de investigación

Artículo 1

High prevalence of probable sarcopenia in a representative sample from Colombia: Implications for geriatrics in Latin America

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Abstract

Objectives: The European Working Group on Sarcopenia in Older People 2 (EWGSOP2) recently defined the new concept of probable sarcopenia to help improve screening and prevent future sarcopenia. We investigated the prevalence of probable sarcopenia, defined as weak grip strength, in community dwelling older Colombian adults, and examined the long-term associated conditions.

Design: Cross-sectional study.

Setting: Urban and rural Colombian older adults from the "Estudio Nacional de Salud, Bienestar y Envejecimiento (SABE) study".

Participants: 5237 Colombian older adults aged 60 years.

Measurements: Probable sarcopenia was assessed following the cut-off points for weak grip strength recommended by EWGSOP2 guidelines. Odds ratios (ORs) of the relationship between long-term conditions and probable sarcopenia were determined using logistic regression.

Results: The prevalence of probable sarcopenia defined as weak grip strength was 46.5% [95% confidence interval (CI), 45.1-47.8]. Physical inactivity (OR 1.35, 95% CI 1.14-1.59); diabetes (OR 1.32, 95% CI 1.11-1.56); and arthritis, osteoarthritis, and rheumatism (OR 1.44, 95% CI 1.25-1.67) were independently associated with probable sarcopenia.

Conclusions: We found that almost half of all the Colombian older adults in our sample had probable sarcopenia. Individuals with physical inactivity, diabetes, arthritis, or osteoarthritis and rheumatism had a higher prevalence of probable sarcopenia. Probable sarcopenia is clinically highly relevant, and several of the factors associated with this condition are potentially preventable, treatable, and reversible.

Introduction

Sarcopenia is characterized by the progressive and generalized loss of muscle mass and function (strength and performance) (1). There is an extensive body of evidence for an association between sarcopenia and various health problems. Patients with sarcopenia have a poor quality of life and are more likely to have a higher incidence of falls, injuries, and hospitalizations than individuals with healthy muscle mass (2). Sarcopenia is also associated with diabetes (3). cardiovascular illness (4) depression (5), and greater dependency (6). Accordingly, preventing sarcopenia or delaying its appearance is a clinical aspiration, as its prevalence presents a major challenge for public health (7). Occurring commonly as an age-related process, the incidence of sarcopenia rises sharply after the age of 70 years, although the decline in physical performance starts decades before.

Recent studies have found that sarcopenia can be observed even in children and adolescents in association with health problems (8,9). Recently, the European Working Group on Sarcopenia in Older People 2 (EWGSOP2) introduced the new concept of probable sarcopenia (10), which is defined as low muscle strength based on poor performance in the grip strength test or chair rise test, or both, and arises from the need for a diagnosis when it is impossible to measure muscle mass. These new guidelines emphasize that, as indicated previously (1), sarcopenia primarily is an age-related condition but can also occur at younger ages in combination with chronic conditions.

The prevalence of sarcopenia and its relationship with chronic conditions has been examined in detail, with several studies finding an inverse relationship between grip strength and the number of chronic health conditions (11,12). However, comparatively little research has focused on the relationship between associated factors and probable sarcopenia. In Europe, Dodds et al (13) and Sousa-Santos (14) have analyzed the relationship between probable sarcopenia and multimorbidity in middle-aged and older adult populations. In Latin America, the English Longitudinal Study of Aging determined the prevalence and associated factors using the cut-off values recommended by the EWGSOP2 to screen for probable sarcopenia (15) However, because the concept of probable sarcopenia is new and the literature regarding this syndrome is scarce, more studies are needed to determine the prevalence of probable sarcopenia and the factors associated with its development.

Using data from a national cross-sectional survey conducted in Colombia, the "Estudio Nacional de Salud, Bienestar y Envejecimiento (SABE) study," (16) our aims were, first, to describe the prevalence of probable sarcopenia using the updated guidelines in a sample of older adults and, second, to investigate the relationship between probable sarcopenia and its associated factors.

Materials and Methods

Design, Setting, and Participants

Data were obtained from the SABE Colombia survey conducted in 2015 by the Epidemiological Office of the Ministery of Health and Social Protection of Colombia (https://www.minsalud.gov.co/). Details of the study have been published elsewhere (16). The study included the Colombian population ≥ of 60 years old, residing in urban and rural households in all Colombia regions, who were non-institutionalized and Spanish speakers. The indicators were disaggregated by age range, sex, ethnicity, and socioeconomic level. Institutional review boards involved in developing the SABE-Colombia study (University of Caldas, ID protocol CBCS-021-14, and University of Valle, ID protocol 09–014 and O11–015) reviewed and approved the study protocol. Written informed consent was obtained from each individual before inclusion and completion of the first examination. Permissions and details are available at https://www. minsalud.gov.co/. The Human Subjects Committee at the Pontificia Universidad Javeriana approved the secondary analysis study protocol (ACTA ID 20/2017e2017/180, FM-CIE-0459- 17).

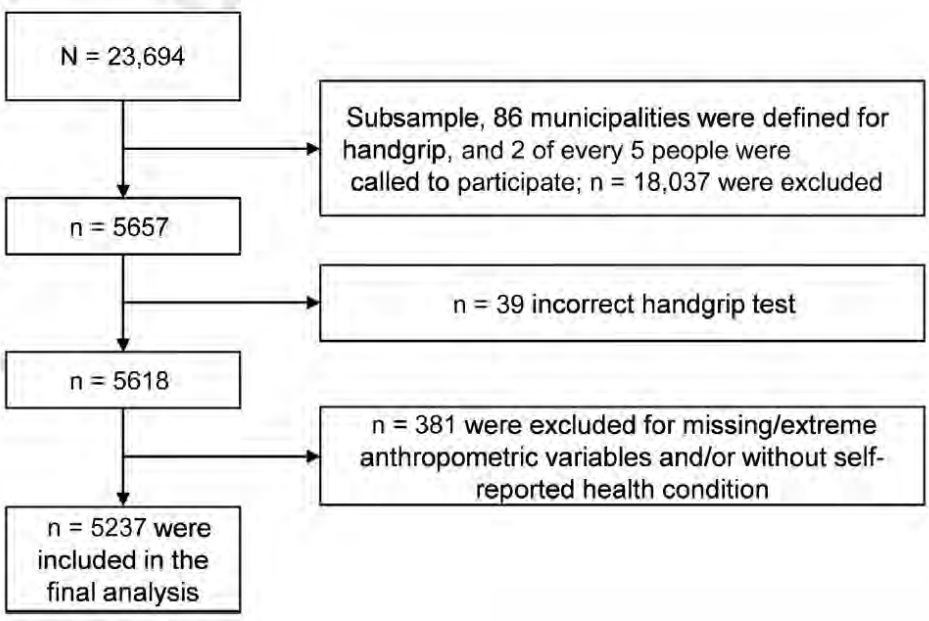

Fig. 1. Flow chart shows the study sample selection from the Colombian Health and Wellbeing and Aging Survey (SABE) 2015. All analyses presented here were based on 5237 surveyed participants, each with complete handgrip and long-term condition data.

The estimated sample size was 24,553 individuals, assuming an 80% response of the target sample of 30,691 individuals (16). The sample was probabilistic, clustered, stratified, and multistage. The sample size for these cities, 3500 individuals per city, was added to the national value by accumulating the sample values for the subregion, region, and country. The original sample size achieved (including 244 municipalities) was 23,694 elderly Colombians (16). For this subsample analysis, 86 municipalities were selected, including the 4 large cities (Bogota, Cali, Medellin, and Barranquilla), for the application of functionality tests and muscle strength assessment. The same formula as for the subsample was used, assuming an expected proportion of 0.07, a design effect of 1.2, a relative standard error of 0.065, and a nonresponse percentage of 20%, obtaining a sample of 4525 people 60 years of age or older (16). The selection of older adults was carried out using systematic sampling, by randomly selecting 2 of 5 individuals of the general sample. Flow-chart diagram is detailed in Figure 1.

Anthropometrics measurement

Trained personnel collected the data. Height and body weight were measured with a portable stadiometer (Seca 213; Seca, Hamburg, Germany) and an electronic scale (Kendall

graduated platform scale). Body mass index (17) was calculated as weight (in kilograms) divided by height (in meters) squared and categorized following the Word Health Organization classification for Latin American populations (18). Waist circumference measurements were taken at the end of a normal expiration to the nearest 0.1 cm, measuring from the middle point between the lower border of the rib cage and the iliac crest midaxillary line.

Assessment of muscle strength

The presence of probable sarcopenia was assessed following the cut-off points for weak grip strength recommended by the EWGSOP2 guidelines: <27 kg in men and <16 kg in women (10,13,19). Grip strength was measured using a Takei dynamometer (Takei Scientific Instruments Co, Tokyo, Japan), which was calibrated before testing to ensure the accuracy of the results. Subjects were asked to perform the task (with elbow joint in full extension) while standing if possible and were given a practice trial to ensure comprehension of the procedure. The grip tests were performed 2 to 3 times on each hand, alternating hands between each trial, and the mean value was recorded. Testers ensured a total of 60 seconds of rest between trials on the same hand.

Potential Associated Factors

To develop the quantitative component, we included the following potential associated factors: socioeconomic data, including age, sex, ethnicity, socioeconomic status, urbanicity, as well as cognition, functionality, and medical and health conditions. For older adults, the questions were answered by a companion or caregiver when the score obtained by the test was lower than (13) points (Folstein Mini-Mental Test) (20,21). For lifestyle characteristics, personal habits regarding alcohol intake and cigarette smoking were also recorded. For the "proxy physical activity" report, the following questions were asked: (i) "Have you regularly exercised, such as jogging or dancing, or performed rigorous physical activity at least 3 times a week for the past year?" (ii) "Do you walk at least 3 times a week between 9 and 20 blocks (1.6 km) without resting?" and (iii) "Do you walk at least 3 times a week 8 blocks (0.5 km) without resting?" Participants were considered physically active if they responded affirmatively to 2 of the 3 questions (22). Medical information including multimorbidity, as well as chronic conditions adapted from the original SABE study, was assessed by asking the participants if they had been medically diagnosed with hypertension, diabetes, chronic obstructive pulmonary disease, cardiovascular disease (heart attack, angina) stroke, cancer, arthritis, osteoporosis,

cholesterol, triglycerides, and mental or sensory problems. Lastly, information on ethnicity (indigenous; black, "mulatto," or Afro-Colombian, white; and others), living area (rural or urban), and socioeconomic status (levels I and II: low; levels III and IV: middle; and levels V and VI: high) were obtained and used as covariables.

Statistical analysis

Data were analyzed using JASP open-source software for statistical analysis (JASP Team 2020 v 0.12.2) for Windows. Continuous variables were expressed as mean ± standard deviation. Categorical variables were expressed as frequencies and percentages. The normality of the variables was verified using Kolmogorov-Smirnov tests and probability plots. The sample consisted of 2 groups: no sarcopenia (normal grip strength) or probable sarcopenia (weak grip strength). Mann-Whitney U tests were applied to identify significant differences in continuous variables, and chi-squared tests were used for categorical variables between groups.

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to explore the relationship between each category of associated factors and probable sarcopenia, adjusting for potential confounding variables such as age, sex, socioeconomic status, body mass index and waist circumference.

Results

A total of 5237 participants had completed data for grip strength, anthropometric measures, and the presence of long-term conditions (see the flowchart in Figure 1). Of the total sample, 2434 individuals showed the presence of probable sarcopenia according to the EWGSOP2 definition, representing 46.5% (95% CI 45.1%-47.8%). By sex, 1041 men (47.9%, 95% CI 45.8%-50.0%) and 1393 women (45.4%, 95% CI 43.6%-47.2%) presented with probable sarcopenia (Table 1). The mean age of the participants was 70.4 (7.8) years, and the majority (52%) were 60-69 years old. The distribution of probable sarcopenia across age groups was similar between the ages of 60-69 and 70-79 years. Most of the individuals in the no-sarcopenia (healthy muscular strength) group (65%) were 60-69 years old. Individuals in the lowest socioeconomic status group (levels I and II) had the highest prevalence of probable sarcopenia (76.2%). Finally, a high prevalence of probable sarcopenia was found in individuals of white ethnicity living in urbans areas.

Table 1. Participants' socio-demographics characteristics anthropometric, lifestyle and long-term conditions information and the probable sarcopenia status (n = 5.237)

	Total n (%)	Presence of probable sarcopenia n = 2434 (46.5%)	No sarcopenia n = 2803 (53.5%)
Age (years)	70.4 (7.8)	73.2 (8.4)	68.06 (6.3)
Age group			
60-69	2744 (52.4)	921 (37.8)	1823 (65.0)
70-79	1717 (32.8)	909 (37.3)	808 (28.8)
80+	776 (14.8)	604 (24.8)	172 (6.1)
Gender			
Male	2172 (41.5)	1041 (42.8)	1131 (40.3)
Female	3065 (58.5)	1393 (57.2)	1672 (59.7)
Socioeconomic status			
Level I-II (low)	3985 (76.1)	1855 (76.2)	2130 (76.0)
Level III-IV (middle)	1207 (23.0)	565 (23.2)	642 (22.9)
Level V-VI (high)	45 (0.9)	14 (0.6)	31 (1.1)
Living area			
Urban	4055 (77.4)	1897 (77.9)	2158 (77.0)
Rural	1182 (22.6)	537 (22.1)	645 (23.0)
Ethnicity			
Indigenous	313 (7.1)	135 (7.2)	178 (6.9)
Black or "mulato."	428 (9.7)	165 (8.8)	263 (10.3)
White	1388 (31.3)	619 (33.0)	769 (30.0)
Others	2306 (52.0)	954 (50.9)	1352 (52.8)
BMI (kg/m2)	27.4 (5.01)	26.7 (4.9)	27.9 (4.9)
BMI categories			
Underweight	101 (1.9)	57 (2.3)	44 (1.6)
Normal weight	1443 (30.4)	737 (30.3)	706 (25.2)
Overweight	1926 (40.6)	847 (34.8)	1079 (38.5)
Obese	1274 (26.9)	461 (18.9)	813 (29.0)
Missing	493 (9.4)	332 (13.6)	161 (5.7)
Waist circumference (cm)	92.4 (11.1)	91.3 (11.1)	93.3 (10.9)

Calf circumference (cm)	34.5 (3.8)	33.7 (3.7)	35.1 (3.8)
Muscle strength			
Grip strength (kg)	20.8 (8.5)	15.2 (5.3)	25.7 (7.8)
Relative grip strength (kg/kg weight)	0.32 (0.12)	0.25 (0.1)	0.38 (0.1)
Factors associated			
Smoke	548 (10.5)	237 (9.7)	311 (11.1)
Alcohol intake	645 (12.3)	250 (10.2)	395 (14.1)
Non-Physically active	4313 (82.5)	2095 (86.1)	2218 (79.1)
Hypertension	2929 (56.0)	1441 (59.2)	1488 (53.1)
Diabetes	868 (16.6)	442 (18.2)	426 (15.2)
History of cancer	259 (5.0)	124 (5.1)	135 (4.8)
Respiratory diseases	568 (10.9)	302 (12.4)	266 (9.5)
Cardiovascular	749 (14.3)	370 (15.2)	379 (13.5)
Stroke	225 (4.3)	128 (5.3)	97 (3.5)
Arthritis. osteoarthritis. rheumatism	1458 (27.9)	766 (31.5)	692 (24.7)
Osteoporosis	644 (12.4)	349 (14.3)	295 (10.5)
Cholesterol	2536 (48.7)	1161 (47.7)	1375 (49.1)
Triglycerides	1952 (37.8)	884 (36.3)	1068 (38.1)
Mental	465 (8.9)	238 (9.8)	227 (8.1)
Hearing problems	1300 (24.9)	722 (29.7)	578 (20.6)
Vision problems	2902 (65.5)	1276 (52.4)	1626 (58.0)

Data expressed as frequencies and percentage. Frequencies in factors associated are reported as "yes"

According to anthropometric and lifestyle characteristics and long-term health conditions (Table 1), body mass index, waist circumference, and calf circumference were all slightly higher in nonsarcopenic individuals than in probable sarcopenic peers. As expected, similar results were obtained for muscular strength, with nonsarcopenic individuals showing better absolute and relative grip strength to body weight values. Regarding long-term health conditions, individuals with probable sarcopenia had a higher prevalence of diseases than nonsarcopenic individuals: hypertension 59.2%, diabetes 18.2%, arthritis 31.5%, cholesterol 47.7%, and altered triglycerides 36.3%. Finally, the probable sarcopenia group had a greater

number of individuals who failed to achieve the minimum level of physical activity. Based on the data, physical inactivity was the most important modifiable risk factor, and hypertension was the most prevalent long-term illness in individuals with probable sarcopenia.

The results from logistic regression analyses are shown in Figure 2. Seven long-term health conditions were significantly related to probable sarcopenia. Specifically, individuals not accomplishing the minimum level of physical activity were more likely to have probable sarcopenia (OR 1.35, 95% CI 1.14-1.59). Similarly, those with diabetes (OR 1.32, 95% CI 1.11-1.56); mental disorders (OR 1.28, 95% CI 1.03-1.59); arthritis, osteoarthritis, and rheumatism (OR 1.44, 95% CI 1.25-1.67); osteoporosis (OR 1.27, 95% CI 1.05-1.67); vision (OR 1.24, 95% CI 1.07-1.42); and hearing problems (OR 1.22, 95% CI 1.06-1.42) were more likely to have probable sarcopenia. Other chronic long-term conditions related to cardiovascular health, triglycerides, cholesterol, or stroke were not significantly associated with probable sarcopenia.

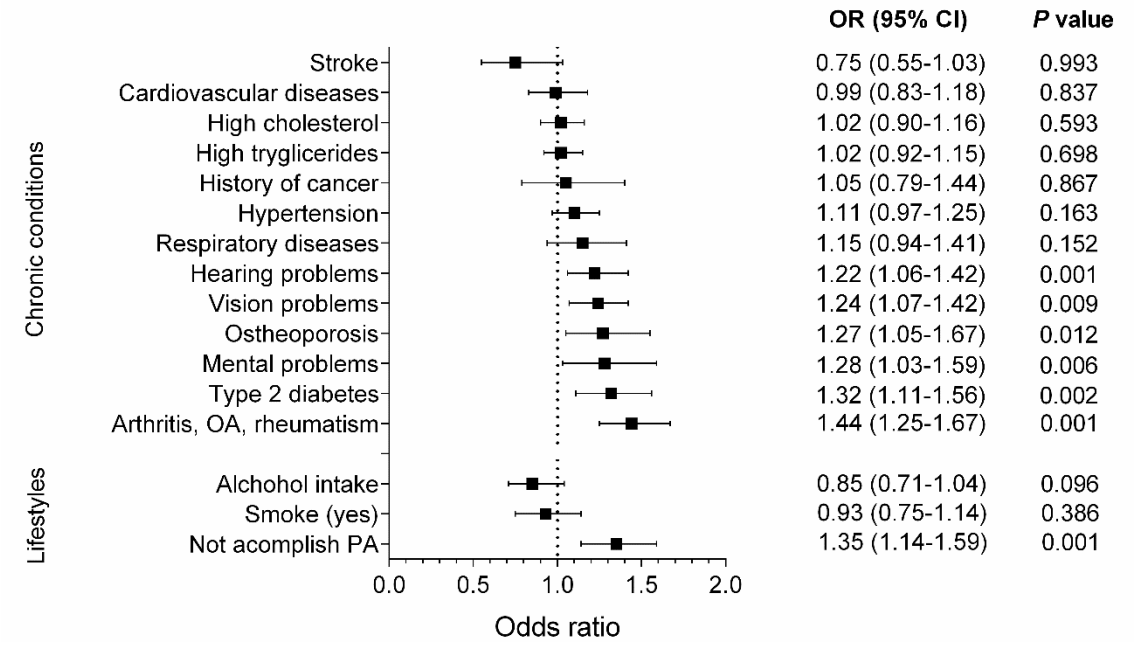

Figure 2. Independent associations between probable sarcopenia and each category of chronic conditions. ORs obtained through the logistic regression model showing an independent association between having +1 or more chronic conditions in each category and probable sarcopenia. Analysis adjusted of following covariates: sex, age, BMI, and WC (both as a linear term).

Discussion

In the present study, we examined the prevalence of probable sarcopenia and its associated factors in a nationally representative sample of older adults. We found that probable sarcopenia has a high prevalence in Latin American older adults and is associated with several chronic conditions and physical inactivity. To our knowledge, this is the first study in a Latin American country to use the new diagnosis of probable sarcopenia and to assess its relationship with associated factors. Our findings highlight that the prevalence of probable sarcopenia is 46.5% (95% CI 45.1%-47.8%) in Colombian older adults and is associated with several risk factors such as physical inactivity, vision, hearing and mental disorders, and also osteoporosis, arthritis, and diabetes.

Several studies have reported the prevalence of probable sarcopenia in different countries using the handgrip strength cut-off points recommended by the EWGSOP2 guidelines (men <27 kg; women <16 kg). For instance, Dodds et al (13) found a prevalence of 5.3% in British adults aged 40-70 years, whereas Pal et al (23) found a prevalence of 14.6% in Indian adults aged ± 20 years (mean age 44 years). A study in Portugal (14) found a prevalence of probable sarcopenia of 36% in adults aged >65 years. Using data from the Brazilian Longitudinal Study of Aging, Borges (24) found a prevalence of 17.6% among men and 17.7% among women in 8396 individuals aged >50 years. Lastly, a study in an Australian population aged >60 years (25) reported a mean prevalence of probable sarcopenia of 13.4% and 2.7% for men and women, respectively. It is clear that our results show a higher prevalence of probable sarcopenia than the aforementioned studies. Considering that decreases in muscular strength are closely related to age, the age range of individuals tested might explain this difference. Our study tested individuals aged >60 years, whereas the studies in the United Kingdom, India, and Brazil are based on a population aged >40 years. Also, our study is based on a nationally representative sample of older adults (n = 5237), and so our findings should be considered more robust.

Also worthy of note is the high proportion of overweight and obese older adults in our cohort. Latin Americans are more predisposed to overweight or obesity due to sociocultural, diet, or genetic factors (26). Our findings are of clinical relevance, as obese individuals showed probable sarcopenia using a functional test based on handgrip strength. This points to the potential clinical utility of the handgrip test, now also to evaluate older adults or future

sarcopenia. We found that physical inactivity and some chronic conditions might negatively influence the presence of probable sarcopenia. Physical inactivity seems to be the most damaging factor for muscle deterioration and consequent probable sarcopenia. Several studies have reported that physical inactivity is the primary risk factor for muscle loss and weakness, (27-29) whereas regular physical activity attenuates the aging effect on muscular health (30). Accordingly, the Word Health Organization recommends at least 3 days per week of physical activity for adults and older people. As seen from our results, the proportion of individuals with probable sarcopenia and physical inactivity is relatively important predictor of sarcopenia, with more than twice the prevalence of sarcopenia in individuals with diabetes than in nondiabetic individuals (31). Likewise, the English Longitudinal Study of Aging showed an increase in probable sarcopenia in men with diabetes but not women with diabetes 8 years later (32). The main component involved in muscle strength deterioration in patients with diabetes (i.e., diabetic myopathy) seems to be low-grade systemic inflammation (33).

Osteoporosis, arthritis, osteoarthritis, and rheumatism were also factors associated with probable sarcopenia in our study. The evidence regarding these relationships is not clear. Until recently, the widely held view was that sarcopenia precedes osteoporosis, as reduction in muscle function (such as with sarcopenia or cachexia) leads to reductions in bone mass. However, during the last decade the concept of a “muscle-bone” unit has gained acceptance. Bone and muscle tissue comprise a unit of paracrine and endocrine exchange by adapting their response to loading, aging, and to additional factors such as adipose tissue (34,35) and share interconnecting biochemical pathways (34). Several studies have demonstrated that individuals show muscle weakness after hip fracture (reviewed in Yeung et al36). In a similar manner, the relationship between sarcopenia and osteoporosis cannot be understood without involving the cartilage and that a deterioration of the latter is also closely linked to sarcopenia and osteoporosis (34,37). Accordingly, all 3 components are interrelated as a triad of cofactors.

We also found that sensory disorders were related to sarcopenia. Aging is associated with the development of hearing and visual deterioration (38) leading to functional limitations, and often resulting in a complicated relationship with cognitive disturbance and mental health impairment (38). Therefore, a reduction in input information may lead to decreases in proprioception and balance during walking, affecting mobility and, ultimately, physical activity. This might explain the probable sarcopenia in individuals with these characteristics.

Also, the mean age of participants in our study was 70.4 years, and the prevalence of sensory impairment, mainly visual, was high.

Our findings confirm the importance of modifiable risk factors for controlling probable sarcopenia among older adults. Our data show that physical inactivity increases the odds of having probable sarcopenia. It is nevertheless remarkable that diabetes, osteoporosis high, which could explain, in part, the higher prevalence of probable sarcopenia found in this study. Diabetes was also strongly associated with probable sarcopenia in our sample. Diabetes is known to increase the risk of developing sarcopenia in older people. In the Korean Sarcopenic Obesity Study, diabetes was found to be an arthritis, and sensory problems significantly affect probable sarcopenia development. Early detection of muscle weakness using a simple clinical practice tool, such as handgrip strength, might help prevent or alleviate future risks in subjects with these health conditions. For example, sarcopenia is associated with functional dependence, one of the main factors affecting disability and quality of life (39). Therefore, knowing the factors associated with probable sarcopenia would help health officials focus on screening for probable sarcopenia in older adults with chronic conditions.

Our study has several strengths, including the large sample size of older adults within a nationally representative proportion of persons aged ≥60 years, and the novelty of using a simple and practical method (handgrip) to screen for probable sarcopenia. However, several limitations should be considered. First, the work was based on baseline data from a cross-sectional study, and it is not possible to infer causality. Second, there were no objective body composition measures to compare the group with probable sarcopenia to the group with confirmed sarcopenia. Third, the associated factors were self-reported by participants, so different types of response biases may have been introduced.

Conclusions

There is a high prevalence of probable sarcopenia in older Latin American individuals that might be influenced by several factors. Older adults with diabetes, osteoporosis, arthrosis, and sensory disorders and those who do not accomplish the minimum of physical activity recommended have a higher prevalence of probable sarcopenia. Therefore, older adults with these characteristics should be the target of prevention strategies.

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Artículo 2

Gait speed moderates the adverse effect of obesity on dependency in older Colombian adult

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Abstract

Introduction: Gait speed worsens with the presence of obesity, and is a powerful marker of functional dependence. Accordingly, gait speed could be a factor that improves or worsens the relationship between obesity and dependence in activities of daily living (ADL). However, to date this potential role has not been examined and the minimum gait speed threshold in the relationship between obesity and ADL is not known. The aim of this study was to determine whether speed moderates the association between obesity and dependence in ADL, and also define the gait speed threshold of this relationship.

Methods: A total of 20,507 community-dwelling older adults from a cross-sectional analysis of national survey data – the Colombian Health, Well-being and Aging study (SABE, 2015) – were surveyed. The research data were collected using structured questionnaires, including basic information, ADL measured using the Barthel Index, body mass index, and gait speed (3 m). The Johnson-Neyman technique was applied to determine the gait speed threshold adjusted for age, sex and comorbidities.

Results: Regression analysis showed a significant detrimental effect of obesity on dependence in ADL, which was moderated by gait speed (β=0.081; 95%CI: 0.045 to 0.117; $p < 0.001$). Adjusted for major covariates, the Johnson-Neyman technique defined two gait speed thresholds:<0.77 m/s, indicating an aggravated adverse effect; and>1.06 m/s, indicating a positive effect.

Conclusions: The adverse effect of obesity on dependence in ADL is moderated by gait speed. Considering these thresholds, the distribution of older adults in each of the proposed areas of significance were: below 0.77 (m/s) =14,324 (70.0%), above 1.06 (m/s)=1553 older adults (7.5%) and between areas=4630 older adults (22.5%).

Introduction

Obesity is the result of complex genetic and environmental interactions that lead to an excess of body fat, which has an unfavourable effect on health (1) and increases the risk of several dis- eases including hyperlipidaemia and type 2 diabetes mellitus (2) as well as morbidity and mortality (3) among the elderly. Obesity in the elderly may also accelerate the decline of functional performance (4) and can adversely affect activities of daily living (ADL) (5), which is also related to high body mass index (BMI). In this context, gait speed, balance and muscle strength are central components of an individual's functional ability to perform basic ADL (6) and the assessment of gait speed is a valid and reliable method to detect cognitive impairment, functional independence, and health state (7).

In recent years, there has been an increasing interest in gait speed as a measure of functional status in the elderly, as highlighted by some key findings. First, there is a strong association between obesity and decline in gait speed in older adults (8,9); second, gait speed predicts the reduction in dependency in ADL (10–12)). Finally, gait speed is a predictor of mortality, cardiovascular disease and cancer (13). In this line, a gait speed of 0.80 m/s is considered as the threshold to predict adverse health outcomes in older people (14,15). Furthermore, the assessment of gait speed is a valid and reliable method to detect cognitive impairment, functional independence, and health state (7). Disability in ADL is considered the most serious form of disability measure, and is defined as difficulty in undertaking activities in any areas of daily life because of a health or a physical condition (16). Evidence suggests that obese older adults typically have a reduced physical performance to body mass ratio compared with non- obese peers, particularly for tasks that require lower extremity strength, such as walking and rising from a chair (6). The interaction between obesity and physical disability has been the focus of investigation in both epidemiological and clinical contexts (17). In this sense, the subset of older adults with excess body fat appears to be at the greatest risk for physical disability, and data show that high body weight and BMI are associated with increased risk for functional impairment and disability (18,19). Therefore, both obesity and functional impairment in ADL places older adults at high risk for adverse clinical out- comes including disability, hospitalization, and ultimately mortality(20–22). Irrespective of how disability in ADL is measured (17), many studies have addressed the association between BMI and disability in ADL at older ages, and both cross-sectional (18,19,23) and longitudinal studies (20–22) have consistently found that excess body fat is an independent risk factor for disability in ADL in

older adults. Gait abnormalities due to excess body fat result in reduced gait speed, distance, and efficiency, leading to significantly limited functional performance and increase the energy cost (in over 30%) (24–27). Also, the stability during the walk is weakens affecting to spatiotemporal adaptations, which can lead to falls and injuries (28). When obesity is combined with increased disability or musculoskeletal disorders, the obesity cycle is perpetuated by encouraging sedentary behaviour for prolonged periods. Therefore, excess body fat can affect to disability in the ADL being the gait performance the modulator of these effect. Nonetheless, in these contexts, it is necessary to know under what circumstances a certain effect is produced or not. Against this back- ground, moderation analysis can be used to test the relationship between two variables as a function of a third, moderator variable (29). Similarly, advanced statistical methods for example Johnson-Neyman procedures (29), can provide a region of significance or threshold of moderator values between a relationship. Little is known regarding the relationship between BMI and disability among the elderly and a “plausible” determinant of physical performance (gait speed). Based on prior research, we tested the moderation effect of gait speed between the adverse effect of BMI on functional dependence in ADL, and evaluated the gait speed thresholds that moderated negatively or positively that effect. This is particularly re- levant for older adults, who have lower physical performance, greater adiposity and lower ADL functioning relative to their healthy counterparts.

Accordingly, the aim of this study was twofold: to first examine whether gait speed moderates the association between weight status and dependency in ADL; and secondly, to determine the gait speed threshold regarding this relationship.

Materials and Methods

Study design, setting, and participants

This study is part of the 2015 SABE study Survey on Health, Well-Being, and Aging in Latin America and the Caribbean, which is a multicenter project conducted by the Pan-American Health Organization and supported by the Epidemiological Office of the National Health Ministry in Bogotá, Colombia (https://www.minsalud. gov.co/). Details of the survey have been published elsewhere (30). Institutional review boards involved in developing the SABE Colombia study (University of Caldas, ID protocol CBCS-021-14, and University of

Valle, ID protocol 09–014 and O11–015) reviewed and approved the study protocol. Written informed consent was obtained from each individual before inclusion and completion of the first ex- amination. Permissions and details are available at https://www. minsalud.gov.co/. The study protocol of the secondary analysis was approved by the Human Subjects Committee at the Pontificia Universidad Javeriana (ACTA ID 20/2017–2017/180, FM-CIE-0459- 17).

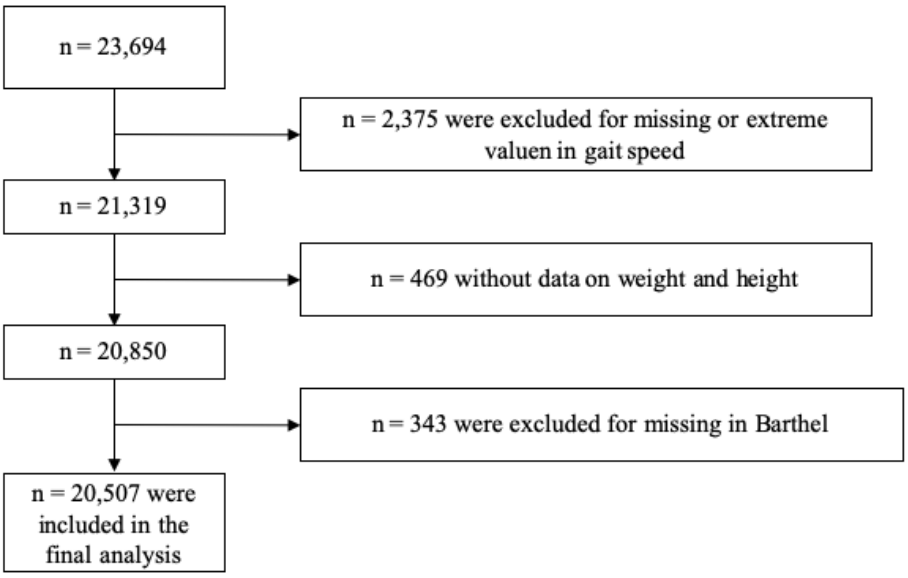

Figure 1. Flow chart showing the selection of the study sample from the SABE 2015 Survey. All analyses presented in this paper are based on 20,507 participants with complete data on anthropometric, gait speed, Barthel index and covariables.

This was a secondary analysis the SABE observational study. The estimated sample size was 24,553 individuals, assuming an 80% response of the target sample of 30,691 individuals (30). The original sample size achieved (including 244 municipalities) was 23,694 elderly Colombians. A total of 20,507 remained in the present analysis after excluding participants with extreme values and outliers for gait speed (n=2375), body mass index (n=469), and Barthel index (n=343) (see Fig. 1). Data collection staff were trained by the research teams of the coordinating centers (Universities of Caldas and Valle) for face-to-face interviews and physical measurements. The target population for SABE-Colombia included all adults aged 60 years and above residing in households. Following conventional practice for population surveys,

institutionalized persons (of prisons, jails, nursing homes, and long- term or dependent care facilities) were excluded.

Measures

Anthropometry measurements included height and body weight, which were measured with a portable stadiometer (SECA 213®, Hamburg, Germany) and an electronic scale (Kendall graduated plat- form scale), respectively. BMI (31) was estimated in kg/m2 from the measured weight and height. Underweight (BMI<18.5 kg/m2), healthy weight (18.5–24.9 kg/m2), overweight (BMI ≥25 kg/m2) and obese (BMI ≥30 kg/m2) were defined according to the World Health Organization (WHO) recommendations for Latin- American populations (National Clinical Guideline Centre. Obesity Identification, assessment and management of overweight and obesity in children, young people and adults Partial update of CG43 Methods, evidence and recommendations Obesity (update) Contents, 2014). The self-reported comorbidities or medical conditions category was assessed by asking the participants if they had been diagnosed by a physician with hypertension, diabetes, respiratory diseases, cardiovascular dis- eases, cancer, osteoporosis, arthritis, auditive and vision problems. Drug use (intake>3 medications) was evaluated with the following question: “Do you currently take or use any prescription medication”?. Gait speed was measured as the time taken to complete a 3m distance. Participants were instructed to walk from a standing start at a pace that was normal and comfortable until they reached the end of the marked path, using an assistive device if needed. Speed of walking (m/s) was computed as distance (m) divided by time taken to cover the distance (seconds) (32). The mean of the three measurements was used for analyses by a trained researcher. Functional impairment was assessed with an ADL evaluation using a Spanish-adapted version of the physical level ADL (Barthel Index). The scale is composed of 10 items and its total score ranges from 0 to 100 points. This index provides quantitative information about the level of de- pendency, measuring the execution of ten daily life activities. The items are weighted: a maximum score of 100 indicates independence, 91–99 minimal dependence, 75–90 mild dependence, 50–74 moderate dependence, 25–49 severe dependence, and 0–24 total dependence (33). The ADL showed an acceptable reliability (0.86–0.92). Socioeconomic status was determined based on the housing stratum (1 to 6), with level 1 being the highest poverty and level 6 the highest wealth. This classification is a measure developed by the National Government of Colombia that considers physical characteristics of the dwellings and their surroundings.

Statistical analysis

Descriptive statistics were calculated for the total sample on all variables through mean and standard deviation (SD) for continuous variables and frequencies and percentage for categorical variables. The Shapiro-Wilk test was used to assess conformity with a normal distribution. To test the distribution differences of main variables and covariables for participants by weight status Chi-squared and analysis of variance tests were applied. To explore the associations between predictor variable (BMI categories), gait speed as moderator variable (linear variable "W") and dependency (treated as categorical variable "Y", being "0" total dependency, "1" severe dependency, "2" moderate dependency, "3" mild dependency and "4" independency), moderation analysis was conducted. To explore whether gait speed moderated the adverse effect of high bodyweight status on dependency, interaction analysis was conducted. Additionally, the Johnson-Neyman technique was used to identify the point(s) at which the gait speed value (m/s) moderated the relationship between bodyweight status and Barthel categories. The Johnson-Neyman technique determines along the continuum of moderator values the region of significance for the relationship between independent and dependent variables (34). All analysis was performed using the PROCESS macro for SPSS (IBM, version 24) with a bootstrap threshold of 5000 and 95% confidence intervals (CI) (35).

Results

An overview of the sample characteristics is shown in Table 1. From a total of 20,507 participants, 55.9% were women. The mean age (SD) of the participants was 70 (7.6) years. In total, 97.0% of the participants were of a low-medium socioeconomic status. More than 50% presented high blood pressure and vision problems. The mean (SD) BMI of the participants was 27.0 (5.0).

Table 1. Study population (N = 20,507)

Sample characteristics	
Age	70 (7.6)
Sex*	
Women	11,466 (55.9)

Men	9,041 (44.1)
Socio-economic status*	
Low to medium (1-3)	19,899 (97.0)
High (4-6)	608 (3.0)
Self -reported comorbidities*	
High blood pressure	10,769 (52.5)
Diabetes mellitus	3,324 (16.2)
COPD	1,976 (9.6)
Coronary heart disease	2,688 (13.1)
Stroke	789 (3.8)
Cancer	861 (4.2)
Auditive problems	4,614 (22.5)
Vision problems	11,240 (54.8)
Intake > 3 medications	3,176 (15.5)
Anthropometry	
Weight (kg)	64.8 (13.1)
Height (cm)	156.5 (8.8)
BMI (kg/m^2)	27.0 (5.0)

Data are reported as mean values (standard deviation, SD) or number (percentages)*. COPD: chronic obstructive pulmonary disease; BMI: body mass index

Participant characteristics stratified by bodyweight status are shown in Table 2. The distribution of samples between weight status groups was widely in favor of the overweight group. The prevalence of obesity was 25.1%, and the prevalence of overweight was 39.0%. Moreover, significant differences ($p < 0.05$) were found in all health status categories, except for stroke and vision problems, with a higher pre- valence of participants with clinical conditions in the overweight group. As shown in Table 2, the participants with higher BMI (overweight and obese) had high blood pressure (54.1% and 64.9%); vision problems (65.5% and 65.7%); and intake more than 3 medication (69.5% and 78.2%, respectively), as well as more prevalence of moderate and severe dependency in ADL. Also, gait speed was significantly different between groups. After posthoc analysis, we found that healthy weight older adults and

overweighted have the same gait speed p=0.38 (0.77 m/s). However, there are significant differences between obese and the rest of the groups.

Table 2. Sample characteristics stratified by nutritional status

Sample characteristics (n / %)	Underweight (546 / 2.7)	Healthy Weight (6,812 / 33.2)	Overweight (7,998 / 39.0)	Obese (5,151 / 25.1)	P-value
Sex, n (%)					
Female	285 (52.2)	3,111 (45.7)	4,377 (54.7)	3,693 (71.7)	<0.001
Male	261 (47.8)	3,701 (54.3)	3,621 (45.3)	1,458 (28.3)	<0.001
Age group, n (%)					
60 - 64	106 (19.4)	1,709 (25.1)	2,439 (30.5)	1,817 (35.3)	<0.001
65 - 69	112 (20.6)	1,579 (23.2)	1,970 (24.6)	1,385 (26.9)	<0.001
70 - 74	90 (16.5)	1,265 (18.6)	1,533 (19.2)	946 (18.4)	<0.001
75 - 79	86 (15.8)	1,037 (15.2)	1,133 (14.2)	588 (11.4)	<0.001
80 - 84	89 (16.3)	714 (10.5)	590 (7.4)	275 (5.3)	<0.001
85 +	63 (11.5)	508 (7.5)	333 (4.2)	140 (2.7)	<0.001
Comorbidities, n (%)					
High blood pressure	194 (35.6)	2,918 (42.9)	4,316 (54.1)	3,341 (64.9)	<0.001
Diabetes mellitus	44 (8.1)	773 (11.4)	1,400 (17.6)	1,107 (21.6)	<0.001
COPD	84 (15.4)	621 (9.1)	739 (9.3)	532 (10.4)	<0.001
Coronary heart disease	59 (10.8)	767 (11.3)	1069 (13.4)	793 (15.4)	<0.001
Stroke	21 (3.8)	257 (3.8)	322 (4.0)	189 (3.7)	0.749
Cancer	24 (4.4)	249 (3.7)	340 (4.3)	248 (4.8)	0.019
Auditive problems	129 (23.8)	1,617 (23.8)	1784 (22.4)	1084 (21.1)	0.006
Vision problems	236 (65.4)	3,523 (65.7)	4,507 (65.5)	2,974 (65.7)	0.994
Intake > 3 medications	330 (60.4)	4,063 (59.6)	5,555 (69.5)	4,029 (78.2)	<0.001
Dependency, n (%)					
Non-dependency	395 (72.3)	5,648 (82.9)	6,722 (84.0)	4,140 (80.4)	<0.001
Mild	70 (12.8)	600 (8.8)	716 (9.0)	554 (10.8)	<0.001

Moderate	69 (12.6)	527 (7.7)	534 (6.7)	441 (8.6)	<0.001
Severe	11 (2.0)	37 (0.5)	26 (0.3)	15 (0.3)	<0.001
Total dependence	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)	–
Gait speed (m/s)**	0.75 (0.28)	0.77 (0.25)	0.77 (0.25)	0.73 (0.23)	<0.001

Table 3 shows the results from the moderation analysis executed through the PROCESS macro. Higher bodyweight status was found to have a significant adverse effect on dependency (β=−0.070; 95% confidence interval [CI]: −0.101 to −0.043; p < 0.001). The association between gait speed and dependency was positive since a higher gait speed was related to more independency (β=0.101; 95% CI: 0.033 to 0.170; p=0.015). Also, the covariables included in the model were significantly associated with dependence, that is, the presence of co- morbidities worsened the dependency. Finally, to test the main hypothesis of our study, the interaction term, which establishes the possible indirect effect of the moderator variable in the relationship between bodyweight status and dependency, was statistically significant (β=0.081; 95%CI: 0.045 to 0.117; p < 0.001). Moreover, the lower values in SE showed that the regression model is extremely precise and indicate that the observed values fit to the regression line.

Table 3. Adjusted model of regression for moderation analysis for variable Y (dependency)

Predictor	**β**	**SE**	**P value**	**95% CIs**
Bodyweight status (variable X)	−0.070	0.014	<0.001	(−0.101 to −0.043)
Gait speed (moderator)	0.101	0.035	0.003	(0.033 to 0.170)
Interaction	0.081	0.018	<0.001	(0.045 to 0.117)
Sex (covariable)	0.029	0.008	<0.001	(0.013 to 0.044)
Age (covariable)	−0.011	0.000	<0.001	(−0.012 to −0.010)
High blood pressure (covariable)	−0.031	0.007	<0.001	(−0.046 to −0.015)
Diabetes mellitus (covariable)	−0.043	0.010	<0.001	(−0.064 to −0.023)
Cancer (covariable)	−0.069	0.019	<0.001	(−0.106 to −0.032)
COPD (covariable)	−0.117	0.013	<0.001	(−0.143 to −0.092)
Coronary heart disease (covariable)	−0.033	0.011	0.003	(−0.056 to −0.011)
Stroke (covariable)	−0.054	0.015	<0.001	(−0.025 to −0.084)
Artritis (covariable)	−0.100	0.009	<0.001	(−0.118 to −0.082)

Osteoporosis (covariable)	−0.069	0.012	<0.001	(−0.094 to −0.044)

SE: standard error; CI: confidence interval; COPD: chronic obstructive pulmonary disease.

These results are illustrated in Fig. 2, where the continuum values of moderator variable (gait speed) with 95% CI and the significant regions for the adverse effect of high bodyweight status on dependency level in ADL can be seen. In this regard, the Johnson-Neyman procedure revealed two-point estimates or thresholds. The first was at<0.77 m/s. which indicates that in those subjects whose gait speed was lower than this threshold, the adverse effect of high bodyweight status (overweight or obesity) on dependency level is negatively moderated; that is, this relationship is aggravated with poor gait speed. The second threshold was established at 1.06 m/s, representing a beneficial effect of gait speed on the negative effect of high bodyweight status on dependency. Considering these thresholds, the distribution of older adults in each of the proposed areas of significance were: below 0.77 (m/s)=14,324 (70.0%), above 1.06 (m/s)=1553 older adults (7.5%) and between areas=4630 older adults (22.5%).

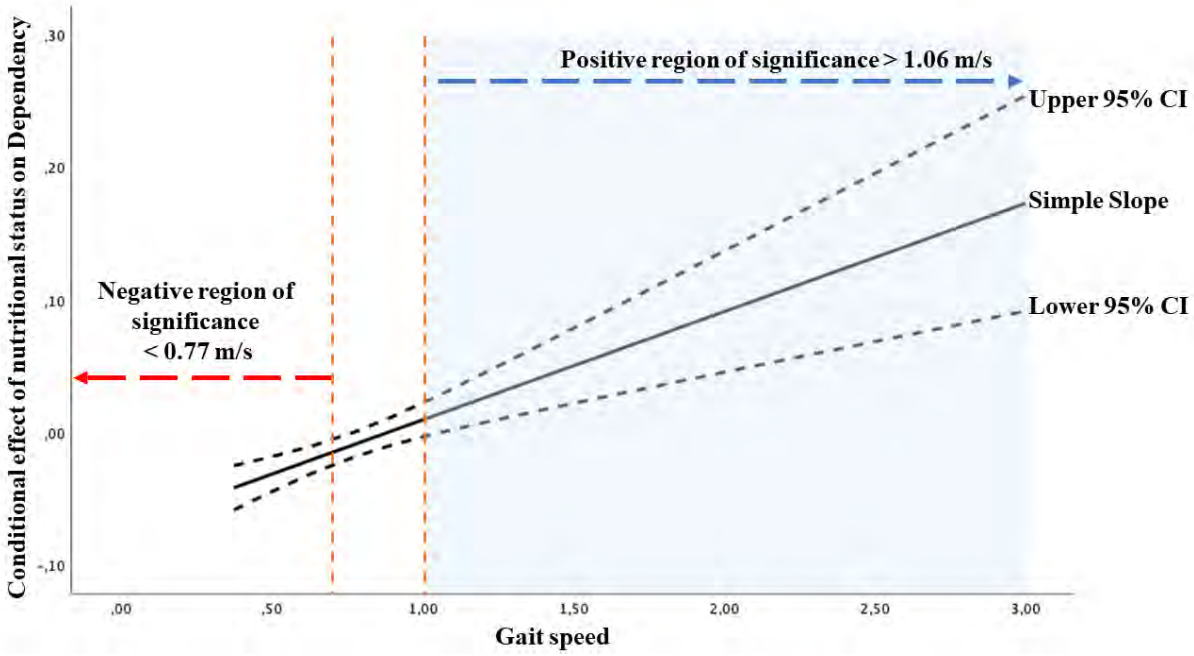

Figure 2. Regression slope estimate and 95% confidence intervals for the relationship between moderator variable (gait speed) and adverse effect of bodyweight status and dependency level in ADL, based on the Johnson-Neyman procedure.

Discussion

In the present study of 20,507 community-dwelling older-adults, we found a moderating effect of gait speed on the relationship between the detrimental effect of overweight or obesity and dependence in ADL, independently of age, sex and comorbidities. Our results show a significant link between higher bodyweight status and dependence, such that overweight or obese older adults present more dependence in ADL than older healthy weight adults. These findings are in line with a previous study performed in a similar population in which a relationship was found between high BMI and more prevalence in dependency in ADL (5). A uniqueness of the present study was the significant association between gait speed, obesity and dependence in the elderly. Similar to what has been reported in other studies (10,12), we found that a low gait speed has a negative impact on independence. Likewise, we found that overweight or obese older adults had a lower gait speed than healthy weight older adults, which is also similar to the results of previous studies (4,8,9). Accordingly, our hypothesis on the regression model to test moderation – in which gait speed can be a moderator – was supported. Thus, our main finding was that gait speed could act as moderator of the relationship between obesity and dependence; namely, the negative effect of overweight or obese on dependency level in older adults was moderated positively or negatively by gait speed. According to the literature, mobility impairment is defined as a gait speed ≤0.8 m/s, as this cut-off value can predict disability and reduced overall survival (14,15). This threshold is similar to our results, since we found that overweight or obese older adults with a gait speed below 0.77 m/s could have more dependence, whereas those with a gait speed above 1.06 m/s are likely to show lower dependence. This result has not previously been de- scribed, since the literature reports>0.8 m/s as the recommended minimum gate speed to prevent disability. We also show that<0.77 m/s would indicate that the negative effect of a high bodyweight status on dependence could increase, and a value>1.06 m/s would indicate that the negative effect of a high bodyweight status on dependence could be reduced. Also, there is a non-significant region between ≥0.77 and ≤1.06 m/s in which the gait speed has no effect for the association studied. To the best of our knowledge, this is the first time that the moderating effect of gait speed on the relationship between bodyweight status and dependency has been studied. However, there are related studies that support our findings. For example, a high BMI is associated with lower muscle quality (36–38) due to changes in contractile function (39), which impairs isometric, concentric and eccentric muscle force production (38,40) and leads to alterations of kinematics and gait

posture. Also, aging is related to a substantial decline in muscle strength, known as dynapenia (41), which is linked to a series of mechanisms such as a reduction in central activation, a decrease in motor unit number and size, as well as an alteration in the excitation- contraction cycle (42). Thus, neuromuscular deterioration could negatively influence gait speed (43). A third factor is a concurrence of fat accumulation and dynapenia during aging (44). Finally, pro-inflammatory adipokines, which are related to fat accumulation and aging (45), seem also to be responsible for declines in gait speed (46). Therefore, these four factors feed a vicious cycle where the essential physical function affected is the gait speed. Accordingly, physical exercise focused to maintain an optimal gait speed (~1.06 m/s) could play a protector role against these factors to avoid a decline in ADL.

The strengths of the present research include the large population-based study with>20,000 older adults. Also, the statistical procedures based on moderation analysis with the Johnson-Neyman procedure provide a better knowledge of thresholds, in our case of gait speed, in the relationship between obesity and dependence. As far as we know, this is the first study to explore the moderating effect of gait speed between overweight or obesity and dependence and also the first establishing a new threshold for this relationship based on the Johnson-Neyman procedure. Our study has several limitations. Firstly, the cross-sectional design limits our ability to draw causal inferences. Secondly, BMI is not a perfect measure of actual adiposity and fat mass. Thirdly, the classification between independence-dependence categories was established through a self-reported index. Fourthly, we cannot entirely rule out the possibility of unmeasured or unknown confounding factors including behavioural habits, especially those related to nutrition, objective physical activity, and sleep in elders, which were not considered. However, the homogeneity of the study population and comprehensive data on the risk factors minimized potential confounding factors. Thus, we believe that our main findings will be broadly applicable.

Conclusions

The present results reveal that gait speed moderates the harmful effect of high bodyweight status on dependence in a large population- based study. Our results allow us to establish two thresholds: <0.77 m/ s, below which the detrimental effect of overweight or

obesity on dependence could be aggravated; and > 1.06, above which the effect could be alleviated.

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Artículo 3

Relative Handgrip Strength Diminishes the Negative Effects of Excess Adiposity on Dependence in Older Adults: A Moderation Analysis

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Abstract

Introduction: The adverse effects of fat mass on functional dependence might be attenuated or worsened, depending on the level of muscular strength. The aim of this study was to determine (i) the detrimental effect of excess adiposity on dependence in activities of daily living (ADL), and (ii) whether relative handgrip strength (HGS) moderates the adverse effect of excess adiposity on dependence, and to provide the threshold of relative HGS from which the adverse effect could be improved or worsened.

Methods: A total of 4169 participants (69.3 ± 7.0 years old) from 244 municipalities were selected following a multistage area probability sampling design. Measurements included anthropometric/adiposity markers (weight, height, body mass index, waist circumference, and waist-to-height ratio (WHtR)), HGS, sarcopenia "proxy" (calf circumference), and ADL (Barthel Index scale). Moderation analyses were performed to identify associations between the independent variable (WHtR) and outcomes (dependence), as well as to determine whether relative HGS moderates the relationship between excess adiposity and dependence.

Results: The study demonstrated that (i) the adverse effect of having a higher WHtR level on dependence in ADL was moderated by relative HGS, and (ii) two moderation thresholds of relative HGS were estimated: 0.35, below which the adverse effect of WHtR levels on dependency is aggravated, and 0.62, above which the adverse effect of fat on dependency could be improved.

Conclusions: Because muscular strength represents a critically important and modifiable predictor of ADL, and the increase in adiposity is inherent in aging, our results underscore the importance of an optimal level of relative HGS in the older adult population.

Introduction

Muscle strength and mass decline with aging (1). The importance of preserving optimal muscle strength in middle- and older-age adults has been recently highlighted in epidemiological studies showing that muscle strength is an important predictor for all-cause (2) and cancer (3) mortality. Physical function in older adults declines with the loss of skeletal muscle (1,4), and a recent study reported that a non-weak handgrip strength (HGS) level (cut-off points ranged from 17.4 to 8.6 in men and 10.1 to 4.9 in women) is related to decreased odds of intrinsic capacity impairments (i.e., the interaction between the physical and mental capacity of an individual) among older adults (5).

Several studies have indicated that the aging process produces a series of changes in body composition, usually without affecting the body mass index or weight, but producing an accumulation of fat as individuals get older (6,7). Beyond its corresponding effect on health, excess adiposity has a harmful impact on muscle quality and quantity (8). Consequently, the convergence of aging and fat mass may create a perfect storm for skeletal muscle catabolism (9) and a decline in physical function (10).

Handgrip strength (HGS) is the most common index of muscle strength, owing to its ease of assessment, low cost, and simplicity, and it is considered a valid “proxy” of overall muscle strength for clinical and epidemiological studies (11). Lower HGS correlates strongly with cardiovascular disease (2) and mortality (12), and several studies (13,14) have highlighted its protective role against activities of daily living (ADL) dependence in older adults. Thus, maintaining an optimum HGS is an effective determinant factor for healthy aging (5,15). In this context, several studies have shown that aging is associated with a decline in handgrip strength, and several studies have highlighted the fact that an increase in fat mass contributes to a deterioration of HGS in older adults (8,16). These aforementioned processes can be viewed as a cascade of events, beginning with aging, which are associated with greater muscle fat infiltration (17,18). Aging and accumulation of infiltrating fat leads to a decline in muscle quality and quantity—therefore resulting in a poorer performance (lower muscle strength)—and, ultimately, affecting functional dependence in ADL (19,20).

This worsening of muscle strength can be explained several biological factors. First, fat infiltration induces changes in contractile function (21) in the different manifestations of strength (isometric, concentric, and eccentric) (22,23). Second, aging and fat infiltration coexist

in an environment marked by a loss of muscle strength and power, also known as dynapenia (24), which is related to a reduction in central activation, a decrease in motor unit number and size, and an alteration in the excitation–contraction cycle (25). Finally, aging and dynapenia are related to a greater presence of proinflammatory activity, which seem to be responsible for the deterioration of muscular function (fat infiltration into muscle), and visceral fat increases and subcutaneous fat decreases with aging (26). We therefore hypothesized that muscle strength could play a preventive role in this association.

The adverse effects of abdominal obesity on functional dependence, might be attenuated or worsened depending on the level of muscular strength. Additionally, relative handgrip strength is associated with functional dependence. Thus, central adiposity may have an effect between dependence status and relative handgrip strength after potential confounding variables such as age, gender, and/or lifestyle. Accordingly, describing the magnitude of these risk factors in older adults could be important for prioritizing prevention and public health efforts. Nevertheless, to our knowledge, no studies have examined the moderator role of muscle strength based on HGS between excess of central adiposity and functional dependence.

The aim of the present study was two-fold: (i) to examine the detrimental effect of abdominal obesity on functional dependence in ADL, and (ii) to discern whether relative HGS moderates the adverse effect of abdominal obesity on dependence, as well as to provide the threshold of relative HGS from which the adverse effect could be improved or worsened.

Materials and Methods

Study Design and Sample Population

The data for this secondary cross-sectional study were obtained from the Health and Well-being and Aging Survey in Colombia 2015 (SABE, from initials in Spanish: Salud, Bienestar y Envejecimiento, 2015), a multicenter project conducted from 2014 to 2015 by (in Spanish: Ministerio de Salud y la Protección Social de Colombia) (27). The study included the Colombian population aged ≥60 years, and the indicators were disaggregated by age ranges, sex, ethnicity, and socioeconomic level.

A total of 23,694 surveys were conducted at the national level. A total of 6530 segments were planned to obtain the surveys (4928 urban and 1602 rural), with an expected average of 4.7 adults per segment. The standardized process for each home visit involved the identification

of the participants, the registration of the demographic data, the signing of the informed consent, the application of the established filters and the selection criteria, the signing of assent when necessary, and the completion of the questionnaire by the interviewer. For this subsample, the calculation of the sample size was carried out, taking into account national representation. A total of 86 municipalities were selected, including the four large cities. For this analysis, we used data from 4169 participants included as a subsample with HGS measures. The rationale and detailed methodology of the SABE Colombia has been described in another document (28).

Institutional review boards involved in developing the SABE 2015 study (University of Caldas, ID protocol CBCS-021-14, and University of Valle, ID protocol 09-014 and O11-015) reviewed and approved the study protocol. The study protocol for the secondary analysis was approved by the Human Subjects Committee at the Pontificia Universidad Javeriana (ID protocol 20/2017-2017/180, FM-CIE-0459-17) in accordance with the Declaration of Helsinki of the World Medical Association and Resolution 8430 of 1993 of the then Ministry of Health of Colombia on technical, scientific, and administrative standards for conducting research with humans. All participants provided written informed consent.

Measurements

Data collection staff were trained by the research teams of the coordinating centers (University of Caldas, and University of Valle, from Colombia) for face-to-face interviews and physical measurements. Anthropometry measurements included height and body weight, which were measured with a portable stadiometer (SECA 213, Hamburg, Germany) and an electronic scale (Kendall graduated platform scale), respectively. Body mass index (BMI) was calculated in kilograms per square meter from the measured body weight and height. Waist circumference (WC) was measured over the midpoint between the lower border of the ribs and iliac crest in the midaxillary plane, at the end of normal expiration. The waist-to-height ratio (WHtR) was measured as the ratio of the waist circumference (in cm) to the height (in cm). We used WHtR as a measure for abdominal obesity because is a useful tool in clinical practice and has been shown to be a reliable parameter for predicting whole-body fat percentage and visceral adipose tissue (28). The calf circumference was used for screening sarcopenia because it is a reliable, easy, and low-cost tool in clinical practice (4). Following the recommendation of the WHO Expert Committee (29) and Rolland et al. (4), a cut-off of calf circumference $\leq$31 cm was considered as sarcopenia. HGS, including absolute and relative—HGS (kg)/body mass (kg)—were assessed with a Takei dynamometer (T.K.K., Takei Scientific Instruments Co., Ltd.,

Niigata, Japan), including the highest value (kg) from two attempts (both hands). This allowed us to be more accurate when comparing older adults with different body sizes and to focus on muscle quality rather than muscle quantity. The coefficients of variation for body weight, height, waist circumference, calf circumference, and HGS were 23.2%, 6.5%, 12.2%, 11.2%, and 42.2%, respectively.

Nutritional status was evaluated through Mini-Nutritional Assessment extended version (30). Functional impairment was assessed with an ADL evaluation using a Spanish-adapted version of the physical level ADL (Barthel Index), recommended for epidemiological studies in older adults (31). The Barthel Index scores are in multiples of five, ranging from 0 (completely dependent) to 100 (independent in basic). The Barthel index scores are classified as follows: 100 means independence, 91–99 low-level dependency, 75–90 mild dependency, 50–74 moderate dependency, 25–49 severe dependency, and 0–24 total dependency (32).

For lifestyle characteristics, personal habits regarding alcohol intake (participants were categorized as those who do not drink and those who drink less than 1 day per week, 2 to 6 days a week, or every day) and cigarette smoking (participants were categorized as those who do not smoke and those who have never-smoked, those who currently smoke, or those who previously smoked) were recorded. A “proxy physical activity” report was conducted by the following questions: (i) “Have you regularly exercised, such as jogging or dancing, or performed rigorous physical activity at least three times a week for the past year?”; (ii) “Walk, at least three times a week, between 9 and 20 blocks (0.6 to 1.2 km) without resting?”; (iii) “Walk, at least three times a week, eight blocks (0.5 km) without resting?”. Participants were considered physically active if they responded affirmatively to two of the three questions. Medical information including multimorbidity, as well as chronic conditions adapted from the original SABE study, were assessed by asking the participants if they had been diagnosed, by a physician, with hypertension, type 2 diabetes mellitus, chronic obstructive pulmonary disease, cardiovascular diseases (heart attack, angina), stroke, cancer, arthritis, osteoporosis, or sensory impairments (vision and hearing loss). Medication use was evaluated with the question “do you currently take or use any prescription medication?”.

Race/ethnicity grouped as indigenous (people belonging to various indigenous groups, such as Ika, Kankuamo, Emberá, Misak, Nasa, Wayuu, Awuá, Mokane), black “mulato” or Afro-Colombian, white, and others (mestizo, gypsy, etc.) was assessed by self-reporting.

Socioeconomic status (SES) was determined on the basis of the housing stratum (1 to 6), with level 1 being the highest poverty and level 6 the highest wealth. This classification is a measure developed by the National Government of Colombia that considers physical characteristics of the dwellings and their surroundings. The classification in any of the six strata approximated the hierarchical socioeconomic difference from poverty to wealth and vice versa.

Statistical Analysis

Descriptive analyses using mean ± standard deviation (SD) for the continuous variables and frequency distribution for categorical variables were used to obtain the characteristics of the sample. The normality of the data was examined by the Kolmogorov–Smirnoff test. Significant differences between men and women were analyzed using Student's *t*-test or the chi-square (χ^2) post-hoc test.

The PROCESS macro in the SPSS statistical software package, version 24.0 (IBM, Chicago, IL, USA) for Windows, was used to conduct a moderation analysis. Preliminary analysis showed no significant interactions between gender and abdominal obesity in relation to functional dependence ($p = 0.814$); therefore, all analyses were performed with men and women together. Moderation analysis was conducted to examine whether WHtR levels were related to increased dependence and to determine whether this negative effect was moderated by relative HGS. This relationship used ordinary least squares regression analysis when predicting continuous variables (WHtR and relative HGS in the study). A simple slope plot was used to visualize the effect of the moderator. The Johnson–Neyman approach was used to test the point in which the relative HGS value moderated the relationship between WHtR levels and dependence. The Johnson–Neyman technique determined, along a continuum of moderator values (relative HGS), the region of significance on the relationship between the independent and dependent variables (33). All tests were adjusted for sex, age, alcohol, smoking status, and physical activity habits.

Table 1. Characteristics of the study participants

Characteristics	**Men (*n* = 1825, 43.8%)**	**Women (*n* = 2344, 56.2%)**	**Overall (*n* = 4169)**	***P* for Gender**
Anthropometric, mean ± SD				

Age (years)	69.9 ± 7.2	68.9 ± 6.9	69.3 ± 7.0	<0.0001
Height (cm)	163.1 ± 6.7	151.1 ± 6.2	156.4 ± 8.7	<0.0001
Body weight (kg)	68.1 ± 11.8	63.3 ± 11.9	65.4 ± 12.1	<0.0001
BMI (kg/m2)	26.1 ± 3.9	28.3 ± 4.9	27.3 ± 4.6	<0.0001
Waist circumference (cm)	93.2 ± 10.7	91.6 ± 10.9	92.3 ± 10.8	<0.0001
Waist-to-height ratio	0.57 ± 0.1	0.60 ± 0.1	0.59 ± 0.1	<0.0001
Calf circumference (cm)	34.7 ± 3.3	34.7 ± 3.8	34.7 ± 3.6	0.807
Functional performance, mean ± SD				
Absolute HGS (kg)	27.5 ± 8.0	17.3 ± 5.3	21.8 ± 8.3	<0.0001
Relative HGS/body weight (kg/kg)	0.41 ± 0.1	0.27 ± 0.1	0.33 ± 0.1	<0.0001
Race/ethnic group, *n* (%)				
Indigenous	149 (9.1)	103 (5.0)	252 (6.8)	0.004
Black “mulato” or Afro-Colombian	173 (10.6)	181 (8.7)	354 (9.6)	0.671
White	478 (29.3)	696 (33.6)	1174 (31.7)	<0.0001
Others *	831 (51.0)	1092 (52.7)	1923 (51.9)	<0.0001
Missing	194	272	466	-
Socioeconomic status, *n* (%)				
Level I	689 (37.8)	752 (32.1)	1441 (34.6)	0.097
Level II	755 (41.4)	987 (42.1)	1742 (41.8)	<0.0001
Level III	345 (18.9)	511 (21.8)	856 (20.5)	<0.0001
Level IV	27 (1.5)	67 (2.9)	94 (2.3)	<0.0001
Level V–VI	9 (0.5)	27 (1.2)	36 (0.9)	0.003
Lifestyle outcomes, *n* (%)				
Alcohol intake	451 (24.7)	122 (5.2)	573 (13.7)	<0.0001
Smoking	287 (15.7)	171 (7.3)	458 (11.0)	<0.0001
Physical activity “proxy”	1375 (75.3)	1965 (83.8)	3340 (80.1)	<0.0001
Multimorbidity/chronic conditions, *n* (%)				
Hearing loss	492 (26.9)	463 (19.7)	955 (22.9)	<0.0001
Visual loss	1029 (56.3)	1378 (58.7)	2407 (57.7)	0.029
High blood pressure	844 (46.2)	1395 (59.5)	2239 (53.7)	<0.0001
Diabetes mellitus 2	258 (14.1)	410 (17.5)	668 (16.0)	0.004
Chronic pulmonary disease	168 (9.2)	244 (10.4)	412 (9.9)	0.195
Coronary heart disease	235 (12.8)	326 (13.9)	561 (13.4)	0.340

Stroke	73 (4.0)	78 (3.3)	151 (3.6)	0.267
Cancer	74 (4.1)	124 (5.3)	198 (4.7)	0.062
Arthritis	285 (15.6)	822 (35.1)	1107 (26.5)	<0.0001
Osteoporosis	82 (4.5)	378 (16.1)	460 (11.0)	<0.0001
Medication use, *n* (%)	451 (24.7)	122 (5.2)	573 (13.7)	<0.0001
Nutritional status				
Malnutrition	31 (1.9)	66 (3.2)	97 (2.7)	<0.0001
Risk of malnutrition	502 (31.3)	718 (35.0)	1220 (33.4)	<0.0001
Normal nutritional status	1073 (66.8)	1267 (61.8)	2340 (64.0)	<0.0001
Missing	219	293	512	-
Functional dependence, *n* (%)				
Severe dependency	0 (0.0)	3 (0.1)	3 (0.1)	-
Moderate dependency	68 (3.7)	113 (4.8)	181 (4.3)	<0.0001
Mild dependency	101 (5.5)	237 (10.1)	338 (8.1)	<0.0001
Non-dependency	1656 (90.7)	1991 (84.9)	3647 (87.5)	<0.0001

Data are presented as mean ± SD or number (percentage) of participants. Significant differences between the men and women groups were analyzed by Student's *t*-test or χ^2 test. BMI: body mass index. * Others (mestizo, gypsy, etc

Results

Of the 4169 study participants, 56.2% were female and 43.8% were male (**Table 1**). Anthropometric data, including BMI, waist circumference, and WHtR, described the principal characteristics of the sample, such as overweight or obesity and an excess of fat mass. The differences between sex for these variables were significant ($p < 0.05$), with the exception of calf circumference. Regarding performance outcomes—computed from absolute HGS and relative HGS—men showed a significantly higher performance than women. Additionally, the ethnic distribution was dissimilar between sexes, except for the Afro-Colombian ethnic group. We observed a major proportion of white and other ethnic groups (mestizo, gypsy, etc.). A major proportion of participants were found to be in SES level 2 and significant differences were observed between sexes in all SES levels except level 1.

Likewise, there were significant differences between sexes regarding lifestyle habits including smoking, alcohol consumption, and physical activity "proxy" recommendations.

According to self-report comorbidities presented by participants, there was a prevalence of visual problems (57.7%) and high blood pressure (53.7%) in both sexes. Regarding the distribution difference between males and females, we found significant differences in hearing problems, high blood pressure, type 2 diabetes mellitus, arthritis, and osteoporosis. In addition, there were significant differences in medication use and nutritional status. Finally, the prevalence of dependency was 8.1% and 4.3% for mild and moderate dependency, respectively. However, when we combined all three levels of dependency (mild, moderate, and severe) this rose to 12.5%, with 522 older adults dependent in ADL.

Figure 1 shows the results from the regression model, where it shows the moderation analysis based on ordinary least squares regression, in which there is an inverse relationship between the excess of adiposity, measured via WHtR, on functional dependence in older adults. This path known as direct effect (β = −0.11 (−0.23, −0.01)) was moderated by relative HGS. Therefore, the adverse effect of excess adiposity on functional dependence was moderated by relative HGS (β = 19.08 (8.49, 29.66)).

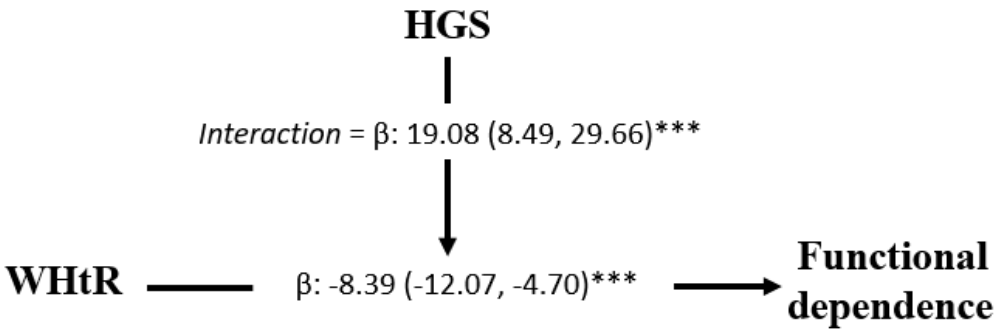

Figure 1. Moderation models. Beta expressed as unstandardized regression coefficients and 95% confidence interval. Because there was substantial covariance between strength capacity and body mass—and, moreover, the links between muscle strength and both physical function and chronic health were mediated by the proportion of strength relative to body mass—grip strength (HGS) was relative as strength per body mass (i.e., (HGS in kilograms)/(body mass in kilograms)). Moderation analysis in which relative handgrip strength moderate the relationship between waist-to-height ratio (WHtR) and functional dependence, adjusted by age, gender, and lifestyle (alcohol intake, smoking, and physical activity "proxy"); * $p < 0.01$; ** $p < 0.001$.

To elucidate a possible estimate point from which the moderator value has a moderator effect, the Johnson–Neyman statistical approach was used. The result is shown in **Figure 2**. The slope shows the continuum of the moderator (relative HGS expressed as kilogram per kilogram of body weight) and the different regions of significance. The first region was found to be less than 0.35, denoting that the adverse effect of excess adiposity, based on WHtR, on dependence could be aggravated for those in this region. Secondly, a significant positive region was found from 0.62, indicating that the adverse effect of WHtR could be ameliorated for those who were above this point. Lastly, a "black" region was observed, which indicated that the adverse effect did not improve or worsen in those with an HGS between the lower and upper thresholds.

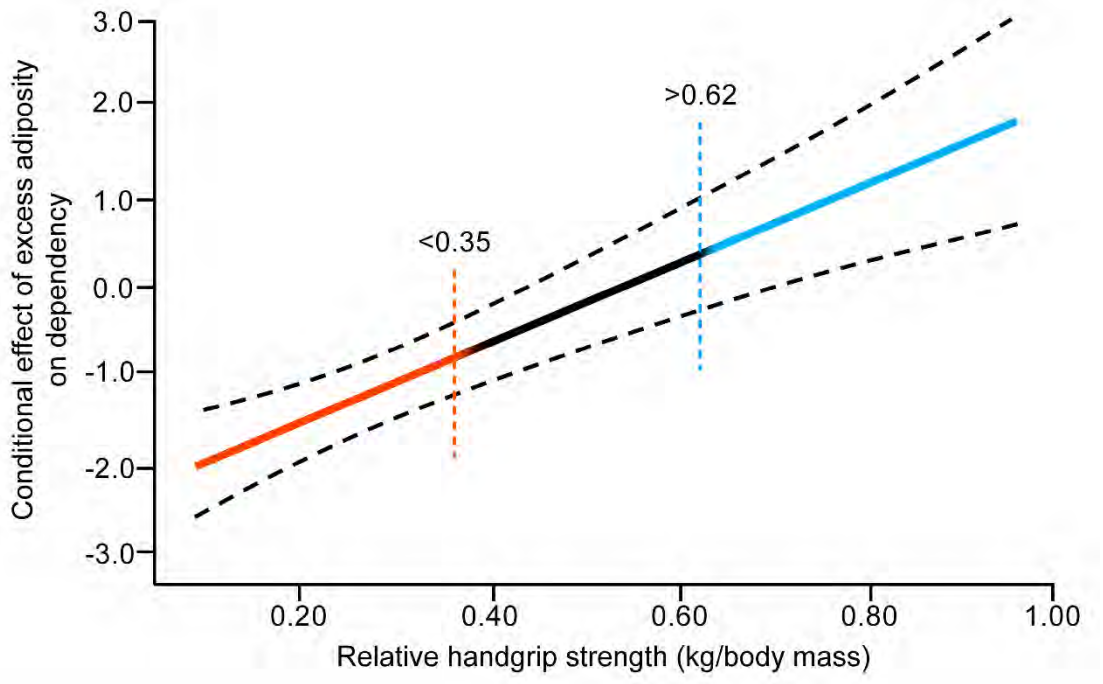

Figure 2. Regression slope estimate and 95% confidence intervals for the relationship between moderator variable (relative HGS) and adverse effect of WHtR levels on dependency level in activities of daily living (ADL), based on the Johnson–Neyman procedure. Red line indicates negative region of significance at moderator value (<0.35 of relative HGS). Blue line indicates the positive region of significance at moderator value (>0.62 of relative HGS). Black line represents neutral region of significance.

Discussion

The present study investigated the moderator role of HGS on the adverse effect of WHtR on dependency in older Colombian adults. The major finding of the study was that the adverse effects of high WHtR levels on dependency were found to be moderated by relative HGS. Two moderation thresholds of relative HGS were estimated: 0.35, below which the adverse effect of WHtR levels on dependency was aggravated, and 0.62, above which the adverse effect of fat on dependency improved. Accordingly, our results indicated that older adults with higher WHtR could experience more dependence in ADL than older adults with lower WHtR; however, this unfavourable effect was moderated by relative HGS. Consequently, older adults with high relative HGS levels could attenuate the negative effect of adiposity. Therefore, age-related declines in muscle mass and strength are often detected by reductions in HGS.

The findings of the present study are supported by several previous studies. For example, de Carvalho et al. (8) found that abdominal obesity is associated with lower HGS, accelerating the decline of muscle strength. A possible explanation for this phenomenon is that excessive adiposity can downregulate the anabolic actions of testosterone (34), growth hormones (35), and insulin (36), which may contribute to a progressive loss of muscle mass and associated function in both sexes. Additionally, excessive adipose tissue can induce a proinflammatory state by the action of several cytokines (e.g., higher plasma concentrations of tumor necrosis factor-alpha and interleukin-6), which is associated with lower muscle strength (37) and disability in older adults (38).

No previous studies have reported a moderator role of HGS on the relationships studied here. We found that higher relative HGS could attenuate the adverse effect of abdominal obesity on functional dependence in older adults. Our findings show that higher central obesity has an adverse effect on functional independence. It is therefore likely that functional independence in ADL will be reduced in those older adults with abdominal obesity. However, this negative effect could be moderated by relative HGS. Consequently, the adverse effect may worsen, improve, or even disappear, depending on the relative HGS of older adults. Our findings indicate that muscle strength relative to body weight can play a crucial role between WHtR levels and dependency. Specifically, if older adults have a high WHtR value and a relative HGS above 0.62, the adverse effect on dependency could be mitigated or even disappear. Conversely,

if older adults have a high WHtR value and a relative HGS below 0.35, it could worsen the adverse effect on dependency.

Biomechanical and neuromuscular scientific evidence could justify the moderator role of HGS between excess of central adiposity and functional dependence. For example, it is well reported that abdominal obesity is related to a greater body weight, and consequently walking more slowly might help to keep the dynamic balance between steps, as well as to maintain shorter the cadence and length of steps to optimize gait pattern (39). Another plausible reason might be neuromuscular deterioration, as there is an association between obesity/high-fat mass content and poor muscle quality (23,40,41,42), with an impairment of force production relative to body weight (22,23). Conversely, abdominal obesity may be linked to reduced HGS, as every 10 cm increase in WC has been shown to be associated with a 3.56 kg lower HGS in middle-aged and older men (24). Additionally, every 1 kg increase in HGS for older women was associated with a 0.13 s increase in the timed up-and-go test, 0.03 s decrease in 3 m walk time, and 1% decrease in chair rise time (43). With regard to ADL, McGrath et al. (44) determined that high baseline grip strength decreased the odds ratio (OR) of developing disability in ADL (OR 0.95) and instrumental ADL (OR 0.92) among older Mexican Americans. These findings suggest that a minimum level of strength is a prerequisite for physical function and that, when strength is above the minimum required level, it may serve as reserve capacity, which is beneficial in preventing functional limitation in the future (45). Accordingly, maintaining muscle strength is an important factor for maintaining function during the aging process (2,3). Future research should expand upon the longitudinal associations between HGS and clinically relevant health outcomes that are mediated (e.g., in both instrumental activities and ADL) or moderated (e.g., obesity) by other factors (45).

The strengths of the study include the large population-based study in older, Latin-American adults. Additionally, we carried out complex statistical analyses to determine the role of muscle strength to circumvent the detrimental effect of excess adiposity on dependence. As well as this, through the Johnson–Neyman statistical approach, we provided two thresholds of relative HGS, which we believe will add to the knowledge base to improve clinical practice and exercise programs in this population.

There are some limitations of the study design that need to be considered. First, the cross-sectional design limits drawing any causal inferences. Second, the assessment of excess

adiposity can result in bias because of the proxy method (i.e., WHtR levels), and therefore, standardized measures of body composition should be used. Third, the classification of dependency was based on a self-report questionnaire. Thus, we are unable to say whether low grip strength (with or without excess adiposity) leads to higher risk of neuromuscular/ADL abnormalities, or conversely, whether poor neuromuscular/dependency profiles lead to declines in grip strength (i.e., reverse causation). Future research is needed to better describe the age- and sex-specific trajectories of HGS as a predictor of comorbidities across the lifespan, and perhaps, just as importantly, to apply robust analyses that can compartmentalize risk into hierarchical categories. Finally, the thresholds for HGS are open to discussion and the values may vary depending on the comorbidities that individuals present with.

Conclusions

In summary, older adults with excess adiposity have major dependency in ADL. However, this adverse effect can be moderated by relative HGS. Our findings bring two thresholds of relative HGS as moderators of the adverse effect: <0.35, in which the adverse effect of abdominal obesity on dependence could worsen, and >0.62, in which the detrimental effect could be improved or even disappear. Because muscle strength represents a critically important and modifiable predictor of ADL (13,14,43), and an increase in body fat is inherent in aging (46), our results underscore the importance of an optimal level of relative HGS among the older adult population. Thus, this study provides support for the importance of considering both HGS and WHtR as contributors to diagnostic functional disability/dependence, and healthcare professionals should encourage participation in physical activity to improve muscular fitness in old age (47).

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Artículo 4

Glucose Levels as a Mediator of the Detrimental Effect of Abdominal Obesity on Relative Handgrip Strength in Older Adults

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Abstract

Introduction: Excess central adiposity accelerates the decline of muscle strength in older people. Additionally, hyperglycemia, independent of associated comorbidities, is related to the loss of muscle mass and strength, and contributes to functional impairment in older adults. We studied the mediation effect of glucose levels, in the relationship between abdominal obesity and relative handgrip strength (HGS).

Methods: A total of 1571 participants (60.0% women, mean age 69.1 ± 7.0 years) from 86 municipalities were selected following a multistage area probability sampling design. Measurements included demographic and anthropometric/adiposity markers (weight, height, body mass index, and waist circumference). HGS was measured using a digital dynamometer for three sets and the mean value was recorded. The values were normalized to body weight (relative HGS). Fasting glucose was analyzed by enzymatic colorimetric methods. Mediation analyses were performed to identify associations between the independent variable (abdominal obesity) and outcomes (relative HGS), as well as to determine whether fasting glucose levels mediated the relationship between excess adiposity and relative HGS.

Results: A total of 1239 (78.8%) had abdominal obesity. Abdominal obesity had a negative effect on fasting glucose (β = 9.04, 95%CI = 5.87 to 12.21); while fasting glucose to relative HGS was inversely related (β = −0.003, 95%CI = −0.005 to −0.001), $p < 0.001$. The direct effect of abdominal obesity on relative HGS was statistically significant (β = −0.069, 95%CI = −0.082 to −0.057), $p < 0.001$. Lastly, fasting glucose levels mediates the detrimental effect of abdominal obesity on relative HGS (indirect effect β = −0.002, 95%CI = −0.004 to −0.001), $p < 0.001$.

Conclusions: Our results suggest that the glucose level could worsen the association between abdominal obesity status and lower HGS. Thus, it is plausible to consider fasting glucose levels when assessing older adults with excess adiposity and/or suspected loss of muscle mass.

Introduction

Aging is related to a progressive unfavorable change in body composition, particularly abdominal fat accumulation and loss of lean mass (1,2). Abdominal obesity, measured by waist circumference (WC) (3), is associated with systemic inflammation, hyperlipidemia, cardiovascular diseases, impaired fasting glucose, prediabetes, insulin resistance, hyperinsulinemia, and type 2 diabetes (T2DM) (4,5,6,7,8,9,10,11,12,13,14). Specifically, hyperglycemia, independent of associated comorbidities, is related to the loss of muscle mass and strength, and contributes to functional impairment in older adults (9,10,11,12,13). Lower muscle mass is positively associated with central adiposity and an increased risk of developing T2DM (8). Hyperglycemia and the presence of insulin resistance may increase autophagy, muscle protein degradation, and mitochondrial dysfunction, which may negatively impact skeletal muscle function (6). Therefore, the coexistence of aging and abdominal obesity creates the harmful environment for the deterioration of muscle mass. On the other hand, it has been suggested that excessive and naturally occurring deposition of adipose tissue in the abdomen may increase the risk of hyperinsulinemia, metabolic syndrome, and type 2 T2DM (6,7,8).

Handgrip strength (HGS) is a simple and reliable tool for measuring body function and has been suggested as a biomarker for older adults (15). In the past decade, the majority of studies have used the HGS normalized to body weight or body mass index, since has been recommended in the research of muscle health (16,17). In this sense, some evidence that relative handgrip strength is associated with persistent hyperglycemia (18,19). Joule et al. (20) found that upper muscle strength (measured by bench press) was weaker in patients with T2DM than in healthy controls, and similarly, Mee-Ri et al. (21) recently found an inverse relationship between T2DM and HGS. In older adults (> 65 years), hyperinsulinemia increases the risk of falls, dementia, depression, and vision and hearing loss (22), and is associated with a substantial burden of cardiovascular disease (23), and brain abnormalities (24), with significant long-term morbidity and mortality (13). It seems to be that higher level on glucose also affects skeletal musculature (diabetic myopathy), involving contractile weakness, mitochondrial dysfunction, fiber-type changes, slow-to-fast muscle transitions, and decreased oxidative activity (25,26). In addition to this, it has a negative impact on muscular strength and quality in older adults. Park et al. (27,28) found a decline in muscle strength in the lower body in older adults with T2DM. However, these and other studies have not examined muscular strength in lower or upper extremities in individuals with disorders of glucose tolerance (29,30).

Overall, these findings indicate the coexistence of two vectors negatively affecting muscle strength–excess central adiposity and higher level of glucose. However, the exact biological mechanisms are poorly understood. Nevertheless, changes in body composition, particularly declines in lean body mass and the concurrent fat accumulation, coupled with impairment glucose metabolism have been proposed as potential mediators contributing to the declines in muscle strength and quality. Because an increase in body weight (adiposity) typically precedes the development of T2DM, research examining the relationship between HGS and body weight is desirable to know more about how relative HGS is associated with central adiposity, and to test whether fasting glucose has an effect on the relationship between central adiposity and relative HGS. To date, the potential role of fasting glucose in attenuating or modifying the relationship between central adiposity and hepatic relative HGS remains unknown and, to the best of our knowledge, has not been examined in older subjects.

The interplay between sarcopenia and excess adiposity in an ageing population has now emerged as an important public health concern in older populations. Considering the increasing number of obese older adults occurring in parallel with a greater prevalence of declines in muscle strength and quality, this study aimed to investigate the possible mediation effect of fasting glucose on the relationship between central adiposity and relative HGS, in community-dwelling older adults.

Materials and Methods

Study Design and Sample Population

We used the database from the “Health and Well-being and Aging Survey in Colombia, 2015” (SABE, from initials in Spanish: SAlud, Bienestar & Envejecimiento, 2015), a cross-sectional study supported by the Epidemiological Office of the Ministry of Health and Social Protection of Colombia (https://www.minsalud.gov.co/) of a nationally representative sample of Colombian older adults. The sampling design in the SABE study consists of a multistage probability sampling design for participant selection according to the existing municipal cartography as municipalities, urban, rural segments, homes or sidewalks, homes, and people. Therefore, it constitutes 99% of the population residing in private homes in the urban and rural strata of the sample. The study protocol was approved by the Human Subjects Committee for this secondary analysis at the Pontificia Universidad Javeriana (ID protocol 20/2017–2017/180, FM-CIE-0459-17) following the tenets of the Declaration of Helsinki of the World Medical

Association and Resolution 8430 of 1993 of the then Ministry of Health of Colombia on technical, scientific and administrative standards for human research. All participants provided written informed consent. Details of the survey have been published (31).

The SABE assessed 23,694 elderly people from 246 municipalities across all departments of the country. For this subsample, we selected 86 municipalities, including the four large cities. The sample size calculation was carried out, selecting two out of five individuals of the general sample, obtaining a sample of 1571 participants (60.0% women) aged 60 years and over. We included individuals who completed the handgrip strength test and who had available anthropometric/biological data to establish relative handgrip strength (**Figure 1**).

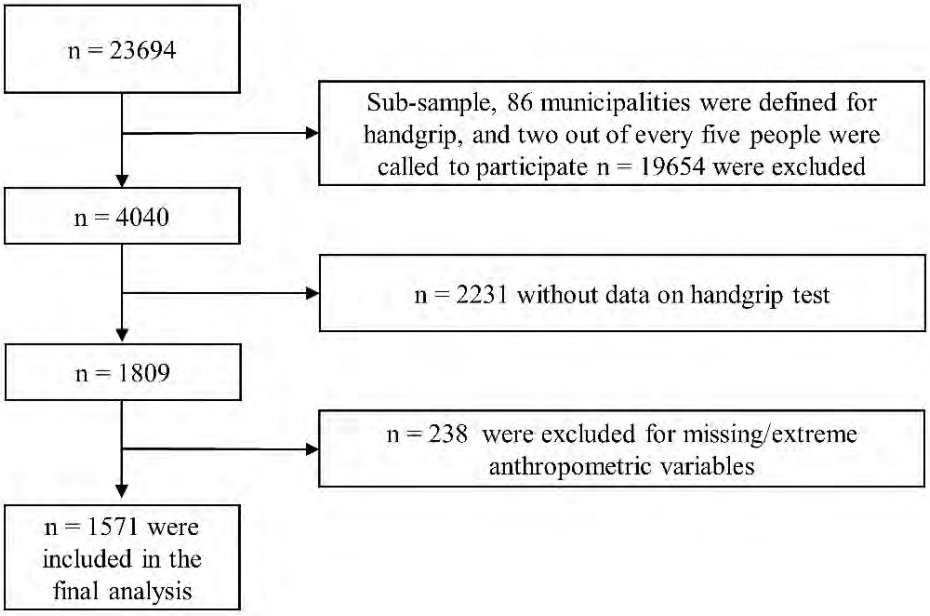

Figure 1. Flow chart showing the selection of the study sample from the SABE 2015 Survey. All analyses presented in this paper are based on 1,571 participants with complete data on anthropometric, glucose and handgrip

Measurements

Trained staff investigators carried out the physical examination, and medical laboratory technicians performed the blood samples and laboratory tests. With the aim to minimize the error, all analysis were performed by the Universities of Caldas and Valle, Colombia. Height and body weight were measured with a portable stadiometer (SECA 213, Hamburg, Germany)

and an electronic scale (Kendall graduated platform scale). BMI was calculated in kg/m2 from the measured body weight and height. WC was measured over the midpoint between the lower border of the ribs and iliac crest in the midaxillary plane, at the end of normal expiration. We used WC as proxy measures of central adiposity since they are useful tools in clinical practice, and are reliable predictors of T2DM and visceral adiposity (32). The HGS of both hands was measured with a digital hand dynamometer (Takei; Scientific Instruments Co., Ltd., Tokyo, Japan). Each participant completed the 3-trial for each hand, and the final estimate of HGS was the average of all measurements. The values were normalized to body weight (relative HGS). After an overnight fast, blood samples were obtained in the morning. Plasma glucose was analyzed by enzymatic colorimetric methods (Dinamica Laboratories, Bogotá, Colombia).

The following detailed demographics were recorded: age, sex, ethnicity, socioeconomic status (for lifestyle characteristics), alcohol intake (participants were categorized as those who do not drink and those who drink less than 1 day per week, 2 to 6 days a week, or every day), and cigarette smoking (participants were categorized as those who do not smoke and those who have never-smoked, those who currently smoke, or those who previously smoked) were recorded. A "proxy physical activity" report was conducted using questions: (i) "Have you regularly exercised, such as jogging or dancing, or performed rigorous physical activity at least three times a week for the past year?"; (ii) "Do you walk, at least three times a week, between 9 and 20 blocks (0.6 to 1.2 km) without resting?"; (iii) "Do you walk, at least three times a week eight blocks (0.5 km) without resting?". Participants were considered physically active if they responded affirmatively to two of the three questions. Demographics such as sex, age, socioeconomic status (low, middle, and high), ethnicity (people belonging to various indigenous groups, i.e., Ika, Kankuamo, Emberá, Misak, Nasa, Wayuu, Awuá, Mokane, etc., black "mulato" or Afro-Colombian, white and others, i.e., mestizo, gypsy, etc.), and urbanicity (urban, rural) were obtained by structured interview.

Statistical Analysis

Descriptive analyses of the study population characteristics were performed through mean ± standard deviation (SD) for the continuous variables and frequency distribution for categorical variables. The normality of the data was examined by the Kolmogorov–Smirnov test. Significant differences between men and women were analyzed using Student's t-test or the chi-square ($\chi 2$) post-hoc test. To elucidate the differences after controlling confounder variables

like sex, age, lifestyle, and sociodemographic characteristics, we performed an analysis of covariance (ANCOVA). Differences were interpreted through Cohen's effect size indices as small (d = 0.2), medium (d = 0.5), or large (d = 0.8) based on benchmarks suggested by Cohen (33). Mediation analysis was conducted to determine the indirect effect of fasting glucose levels on the relationship between abdominal obesity by WC and relative HGS (see Figure 2).

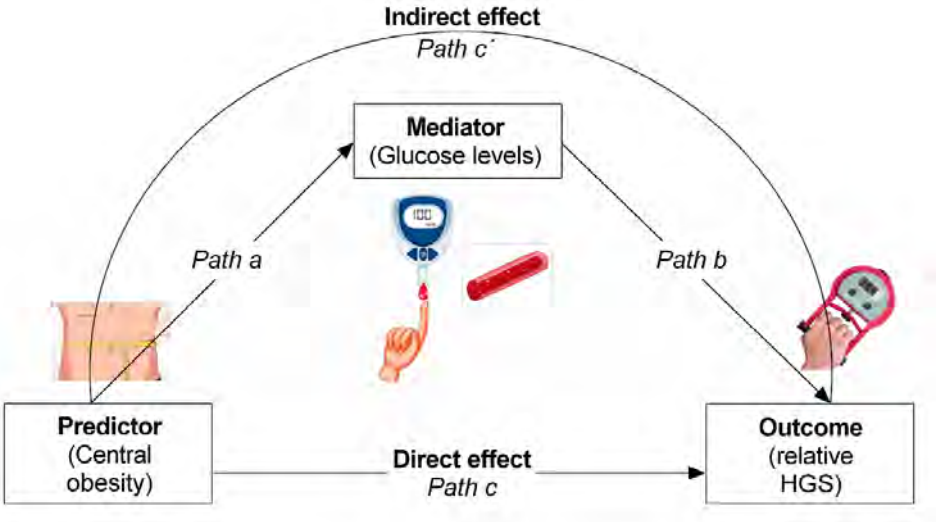

Figure 2. Mediation analysis tests a hypothetical causal chain where one variable X (abdominal obesity status) affects a second variable M (fasting glucose levels) and, in turn, that variable affects a third variable Y (HGS, relative handgrip strength).

In this order, we obtained the direct effect from variable X (categorized as 0 = healthy vs. 1 = abdominal obesity) to Y (relative HGS). Fasting glucose levels were used to know whether it played a mediator role. That is, to know if the detrimental effect of being abdominal obese on poorer muscle health is mediated by fasting glucose. Note that mediator in this case would be understood as the harmful ingredient for such a damaging relationship between abdominal obesity status and muscle health to take place. The analyses were conducted using the PROCESS macro for SPSS, version 3.4.1, developed by Hayes (34). This method provided an estimation of both the direct (Path c) and indirect (Path c') pathways, resulting in the calculation of 95% confidence intervals (CI) for both direct and indirect effects (see **Figure 2** for model depiction). The regression coefficients are displayed in unstandardized form, as the bootstrapped CI's correspond to the unstandardized effects rather than the standardized effects

(β). Mediation results are considered significant if the CI's do not contain 0. A *p*-value < 0.05 was interpreted as statistically significant.

Results

Of the 1571 subjects included in the sample, 1239 (78.8%) had abdominal obesity and 331 were healthy (22.2%). Healthy individuals presented a mean age of 70.5 (8.1) years and abdominal obese individuals 69.6 (7.3) years (see **Table 1**). Statistical differences ($p < 0.05$) between groups were found for all anthropometric characteristics and glucose level with higher values for older adults with central obesity. Healthy individuals presented better performance in muscular strength than obese individuals. Also, statistical differences were found between healthy and obese individuals on ethnicity, socioeconomic status, lifestyle outcomes and urbanicity, $p < 0.05$.

Table 1. Characteristics of the study participants (n = 1.571)

Characteristics	Full sample (n = 1,571)	Healthy (*n* = 331)	Central obese (*n* = 1239)	P-value
Age, years	69.6 (7.3)	70.5 (8.1)	69.6 (7.3)	0.052
Sex, *n* (%)				
Females	943 (60.0)	108 (32.6)	835 (67.3)	<0.001
Anthropometric outcomes, mean (SD)				
Body mass, kg	68.3 (11.5)	55.2 (8.4)	68.3 (11.5)	<0.001
Height, m	1.55 (0.08)	1.59 (0.08)	1.55 (0.08)	<0.001
BMI, Kg/m^2	28.9 (4.3)	22.5 (2.7)	28.9 (4.3)	<0.001
Waist circumference, cm	96.1 (9.1)	79.3 (6.6)	96.1 (9.1)	<0.001
Glucose fasting, mg/mL	100.1 (26.3)	90.4 (18.0)	100.1 (26.3)	<0.001
Muscular strength, mean (SD)				
HGS (kg)	21.1 (8.4)	22.9 (8.6)	20.6 (8.2)	<0.001
Relative HGS (kg/kg)	0.32 (0.12)	0.41 (0.13)	0.30 (0.1)	<0.001
Race/ethnic group, *n* (%)				
Indigenous	79 (5.0)	21 (6.3)	58 (4.7)	<0.001
Black "mulato" or Afro-Colombian	125 (8.0)	32 (9.7)	93 (7.5)	<0.001
White	414 (26.4)	70 (21.1)	344 (27.7)	<0.001
Others *	753 (47.9)	153 (46.2)	600 (48.4)	<0.001
Missing	200 (12.7)	55 (16.6)	145 (11.7)	—
Socioeconomic status, *n* (%)				

Level I-II (low)	1138 (72.4)	247 (74.6)	891 (71.9)	<0.001
Level III-IV (middle)	424 (27.0)	83 (25.1)	341 (27.5)	<0.001
Level V-VI (high)	9 (0.6)	1 (0.3)	8 (0.6)	0.020
Lifestyle outcomes, *n* (%)				
Smoking	152 (9.7)	56 (16.9)	96 (7.7)	0.001
Alcohol intake	203 (12.9)	59 (17.9)	144 (11.6)	<0.001
Physical activity "proxy"	1278 (81.3)	261 (78.9)	1017 (82.2)	<0.001
Urbanicity, *n* (%)				
Urban	1311 (83.5)	247 (74.6)	1064 (85.8)	<0.001
Rural	260 (16.5)	84 (25.4)	176 (14.2)	<0.001

Data are presented as mean ± SD or number (percentage) of participants. Significant differences between the men and women groups were analyzed by Student's *t*-test or χ^2 test.
BMI: body mass index; * Others (mestizo, gypsy, etc.)

Thus, to clarify the differences between central obesity status ("healthy" vs. "abdominal obesity") adjusted by the confounder variables we performed analysis of covariance, **Table 2**. The ANCOVA shows that differences in glucose levels and relative HGS parameters between older adults with and without abdominal obesity were independent after adjusting for sex and age ($p < 0.001$, Model 1), sex, age, and lifestyle ($p < 0.001$, Model 2), and ANCOVA Model 2 was additionally adjusted with socioeconomic status, ethnicity, and urbanicity ($p < 0.001$, Model 3).

Table 2. Comparison of the marginal mean values of the variables glucose, and handgrip strength according to central obesity

Model 1				Model 2				Model 3			
Healthy	**Central obesity**	***P***	***ES***	**Healthy**	**Central obesity**	***P***	***ES***	**Healthy**	**Central obesity**	***P***	***ES***
90.5 (87.8; 93.3)	100.0 (98.6; 101.4)	*	.38	90.9 (88.1; 93.7)	99.9 (98.5; 101.3)	*	.36	90.9 (87.8; 94.0)	100.1 (98.5; 101.5)	*	.36
0.38 (0.37; 0.39)	0.30 (0.29; 0.31)	*	.65	0.38 (0.37; 0.39)	0.31 (0.30; 0.32)	*	.63	0.38 (0.37; 0.39)	0.31 (0.30; 0.32)	*	.62

Data are presented as mean (SD) or number (percentage) of participants., * = p-value <.000

Figure 3 shows the results of mediation analysis to test whether the fasting glucose could be a mediator of the relationship between abdominal obesity and relative HGS. Path a indicated that central obesity status had a statistical significant negative effect on fasting glucose (β = 9.04, 95% CI = 5.87 to 12.21), $p < 0.001$; the *path b* from fasting glucose to relative handgrip strength was inversely related (β = −0.003, 95%CI −0.005 to −0.001), $p < 0.001$. The direct effect of abdominal obesity on relative HGS was statistically significant (β = −0.069, 95% CI = −0.082 to −0.057), $p < 0.001$. Besides, there was a significant indirect effect since the CI did not include zero. Finally, fasting glucose mediates the detrimental effect of abdominal obesity on relative HGS (β = −0.002, 95% CI = −0.004 to −0.001), $p < 0.001$.

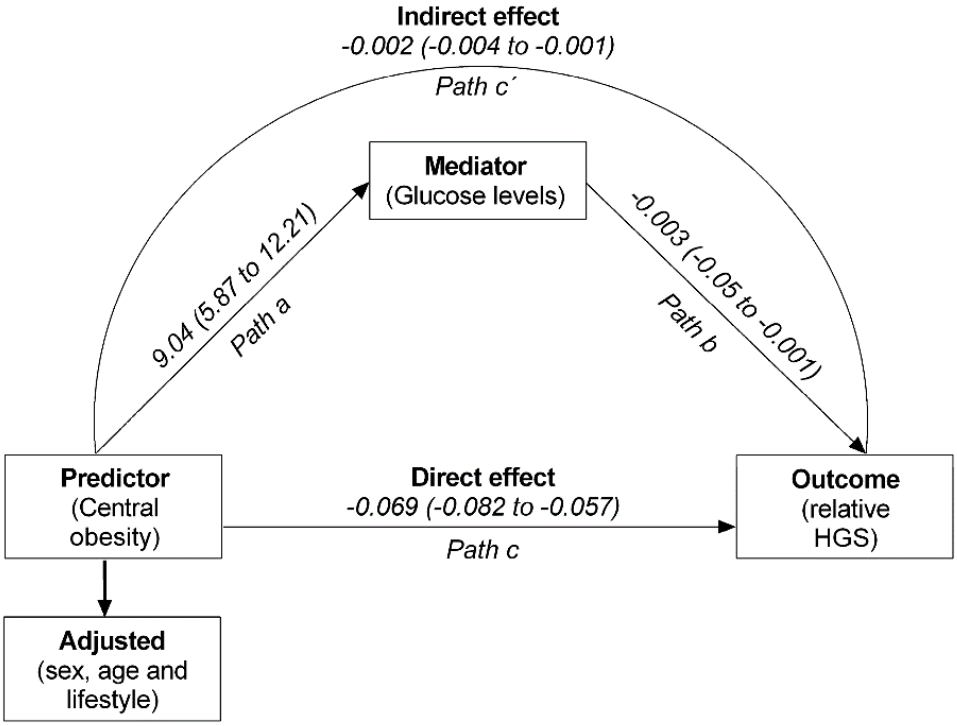

Figure 3. The direct effect of abdominal obesity status (healthy versus unhealthy) on relative HGS gives through fasting glucose level. In the model, abdominal obesity has an inverse relationship with relative HGS. This relationship is mediated by fasting glucose level as the active ingredient (in this case, harmful ingredient). The indirect effect is statistically significant at the 95% confidence interval (CI) when the CI does not include zero.

Discussion

In a cross-sectional study of community-dwelling older adults, we found that central obesity was inversely associated with relative HGS, as a measure of muscular strength, in older Colombian adults. This association was mediated by fasting glucose levels. In the same line, we also showed that the abdominal obesity was associated with higher fasting glucose levels. As far as we know, this is the first study to have examined the mediation role of fasting glucose level for the relationship between abdominal obesity and relative HGS. Our results suggest that the glucose level could worsen the association between abdominal obesity status and lower relative HGS. Also, our results provide novel insight into the mechanisms underlying this relationship.

In this study, WC were used as proxy measures for abdominal obesity which have been widely used in older adults for identification of central obesity in older adults (35). According to the IDF guidelines cutoff point of WC for abdominal obesity, presents a reliable measure of visceral fat (3) in Latin-American people and is strongly associated with metabolic syndrome. Our findings clearly showed that abdominal obesity is associated with a low level of relative HGS. Our results are consistent with previous literature showing that obesity, particularly central adiposity, is inversely associated with strength and/or muscle quality in older adults (8). Also, we found the relationship between WC and impaired fasting glucose, which is in agreement with previous research showing that central adiposity measured by WC is strongly related to more incidents of T2DM (8,35,36).

In a review study, Freemantle et al. (36) found that WC was strongly associated with T2DM, and Wang et al. (37) also found that WC was a better predictor of T2DM than BMI, even in non-obese individuals. Likewise, Son et al. (38) found a strong association between waist-to-height ratio (another proxy marker for central obesity dysfunction) and hyperglycemia. Overall, these findings support a clinically relevant issue which, through a simple measure of central adiposity, could help to screen for chronic metabolic disorder.

In our study, also showed that higher level of fasting glucose was inversely associated with relative HGS. According to the Guidelines on Integrated Care for Older People, handgrip strength is considered a reliable tool for measuring muscular fitness in older adults (39). Low relative HGS is an indicator of poor physical performance (40), and it is clear that low levels of physical fitness are related to a lower level of muscle mass (41). Our results are consistent with

previous research which found an inverse association between muscle strength and impaired fasting glucose (21,42,43).

The key finding of this study was that fasting glucose plays a mediator role in the relationship between abdominal obesity and relative HGS. To the best of our knowledge, this is the first study investigating this hypothesis in older adults. Other studies show that fatness is a mediator of muscular fitness and metabolic syndrome (44) in adolescents and, similarly, Brand et al. (45) and Bailey et al. (46) found that body fat mediated the relationship between cardiorespiratory fitness and cardiovascular risk factors. Also, it has been shown that patients with T2DM and with visceral fat accumulation have low muscle quality (47). Although we did not perform measures of muscle quality per se, previous evidence is suggestive that total and regional adiposity is associated with inter- and intramuscular adipose tissue infiltration, which is considered to be an important anatomical correlation of poor muscle quality (48). Additionally, the aging effect since age is linked to increased body fat accumulation, insulin resistance, and muscle strength decline (48). Several epidemiological studies have previously reported that skeletal muscle fat infiltration with age is associated with a decrease in muscle density, loss of muscle quality, poor lower body extremity performance, and falls risk (16,17,18,19). In the same line, higher level of fasting glucose mediating detrimental effect of abdominal obesity on muscle strength, might be the result of a greater content of glucose causing muscle atrophy (49,50). Skeletal muscle seems to be a protector against diabetes (51). Mechanistically, this might involve better insulin clearance by muscle myocytes. In this line, it has been shown that an insulin molecule activated by an insulin receptor in the muscle offers 2.1- to 3.1-times higher glucose uptake (removal) than the same insulin molecule activated by an insulin receptor in an adipocyte (52). Another protector role of muscle mass is better glycolysis by increased glucose transport via GLUT-4 expression from intracellular pools to the surface cell membrane (53,54). Therefore, individuals who are fit display higher insulin sensitivity than unfit, obese, or sarcopenic individuals (55).

As indicated above, an increase in intramuscular fat could lead to insulin resistance due to the presence of adipocytes, which worsens glucose clearance (52). Additionally, this effect leads to a worsening of the intramuscular mitochondrial function since the concomitant atrophy reduces the oxidative and phosphorylation activity of muscle mitochondria (56). Furthermore, the underlying functions of cytokines and myokines might come into play in this environment. It has been shown that the production of proinflammatory cytokines may be one of the crucial

mechanisms for T2DM development as, without good muscle health, the anti-inflammatory myokines cannot prevent systemic inflammation and development of T2DM (57,58).

The attributable risk for chronic metabolic disorder associated with low HGS has been previously reported from populations with varying ethnic backgrounds in different settings within one region or country (20,59,60). In this line, our findings are consistent with prior reports in the literature as a number of previous studies have emphasized that HGS is inversely associated with plasma glucose after adjusting for age, sex, and BMI (61). Peterson et al. (43) reported that every 0.05 kg decrease in the relative HGS was independently associated with a 1.49 (95% CI: 1.42–1.56) and 1.17 (95% CI: 1.11–1.23) odds for T2DM in American and Chinese adults, respectively, while among older Mexican Americans, muscle weakness was associated with T2DM (hazard ratio: 1.05; 95% CI: 1.02–1.09). (19) Notably, we found that glucose fasting plays a mediator role in the negative effect of abdominal obesity on relative HGS in Colombian older adults. However, since this research used a cross-sectional design, casual relationships cannot be inferred. The precise mechanisms for the observed associations must be examined in future studies.

Therefore, primary care strategies should be developed to prevent the loss of muscle mass and muscular strength (62). Also, maintaining low body fat could help to avoid the deterioration of muscular health associated with insulin resistance or pre-diabetes. These findings can help guide physical exercise programs for coaches, sports technicians or health agents, and nutritionists, prioritizing physical exercise and diet to reduce the accumulation of fat.

Our study has several limitations, including its cross-sectional design, which prevents us from making causal inferences (50). However, the strengths of this study are the mediation analysis that, to our knowledge, is the first to study the role of glucose levels in the relationship between central adiposity and muscular strength in Latin-American older adults. Also, our results are comparable with other health surveys since both muscle strength and abdominal adiposity were measured using simple and reliable tools for clinical practice. Therefore, the results of this study can provide a foundation for developing hypotheses for longitudinal studies.

Conclusions

In summary, fasting glucose level mediates the association between abdominal obesity status and relative HGS in Colombian older adults. Our findings illustrate the importance of glucose control and healthy habits for the prevention of insulin resistance in older with abdominal obesity and the relevance of optimum muscular strength. Longitudinal studies are required in the future to further clarify the influence of glucose levels on this relationship in community-dwelling older adults.

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Artículo 5

Glucose Levels as a Mediator of the Detrimental Effect of Abdominal Obesity on Relative Handgrip Strength in Older Adults

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Abstract

Objectives. We investigated the association between physical fitness and cognitive status. Further, we examined whether physical fitness mediates the association between cognitive functioning and aging. Design. Cross-sectional study. Setting. Urban and rural Colombian older adults. Methods. 4416 participants from the SABE study were included in the current analysis. Physical fitness was assessed with the handgrip test and the usual gait speed test. Cognitive status was evaluated through the Folstein Mini-Mental State Examination. A parallel mediation path was used to test the possible mediator role of physical fitness between aging and cognitive functioning. Results. Older adults with lower handgrip strength (HGS) were more likely to have mild-cognitive status than older adults with healthy HGS (OR = 1.53, 95% CI = 1.15; 2.02). In addition, older adults with a slower gait speed were more likely to have mild cognitive impairment (OR = 2.05, 95% CI = 1.54; 2.78). Age had an inverse relationship with cognitive function (β = −0.110, 95% CI = −0.130; −0.100) and it was also inversely associated with HGS (β = −0.003, 95% CI = −0.005; −0.002) and gait speed (β = −0.010, 95% CI = −0.011; −0.009). The indirect effects, which indicate that the effect of age on cognitive function is transmitted through mediators, showed that both gait speed (β = −0.028, 95% CI = −0.036; −0.020) and HGS (β = −0.014, 95% CI = −0.024; −0.005) were independent mediators of the detrimental effect of aging on cognitive function. Conclusions. Physical fitness mediates the effects of aging on cognitive functioning. Our findings suggest that physical activity can be a key factor to prevent cognitive deterioration during aging process.

Introduction

The Latin-American population is aging fast, and it has been projected that by 2050 the number of people older than 65 will double [1]. Aging is associated with several non-communicable diseases, including mobility disability [2] and cognitive decline [3]. In Colombia (South America), the prevalence of mild cognitive impairment is increasing and currently stands at 5.6% [4]. Mild cognitive impairment in older adults leads to deficits in activities of daily living and quality of life [5], and its progression to more serious cognitive problems (e.g., dementia) is associated with early mortality [6]. Accordingly, identifying risk factors that can help mitigate or delay the appearance of cognitive impairment is a key challenge for health care systems.

Maintenance of physical fitness through the adoption of a physically active lifestyle is known to promote healthy aging [7]. Physical fitness can be defined as a set of measurable attributes that people achieve through physical activity and that are associated with physical and mental well-being [8]. In older adults, physical fitness is typically assessed through specific tests, including handgrip, balance, and gait speed [8], which provide an overview of motor and muscle strength competence.

Physical fitness can decrease dramatically with age, and numerous studies have highlighted the deterioration in muscular strength, balance, gait speed, mobility, and cardiorespiratory performance in men and women aged >60 years of age [9,10,11]. A better physical fitness status is associated with better health and quality of life [12,13].

Accumulating evidence indicates that a relationship between physical fitness and cognition exists and that a decline in physical performance precedes the deterioration of cognitive ability. For example, A recent study based on the UK Biobank study (2007–2010) of 476,559 participants highlighted that muscle strength measured by a handgrip test was positively and prospectively associated with memory and processing speed [14]. A similar study with 6874 older adults found that physical activity level and lower-limb muscle strength predicted a lower cognitive function [5]. Conversely, other studies have found the opposite: cognitive decline leads to a lower physical performance. For example, in a longitudinal study of over 3500 participants from The Netherlands, Stijntjes et al. [15] found that a poorer executive function was associated with a steeper decline in gait speed in people aged 55–90 years. Likewise, in the Baltimore Longitudinal Study of Aging (412 participants aged ≥60 years), Tian et al. [16] found

that the relationship between usual gait speed and executive function was unidirectional, such as a slower walking speed predicted future declines in executive function and memory but not vice versa. Finally, a prospective study of 2876 well-functioning older adults (70–79 years) from the US found that early declines in gait speed predicted a decline in orientation, attention, calculation, language and short-term memory, but the association between early declines in cognition and later declines in gait speed was weaker [17]. Thus, the empirical evidence connecting the two phenomena is rather inconclusive.

Regarding the potential beneficial relationship between exercise training and cognitive functioning, Baker et al. used a rigorously controlled methodology to examine aerobic exercise's effects on cognition in 33 adults (mean age 70 years) with mild cognitive impairment. The authors of the former study found an improvement of executive function through aerobic exercise in older women but not men [18]. Likewise, Zhihui et al. [19] reported in a systematic review of randomized clinical trials on the beneficial effects of resistance training on cognitive function in older adults. Exercise-induced changes in cognitive status could be explained by modifications to brain characteristics and functioning, as exercise induces cognitive plasticity [20], improves cerebral perfusion [21] and cerebrovascular reactivity [22], and reverses hippocampal volume loss, thereby improving memory [23].

While it is clear that aging is associated with cognitive decline and changes to cognitive functioning, to our knowledge, no studies have examined the potential mediating role of physical fitness measured through gait speed and HGS on the association between aging and cognitive decline. Consequently, the present study was designed to evaluate the association between physical fitness and cognitive status and to examine whether physical fitness mediates the decline in cognitive functioning associated with aging.

Materials and Methods

Design, Setting and Participants

We analyzed data from the "Estudio Nacional de Salud, Bienestar y Envejecimiento" (SABE) Colombia survey. SABE is a nationwide, population-based, cross-sectional study that was conducted in 2015 by the Epidemiological Office of the Ministry of Health and Social Protection of Colombia (https://www.minsalud.gov.co/). Data were obtained using a probabilistic sampling scheme by clusters (housing segments) with block stratification. The

estimated sample size was 24,553 adults aged 60 years and above, assuming an 80% response; the target sample was 30,691 individuals [24]. Nonetheless, because of variations in the application of strategies to achieve a response rate of 70% across regions and civil settings (i.e., urban/rural distributions), the final sample size included 23,694 from 244 municipalities across all departments. More details about the study design and protocol can be consulted in the research published by Gomez et al. [24].

For this subsample analysis, 86 municipalities were selected, including the 4 large cities (Bogota, Cali, Medellin and Barranquilla), for the application of functionality tests and muscle strength assessment, obtaining a sample of 5657 people 60 years of age or older. Of these participants, 4146 subjects were selected for this study. We excluded those with missing data of HGS, gait speed tests and/or anthropometric variables and/or without self-reported health condition (see Figure 1). All participants (or their proxy respondent) provided written informed consent for their data to be used in the study.

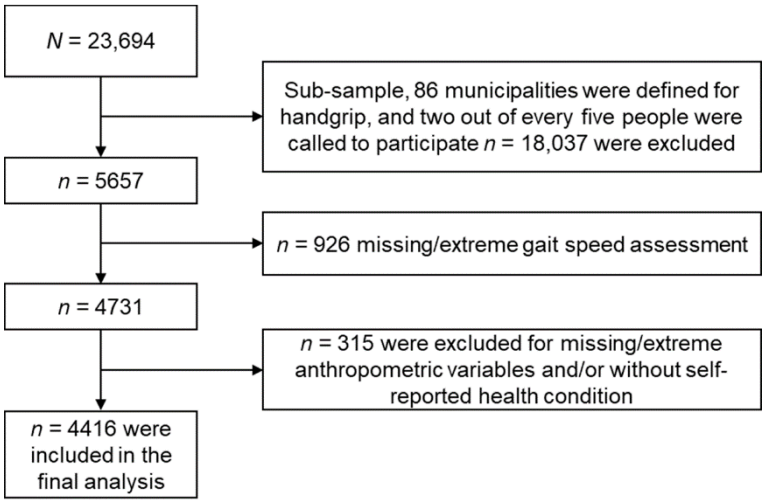

Figure 1. The flow chart shows the study sample selection from the Colombian Health and Wellbeing and Aging Survey (SABE) 2015. All analyses presented here were based on 4416 surveyed participants, each with complete HGS and long-term condition data.

Data Collection

The health survey included medical history examination, physical fitness examination and questionnaires on health disorders history, lifestyle data and anthropometric variables. Physical tests were performed by technical, medical staff following the standardized protocol for the SABE study [24].

Sociodemographic, Health Disorders History and Lifestyle Data

Participants were asked about sociodemographic factors, including ethnic group (indigenous, black "Mulatto" or Afro-Colombian, white, others and non-ethnic), living area (rural or urban), and socioeconomic status (SES): level I–II: low; level II–III: middle; and level V–VI: high. Three lifestyle variables were included in the survey. Alcohol consumption was assessed using the question: "In the last three months, on average, how many days of the week have you had alcoholic beverages?" Responses were divided into four categories: (1) no alcohol consumption, (2) 1–2 glasses per day, (3) 3–5 glasses per day, (4) more than 5 glasses per day. The variable was then dichotomized by grouping categories 2–4 as alcohol consumption, and category 1 as no alcohol consumption.

Smoking was assessed by asking individuals if they were currently smoking or had ever smoked. Answers were divided into four categories: (1) never smoked, (2) former smoker, (3) smokes less than 5 cigarettes per day, (4) smokes more than 5 cigarettes per day. This variable was also dichotomized by grouping categories 1 and 2 as not smokers and 3 and 4 as smokers. The following questions were used to assessed a "proxy" for physical activity: (1) "Have you regularly exercised, such as jogging or dancing, or performed rigorous physical activity at least three times a week for the past year?"; (2) "do you walk at least three times a week between nine and 20 blocks (1.6 km) without resting?"; (3) "do you walk at least three times a week eight blocks (0.5 km) without resting?". Participants were considered physically active if they responded affirmatively to two of the three questions [25].

Medical information including multimorbidity, as well as chronic condition adapted from the original SABE study [24], was assessed by asking the participants if they had been medically diagnosed with hypertension, diabetes, chronic obstructive pulmonary disease, CVD (heart attack, angina), stroke, different types of cancer, arthritis, osteoporosis, cholesterol, triglycerides, mental or sensory problems.

Anthropometrics Measurement

Height and body weight were measured by a portable stadiometer (SECA 213, Hamburg, Germany) and an electronic scale (Kendall graduated platform scale). BMI was calculated as weight in kilograms divided by the square of height in meters.

Physical Fitness Tests

HGS was used to measure the muscle force profile of the upper limb. For this, we used the Takei dynamometer (Takei Scientific Instruments Co., Tokyo, Japan). Prior to the assessment, the dynamometer was calibrated to ensure proper usage and accuracy. Subjects were asked to perform the assessment (with the elbow joint in full extension) while standing if possible and were given a practice trial to ensure comprehension of the procedure. The grip tests were performed three times on each hand, alternating hands between each trial, and the mean value was recorded as the final score of the test. Testers ensured a total of 60 s of rest between trials on the same hand. The values were normalized to body weight (relative HGS).

Usual gait speed (meters/second) was measured by 3 m walking. The participants had to walk two times at the usual pace starting from a standing position.

2.2.4. Cognitive Function

Cognitive status was assessed using the revised version of the Folstein Mini-Mental State Examination (MMSE), a validated international scale translated to Spanish [26]. The modified version ranges from 0 to 19, with a higher score representing better cognitive function.

Statistical Analysis

At first, univariate analysis was used to explore extreme values and Kolmogorov Smirnov was used to examine data distribution. Categorical variables are presented using frequencies and percentages, and continuous variables are presented using means and standard deviations. We applied covariance analysis adjusted by sex, age, lifestyle and comorbidities variables to explore the physical fitness differences between cognitive status groups. Unadjusted and adjusted logistic regressions controlling for age, sex, lifestyle and comorbidities were employed to assess the likelihood of having cognitive impairment based on physical fitness level. According to the literature, the covariates included in the adjusted analyses were based on the conceptual model [14,15,16,17]. For this purpose, we used the European Working Group on

Sarcopenia in Older People 2 (EWGSOP2) guidelines and criteria to determine sarcopenia from the assessment of gait speed (<0.80 m/s) and HGS (<27 kg in men and <16 kg in women) [27].

To test for the possible mediator role of physical fitness between aging and cognitive status, we designed a parallel mediation path analysis (see Figure 2). The mediation model indicated through estimation of indirect effects, what physical fitness components (handgrip strength or/and gait speed) were mediators between the detrimental impact of age on cognitive function as assessed by the MMSE test [26]. To perform the analysis, we used the PROCESS macro for SPSS (IBM, Chicago, IL, USA) [28]. The mediation hypothesis was tested using the bias-corrected bootstrap method with 5000 samples to calculate confidence intervals (95%). The point estimate was considered significant when the confidence interval did not cross zero. In addition, we used the test included in the PROCESS macro to compare indirect effects. Significance was set at the $p \leq 0.05$ level.

Results

The descriptive characteristics of participants are presented in Table 1. The mean age of participants was 69.5 ± 7.1 years. The distribution by sex in the overall sample was 57.3% for females and 42.7% for males. Of the 4416 participants included in the study, 510 (11.5%) showed mild cognitive impairment. Regarding the distribution across the different SES levels, the majority of participants fit in the lowest SES level (level I–II). The lifestyle outcomes showed that the proportion of individuals drinking alcohol and smoking was low, 13.5% and 11.0%, respectively. A significant proportion of older adults (80.6%) did not accomplish the minimum required daily physical activity “proxy”. Regarding comorbidities, visual problems, high blood pressure and cholesterol had the highest percentage of incidence. There were significant differences between healthy individuals and individuals with cognitive impairment for all variables tested.

Table 1. Sample characteristics stratified by cognitive status.

Sociodemographic Characteristics	**Overall**	**No cognitive Impairment *n* = 3906 (88.5%)**	**Cognitive Impairment *n* = 510 (11.5%)**	***p*-Value**
Sex (female), *n* (%)	2531 (57.3)	2224 (56.9)	307 (60.2)	0.001
Sex (male), *n* (%)	1885 (42.7)	1682 (43.1)	203 (39.8)	
Age group, *n* (%)				
60–69	2512 (56.9)	2366 (60.6)	146 (28.6)	
70–79	1431 (32.4)	1234 (31.6)	197 (38.6)	0.001
80+	473 (10.7)	306 (7.8)	167 (32.7)	
Nutritional status, *n* (%)				
Underweight	83 (1.9)	73 (1.9)	10 (2.0)	
Normal weight	1344 (30.4)	1141 (29.2)	203 (39.8)	0.001
Overweight	1809 (41.0)	1628 (41.7)	181 (35.5)	
Obese	1180 (26.7)	1064 (27.2)	116 (22.7)	
Socioeconomic status, *n* (%)				
Level I–II (low)	3371 (76.3)	2934 (75.3)	428 (83.9)	0.001
Level III–IV (medium)	1007 (22.8)	926 (23.7)	81 (15.9)	
Level V–VI (high)	38 (0.8)	37 (0.9)	1 (0.2)	—
Ethnic group, *n* (%)				
Indigenous	267 (6.0)	267 (6.8)	0 (0.0)	—
Black	369 (8.4)	369 (9.4)	0 (0.0)	—
White	1234 (27.9)	1234 (31.6)	0 (0.0)	—
Others	2036 (46.1)	2036 (52.1)	0 (0.0)	—
Non-ethnic	510 (11.5)	0 (0.0)	510 (11.5)	—
Living area, *n* (%)				
Urban	3406 (77.1)	3060 (78.3)	346 (67.8)	0.001
Rural	1010 (22.9)	846 (21.7)	164 (32.2)	
Lifestyle outcomes, *n* (%)				
Alcohol	594 (13.5)	559 (14.3)	35 (6.9)	
Smoking	487 (11.0)	422 (10.8)	65 (12.8)	0.001
Non-physically active	3555 (80.6)	3098 (79.3)	457 (89.8)	
Comorbid chronic diseases, *n* (%)				
HBP	2374 (53.9)	2077 (53.3)	297 (58.3)	0.001

High cholesterol	2159 (49.1)	1930 (49.6)	229 (45.5)
Diabetes	715 (16.2)	635 (16.3)	80 (15.7)
Cancer (any type)	210 (4.8)	195 (5.0)	15 (2.9)
COPD	443 (10.0)	375 (9.6)	68 (13.4)
CVD	600 (13.6)	520 (13.3)	80 (15.7)
Stroke	167 (3.8)	138 (3.5)	29 (5.7)
Arthritis	1192 (27.1)	1075 (27.6)	117 (23.1)
Osteoporosis	499 (11.4)	446 (11.5)	53 (10.4)

Categorical variables are reported as numbers and percentages in brackets. Significant between-cognition status differences $\chi 2$. Comorbidities are reported as "presence/yes". HBP: high blood pressure; COPD: chronic obstructive pulmonary disease; CVD: cardiovascular disease.

Table 2 shows the performance and differences in physical fitness according to cognitive status. Statistically significant differences in HGS relative to body weight were found between older healthy adults and their peers with cognitive impairment after adjusting for sex, age, lifestyle characteristics and comorbidities. The best performance was 0.34 kg/kg versus 0.30 kg/kg in healthy older adults versus peers with poor cognitive functioning. Similar results were observed for gait speed, with older adults without cognitive impairment showing better functioning than those with poor cognition. Analysis of co-variance revealed statistically significant differences ($p < 0.001$) after adjusting for sex, age, lifestyle outcomes and comorbidities.

Table 2. Physical fitness performance in Colombian older adults according to cognitive status

Variables	No cognitive Impairment	Cognitive Impairment	Model 1 p-Value	Model 2 p-Value	Model 3 p-Value
Absolute HGS (kg)	22.08	18.50	<0.001	<0.001	<0.001
Relative HGS (kg/kg)	0.34	0.30	<0.001	<0.001	<0.001
Gait speed ($m \cdot s^{-1}$)	0.77	0.63	<0.001	<0.001	<0.001

Note: Model 1: adjusted by sex and age; Model 2: adjusted by Model 1, ethnicity, urbanicity, socioeconomic status and lifestyle; Model 3: adjusted by Model 2 and comorbidities

Table 3 shows the associations in odds ratios between low HGS and low gait speed according to the EWGSOP2 cut-off and mild cognitive impairment. Older adults with low HGS were

more likely to have mild-cognitive impairment than older adults with healthy muscle strength after adjusting for age, sex, lifestyle characteristics and comorbidities (OR = 1.55, 95% CI = 1.16; 2.03). In addition, older adults with slow gait speed were more likely to have mild cognitive impairment (OR = 2.08, 95% CI = 1.56; 2.80).

Table 3. Physical fitness association with cognitive function in Colombian older adults.

	Model 1			**Model 2**			**Model 3**		
	OR	**95% CI**	**p-Value**	**OR**	**95% CI**	**p-Value**	**OR**	**95% CI**	**p-Value**
Lower HGS	1.45	(1.11; 1.90)	0.006	1.47	(1.11; 1.93)	0.006	1.55	(1.16; 2.03)	0.002
Lower Gait speed	2.12	(1.61; 2.79)	0.007	2.06	(1.55; 2.72)	<0.001	2.08	(1.56; 2.80)	<0.001

Note: Lower HGS and gait speed are defined according to EWGSOP2 guidelines (<0.80 m/s for gait speed) (<27 kg in men and <16 kg in women for HGS). Model 1: adjusted by sex and age; Model 2: adjusted by Model 1, ethnicity, urbanicity, socioeconomic status and lifestyle; Model 3: adjusted by Model 2 and comorbidities.

As shown in the mediation model (Figure 2), we found that the independent variable (age) had an inverse relationship with cognitive function (β = −0.110, 95% CI = −0.130; −0.100). Age was inversely associated with HGS (β = −0.003, 95% CI = −0.005; −0.002) and gait speed (β = −0.010, 95% CI = −0.011; −0.009). The indirect effects showed that both gait speed (β = −0.028, 95% CI = −0.036; −0.020) and HGS (β = −0.014, 95% CI = −0.024; −0.005) were independent mediators of the detrimental effect of aging on cognitive function.

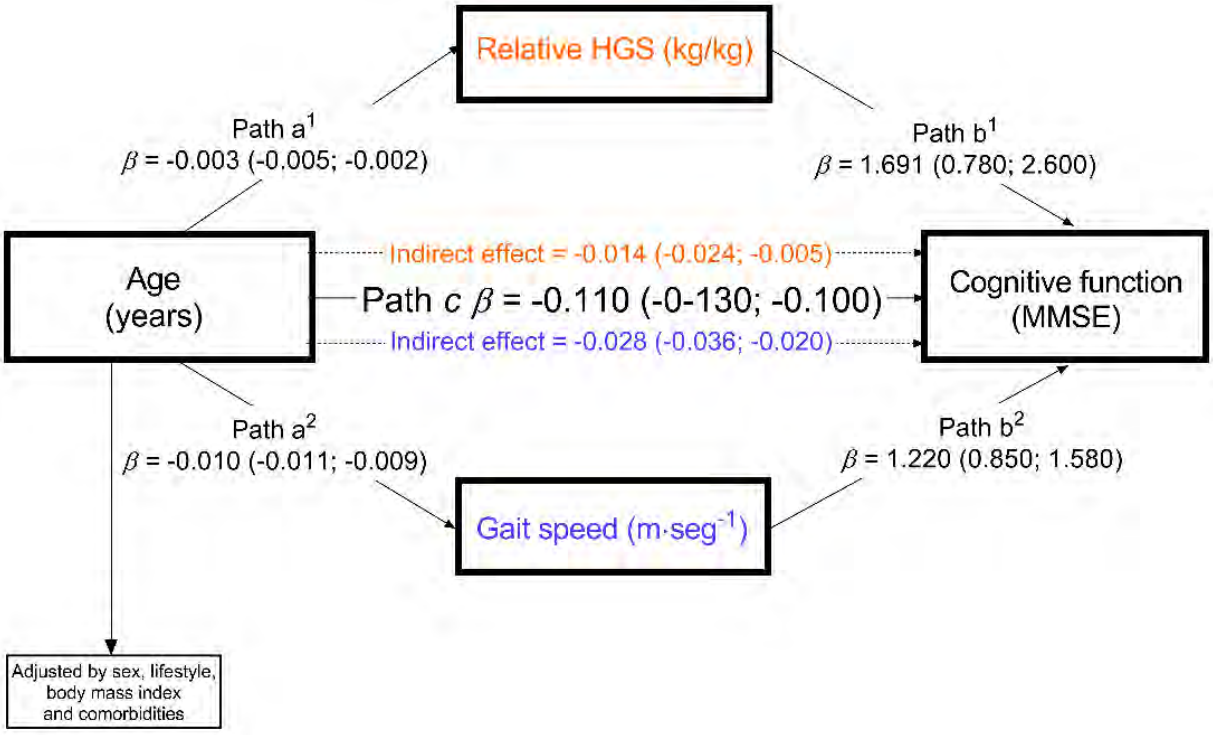

Figure 2. Parallel mediation analysis of aging effects on cognition (MMSE) score through relative HGS (kg) and gait speed (m·seg-1), adjusted by sex, lifestyle, body mass index and comorbidities. Number of bootstrap samples = 5000. The indirect effect is statistically significant at the 95% confidence interval (CI) when the CI does not include 0. Betas (β) are reported as the product of simultaneous regression with bootstrap replacement Path a1 & a2 = association between age and relative HGS and gait speed, respectively; Path b1 & b2 = association between relative HGS and gait speed with cognitive function; Path c = direct effect; orange and blue associations = indirect effect by relative HGS and gait speed, respectively.

Discussion

The present study analyzed a representative sample of Colombian older adults from a National Survey (SABE). We examined the association between low HGS (men <27 kg, women <16 kg) and low gait speed (<0.80 m/s) and cognitive impairment. We also studied the relationship between age and cognitive functioning and whether this relationship was mediated by physical fitness measured through gait speed and HGS.

This study's main finding was the mediator role of gait speed and HGS between aging and cognitive impairment using a parallel mediation model. Our findings suggest that the

association between age and cognition is mediated by the level of HGS and gait speed. Accordingly, the loss in cognitive function associated with age could depend on the individual level of physical fitness. For example, older adults with poorer HGS or/and gait speed would show an accelerated loss in cognitive impairment, and the opposite would be seen in peers with a better performance on HGS or/and gait speed. The findings indicate that gait speed and HGS mediate the deterioration of the cognitive status associated with aging, and thus are active components of the aging effects on cognitive status. To the best of our knowledge, this is the first study examining the mediating role of physical fitness in the relationship between age and cognition. Our findings are consistent with the idea that physical fitness contributes to better cognitive functioning [14,29].

The mediator effect of physical fitness could be explained by the benefits that physical exercise has on cognitive health. For example, Xu et al. [30] found an improvement in cerebral perfusion in older women (but not men) after one session per week of resistance training. Strength training also leads to beneficial changes in white matter atrophy and neuroplasticity [31]. The results from two systematic reviews [31,32] revealed that older adults who participated in a resistance training program maintained or improved their neuroplasticity and brain atrophy. The hippocampus is known to shrink in late adulthood, and exercise training has been shown to increase the hippocampal volume, including high-intensity interval training [33] and strength exercise [34]. Similarly, a multicomponent exercise program, including strength, aerobic and balance exercises, was found to reduce whole brain cortical atrophy in older patients with mild cognitive impairment compared with a control group [35], resulting in improved cognitive function. A possible underlying mechanism for these beneficial changes in brain characteristics and functioning is the increase in production and secretion of brain-derived neurotrophic factor [36–38].

Another finding showed that Colombian older adults with a poor performance in HGS and gait speed were 1.53 and 2.05 times more likely, respectively, to experience mild cognitive impairment. Our findings are supported by prior research showing that a de-cline in cognition is led by lower physical fitness performance. For example, it was shown that lower HGS was associated with a poorer performance in memory and processing speed [14]. Likewise, gait speed was shown to predict cognitive impairment and dementia [39]. However, other studies indicate the opposite, with several showing that the relationship between physical fitness and cognition is bidirectional or that cognitive decline pre-cedes poor HGS and gait speed [15–17].

From our perspective, the deterioration in cognitive function is preceded by low physical activity and, consequently, by poor physical fitness. This is based on the beneficial effects that exercise has on cognitive health, as shown in previous studies [40,41]. With this in mind, the main objective of the present study was to assess whether physical fitness mediates the inverse relationship between age and cognition.

The present study has several strengths. It is based on a large sample size of older adults within a nationally representative proportion of persons aged ≥60 years. In addition, we used a direct measure of physical fitness, a far more reliable and valid measure than self-report questionnaires. HGS and gait speed also are the two most used measures of physical fitness levels used in older adults [42–44]. Moreover, the novelty of examining the mediator role of physical fitness comparing HGS and gait speed should also be considered a strength. Thus, there should be more emphasis on physical fitness in subsequent iterations of the mental health act of Colombia as part of a policy to improve cognitive status across the life course.

Our study does have several limitations. First, the cross-sectional design limits the ability to draw on causal associations. Second, even though we adjusted for potential confounding factors such as sex, lifestyle variables and comorbidities, the population was heterogeneous, especially regarding ethnicity. Some variables were self-reported and are subject to biases. In addition, cognitive status was assessed by a unique self-reported questionnaire, but it is not a clinical diagnosis of cognitive impairment. It would thus be advisable in future studies to combine several questionnaires to avoid bias.

Our finding offers insight into the potential role of fitness on cognitive decline in older adults. Specifically, it is clear that both gait speed and muscle strength must be ad-dressed in future anti-aging programs. Specifically, and following the EWGSOP2 [27] recommendations, the HGS should be above 27 kg for men and 16 kg for women, and gait speed should be >0.80 m/s.

Conclusions

Physical fitness, measured by gait speed and HGS, mediates the relationship of aging on cognitive functioning in older adults in Colombia and elsewhere in Latin America & the Caribbean. Our findings suggest the need to maintain gait speed and HGS in older adults to avoid cognitive function loss.

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TERCERA PARTE

Discusión general

Discusión general

La mayoría de los hallazgos relevantes de esta tesis doctoral están relacionados con el rol que la fuerza de prensión manual y la velocidad de la marcha tienen sobre los efectos adversos asociados al envejecimiento en una muestra representativa nacional de adultos mayores colombianos procedentes del estudio SABE Colombia 2015. Además, se han obtenido resultados de prevalencia de las comorbilidades más en el del adulto mayor. Por ejemplo, tenemos datos de la prevalencia de probable sarcopenia, un nuevo concepto para la detección temprana de sarcopenia (1,2) y sus factores asociados. También se han obtenido puntos de corte para la velocidad de la marcha y para la fuerza de prensión manual, a partir de los cuales, estos componentes de la condición física podrían moderar el cambio entre comorbilidades asociadas. Y, además hemos obtenido un posible mediador, como es el nivel de glucosa en sangre, del efecto adverso que tiene la obesidad abdominal sobre la fuerza muscular. Por consiguiente, nuestros hallazgos suponen un avance en cuanto al conocimiento de los efectos de la senescencia sobre la salud muscular y como esta tiene un rol inexcusable frente al envejecimiento. Los resultados servirán para la elaboración de guías actualizadas sobre el mínimo requerido de fuerza muscular y velocidad de la marcha para un envejecimiento saludable.

Prevalencia de probable sarcopenia (estudio 1)

El principal hallazgo encontrado en este trabajo fue la extraordinaria prevalencia de probable sarcopenia en una muestra representativa de adultos colombianos. En cifras, de los 5237 adultos mayores participantes en este estudio, el 46,5% presentaba probable sarcopenia. Los hombres registraban el 47,9% de la prevalencia frente al 45,4% de las mujeres.

Estudios previos determinando la prevalencia de probable sarcopenia en población latinoamericana son muy limitados ya que este término es de reciente creación por el EWGSOP2 (1,2), tan solo encontramos estudios realizados en Europa donde la prevalencia de probable sarcopenia estaba muy por debajo de nuestros resultados (2,3). La probable sarcopenia se establece a partir de unos puntos de corte de la fuerza de prensión manual los cuales son <27 kg para hombres y <16kg para mujeres (1). Teniendo en cuenta que la media de edad de la muestra participante era de 7.4 con una distribución de un 32,8% entre 70─79 años y un 14.8% por encima de 80 años, los resultados fueron muy significativos. Estos hallazgos nos indican en primer lugar, que la salud muscular de la muestra utilizada fue relativamente pobre y, en

segundo lugar, que los individuos identificados con probable sarcopenia tendrán riesgo de padecer sarcopenia severa en un futuro. Los resultados destacan la importancia del diagnóstico temprano de probable sarcopenia con el objetivo de identificar individuos con alta probabilidad de desarrollo de sarcopenia severa. Además de esto, el método utilizado como es la prensión manual solo requiere de un dinamómetro portable, por lo que es económico, sencillo de aplicar y con una validez y fiabilidad plausible (4).

Asimismo, en este estudio se examinaron los factores asociados a la probable sarcopenia. En este sentido se encontró que la inactividad física, alteraciones de tipo auditivas, visuales mentales, y la presencia de osteoporosis, artritis y diabetes, guardaban una estrecha relación con la probable sarcopenia. De este modo, los individuos que tengan una o más afecciones de las mencionadas anteriormente, tendrían una mayor probabilidad de desarrollar esta probable sarcopenia. Estudios previos han remarcado como la inactividad física es el principal factor asociado a la pérdida de salud muscular (5–7). Diabetes también parece ser un factor de riesgo asociado a la probable sarcopenia, por lo que este hallazgo va en línea con estudios previos (8,9). Detrás de esta debilidad muscular parece ser que están factores proinflamatorios asociados a la diabetes como así se ha documentado en estudios previos (10–12). Osteoporosis y artrosis también estaban fuertemente relacionadas con la prevalencia de probable sarcopenia. Dado que el músculo es un órgano secretor y que en función de la carga recibida (actividad) puede poner en funcionamiento la regeneración del tejido adyacente como son los huesos, tendones y ligamentos (13,14) la relación entre la debilidad muscular y estas dos afecciones podría ser bidireccional. Además de esto, la debilidad muscular podría deberse a la inmovilización del individuo e inactividad física ante la presencia de osteoporosis y artritis. Generalmente, estas dos enfermedades cursan con inactividad física llegando incluso a la quinesofobia ante el temor a sufrir dolor (15,16).

La velocidad de la marcha como moderador del efecto adverso de la obesidad sobre la dependencia (estudio 2)

En este estudio se encontró como la velocidad de la marcha actuaba como moderador del efecto perjudicial que tiene la obesidad sobre el nivel de dependencia en adultos mayores. En el estudio participaron un total de 20,507 colombianos de más de 60 años. Los resultados del estudio destacaron la estrecha relación existente entre un alto IMC y la mayor presencia de dependencia

funcional. Por tanto, adultos mayores con sobrepeso u obesidad tendrían mayor dependencia funcional. No son pocos los estudios previos que han señalado este mismo hallazgo en adultos mayores. Por ejemplo, Kumar et al. (17). encontraron una mayor tasa de dependencia funcional en adultos mayores mejicanos con obesidad. También Jensen et al en dos revisiones entraron sólidas evidencias de una mayor presencia de dependencia funcional asociado a la obesidad (18,19).

Por otra parte, en este estudio también se encontraron como una pobre velocidad de la marcha se relacionaba con una mayor presencia de dependencia funcional. Estos hallazgos van en línea con resultados obtenidos en estudios previos (20,21)

Pero sin lugar a duda el principal hallazgo de este estudio fue el efecto moderador de la velocidad de la marcha sobre el perjudicial efecto de tener un alto IMC sobre la presencia de dependencia funcional. El efecto moderador nos indica como ante el detrimento de la capacidad funcional ocasionado por un exceso de peso, la velocidad de la marcha actuaba positiva o negativamente entre ambas. Para ello, mediante la técnica estadística de Johnson-Neyman se determinaron dos umbrales por debajo o por encima del cual el efecto moderador es significativo. En nuestro estudio, una velocidad de la marcha igual o superior a 0.77 m/s e igual o inferior a 1,06 m/s tendría efecto moderador. Por tanto, aquellos adultos mayores aun teniendo un alto IMC, si su velocidad de la marcha se encontrase entre estos umbrales, el efecto sobre la dependencia funcional se vería reducido o incluso desaparecería. Estudios relacionados con este hallazgo son inexistentes. Sin embargo, el umbral inferior va en línea con el establecido en la literatura de 0,80 m/s (1,22).

A pesar de no encontrar estudios similares, sí que hay bases biológicas capaces de explicar el fenómeno encontrado. En primer lugar, el envejecimiento lleva asociado una pérdida de calidad y cantidad muscular, conocido como sarcopenia (23). A esto se le suma el efecto de la obesidad, teniendo presumiblemente estos individuos sarcodinapenia. Existe evidencia clara de que estos síndromes tienen efectos perjudiciales sobre la función contráctil del músculo empeorando la producción de fuerza y por ende la ejecución de movimientos (24–26). El deterioro neural asociado tanto a obesidad como a la sarcopenia también conlleva una peor sinergia musculo-tendinosa por lo que afectaría a la velocidad de la marcha (27). Y un último factor clave en esta base biológica sería la inflamación asociada tanto al envejecimiento como a la obesidad (28), la cual también se ha relacionado como factor perjudicial para la velocidad de la marcha (29).

Fuerza de prensión manual como moderador del efecto de la adiposidad sobre la dependencia (estudio 3)

Siguiendo la línea del estudio anterior donde encontramos el efecto moderador de la velocidad de la marcha entre la obesidad y la dependencia funcional, en este estudio hallamos similares efectos moderadores, pero ahora con otro componente de la condición física como la fuerza de prensión manual.

Concretamente el principal hallazgo de este estudio fue como la fuerza de prensión manual relativa al peso corporal tuvo un rol moderador entre el efecto nocivo de la obesidad central y la pérdida de independencia funcional. En este estudio participaron 4169 adultos mayores colombianos, por lo que supone una amplia muestra de población. La obesidad central fue evaluada por la ratio cintura altura.

Aquellos individuos que presentaban un mayor índice de cintura altura tenían mayor prevalencia de dependencia funcional. Estos hallazgos son soportados por estudio previos donde encontraron resultados similares en los que la obesidad central se relacionaba con una mayor dependencia funcional (19,30,31).

Por otra parte, también se encontró como la obesidad central se relacionaba con un peor rendimiento en el test de prensión manual. Este hallazgo es similar a otros estudios previos. Por ejemplo Carvalho et al encontró que la obesidad central se relacionaba con un deterioro de la fuerza muscular (32). Esto puede explicarse por el efecto que tiene la adiposidad sobre las funciones anabólicas de la testosterona, hormona del crecimiento o insulina (33–35). Otro factor influyente en esta relación es la producción de proteínas proinflamatorias (citoquinas) de acuerdo con el exceso de adiposidad, las cuales ya se ha señalado en diversos estudios su efecto perjudicial sobre las características del músculo y sus niveles de fuerza (36,37).

El principal hallazgo del estudio fue el efecto moderador de la fuerza de prensión manual relativa al peso corporal sobre el efecto perjudicial del exceso de adiposidad sobre el nivel de dependencia funcional. En este sentido se encontraron dos umbrales. El primero de ellos se situó por debajo de 0,35 kg/kg masa corporal, lo cual indica que aquellos adultos mayores que tengan obesidad central pero una fuerza de prensión manual por debajo de este valor, el efecto se la adiposidad se agrava. moderador. Por el contrario, aquellos que tengan una fuerza de prensión manual superior a 0,62 kg/kg masa corporal el efecto perjudicial mejoraría o incluso

desaparecería. Entre ambos umbrales encontramos una región no significativa por lo cual, aquellos individuos que presente obesidad central pero su fuerza se encuentre entre estos márgenes el efecto sobre la dependencia ni se agrava ni se mejora. Estos hallazgos pueden explicarse en los siguientes: en primer lugar la fuerza de prensión manual es un proxy de la calidad y cantidad muscular de todo el cuerpo (4,38). En segundo lugar, un exceso de adiposidad está asociado a un empeoramiento de la calidad y cantidad muscular debido a que la infiltración de tejido graso en el músculo empeora sus características contráctiles (39,40) y por tanto un peor rendimiento físico (41). En tercer lugar, el exceso de adiposidad está asociado con la proliferación de adipokinas proinflamatorias empeorando la salud muscular (42–44) así como el rendimiento motor (45). Por tanto, los resultados señalan la importancia de preservar un mínimo de fuerza muscular para el mantenimiento de la independencia funcional especialmente si los individuos padecen obesidad central. De acuerdo con la población estudiada, nuestros resultados arrojaron mantener un mínimo 0,35 kg/kg masa corporal de fuerza de prensión manual relativa al peso corporal para que los efectos no sean agravados por la obesidad central, siendo lo recomendable u óptimo una fuerza de prensión manual a partir de 0,62 kg/kg masa corporal.

Glucosa media la pérdida de fuerza muscular asociada al exceso de adiposidad (estudio 4)

El cuarto estudio que compone esta tesis doctoral complementa los hallazgos anteriores destacando como altos niveles de glucosa sanguínea como es la diabetes tipo 2 y sus efectos coadyuvantes, es mediador de la pérdida de fuerza muscular asociado al exceso de adiposidad central. De este modo cuando en los estudios anteriores hablábamos de los efetos moderadores como beneficiosos ante una asociación perjudicial, en este estudio señalamos como ante una relación adversa, tener un índice de glucosa elevado perjudicaría aún más si cabe dicha asociación.

El exceso de adiposidad se examinó mediante la circunferencia de cintura, una medida proxy fiable y válida del contenido de grasa corporal (46). Esta variable estaba estrechamente relacionada con un peor rendimiento muscular en la prueba de prensión manual. Este hallazgo lo respalda estudios previos donde encontraron resultados similares (32).

Otro hallazgo para destacar fue la relación existente el exceso de adiposidad y la presencia de diabetes mellitus tipo 2. En este sentido también son varios los estudios que soportan estos hallazgos (47,48).

En nuestro estudio, también encontramos una asociación inversa entre altos niveles de glucosa en sangre y un peor rendimiento muscular. En este sentido el test de prensión manual es una herramienta válida de la calidad y cantidad muscular siendo una herramienta fiable de la condición física en adultos mayores (49), por lo que un bajo rendimiento de fuerza de prensión manual es significativo de una baja condición física (50).

El principal hallazgo de este estudio fue el efecto mediador de la glucosa sobre el efecto perjudicial del exceso de adiposidad central sobre la fuerza muscular. Estudios previos similares no existen, sin embargo los hallazgos pueden explicarse en otros estudios donde se destacó como el exceso de adiposidad estaba relacionado con una baja calidad muscular en adultos mayores diabéticos (51). Parece ser que el envejecimiento junto al exceso de adiposidad podría jugar un factor clave en el deterioro muscular (4,52). Además un exceso tanto de tejido graso intramuscular como de glucosa en sangre alteraría la actividad del transportador de glucosa GLUT4 (53,54). Un factor clave para explicar el fenómeno estudiado es el efecto neuropático asociado a la diabetes tipo 2. En estudios previos realizados en adultos mayores diabéticos se encontró efectos neuropáticos en la musculatura de miembros distales (55,56) lo cual se traduce en una pérdida de fuerza muscular (57,58).

Nuestros resultados sugieren que elevados niveles de glucosa podrían empeorar la asociación entre el exceso de adiposidad central y una baja fuerza muscular.

Condición física, media el deterioro cognitivo asociado a la edad (estudio 5)

El último trabajo que compone este documento fue el hallazgo del efecto mediador de la condición física sobre la pérdida de la función cognitiva asociada a la edad. El efecto mediador explica que el deterior cognitivo afectado por el envejecimiento viene explicado en parte por una baja condición física. En el modelo, se incluyeron dos componentes de la condición física: la velocidad de la marcha y la fuerza de prensión manual. Ambos componentes son los dos más utilizados para valorar el nivel de condición física en adultos mayores (4,59). La fuerza muscular y velocidad de la marcha son considerados componentes de la condición física

predictores de salud, de este modo, tener bajos niveles de fuerza y/o velocidad de la marcha se ha relacionado con todas las causas de muerte, incluido cáncer (60,61).

Nuestros resultados indicaron una relación entre el envejecimiento y el declive cognitivo. En este sentido son muchos los estudios que indican resultados similares a los nuestros (62). También encontramos la relación inversa entre condición física y deterioro cognitivo. Concretamente, nuestros resultados indicaban como aquellos sujetos con una baja velocidad de la marcha y fuerza muscular, de acuerdo con los criterios utilizado por el EWGSOP2 (1,2), tenían hasta 3 veces más de probabilidad de sufrir deterioro cognitivo. En este sentido son muchos los estudios que indican similares resultados. Por ejemplo, hallazgos procedentes del estudio UK Biobank indican una fuerte relación entre baja fuerza muscular y declive en las funciones memorísticas y procesamiento del lenguaje (63). Sin embargo, hay estudios con resultados contradictorios a los encontrados por nosotros. Dichos estudios indican una relación bidireccional entre la condición física y el deterioro cognitivo. Sin embargo, los resultados no parecen ser del todo claros. Por ejemplo, el estudio longitudinal Baltimore los resultados indicaron que la relación entre la velocidad de la marcha y la función ejecutiva era bidireccional, sin embargo, solo la velocidad de la marcha predice cambios futuros en la función ejecutiva y la memoria, pero no al revés (64). También un estudio prospectivo se encontró que la disminución temprana de la velocidad de la marcha predijo la disminución de la orientación, la atención, el cálculo, el lenguaje y la memoria a corto plazo, pero la asociación entre la disminución temprana de la cognición y la disminución posterior de la velocidad de la marcha fue más débil (65). Por lo tanto, no hay evidencia sólida que apoye esta hipótesis.

Los hallazgos más importantes se vinculan con el modelo de mediación paralela diseñado. En este, se encontró que el efecto perjudicial de la edad sobre el deterioro cognitivo pasa en parte por tener una baja velocidad de la marcha y/o pobre fuerza muscular. Si bien, solo encontramos un estudio relacionado con el efecto mediador (66), existen mecanismos subyacentes que pueden explicar el efecto mediador de la condición física sobre el deterioro cognitivo. Distintos estudios han analizado el potencial efecto del ejercicio físico sobre las funciones cognitivas. Por ejemplo, se ha encontrado como programas de ejercicio físico aeróbico con una duración de entre 6 y 12 meses tiene importantes efectos positivos sobre la cognición (67–69). Los mecanismos tras esta mejora están relacionados con el efecto del ejercicio aeróbico sobre el aumento del tamaño del hipocampo y una mayor proliferación de la proteína Brain-Derived Neurotrofic Factor, encargada del crecimiento del tejido nervioso (70).El ejercicio de fuerza

también tiene efectos beneficiosos contra el deterioro cognitivo. Siguiendo esta línea trabajos como el de Yoo et al (71) o el de Mavros et al (72), destacan como existe una mejora tras un programa de ejercicio físico de fuerza sobre las funciones cognitivas en los adultos mayores. Estos cambios pueden estar explicados por modificaciones en la neuroplasticidad (73), la mejora de la perfusión cerebral (74) y reactividad neuronal (75), así como incremento en el tamaño del hipocampo (68) y mayor presencia de la proteína BDNF (76).

En resumen, nuestros resultados indican que tener niveles óptimos de fuerza muscular y velocidad de la marcha, atenúan el efecto perjudicial que tiene el envejecimiento sobre la cognición.

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CUARTA PARTE

Conclusiones

Estudio 1

La prevalencia de probable sarcopenia fue relativamente alta donde un 46,5% de los 5237 adultos mayores estudiados, presentaban este síndrome geriátrico. Los factores asociados indicaron que adultos mayores que presenten diabetes, osteoartrosis, artritis, déficit visual o auditivo o no cumplan el mínimo requerido de actividad física, mostraron una mayor presencia de probable sarcopenia.

Estudio 2

La velocidad de la marcha modera la relación inversa entre un alto IMC y el nivel de dependencia. El punto de corte se estableció superior a 1.06 m/s a partir del cual el efecto perjudicial sobre la dependencia podría ser aliviado.

Estudio 3

La fuerza de prensión manual moderaba el efecto adverso del exceso de adiposidad central sobre el nivel de dependencia. En nuestro estudio se encontró que aquellos adultos mayores que presentaban una fuerza de prensión manual superior a 0,62 kg/kg de peso corporal el efecto adverso de la adiposidad sobre la dependencia se mitiga o incluso puede llegar a desaparecer.

Estudio 4

El nivel de glucosa en sangre mediaba el efecto adverso del exceso de adiposidad sobre la fuerza muscular.

Estudio 5

La velocidad de la marcha y la fuerza de prensión manual median el efecto adverso del envejecimiento sobre la función cognitiva.

Study 1

The prevalence of probable sarcopenia was relatively high, where 46.5% of the 5237 older adults studied had this geriatric syndrome. Associated factors indicated that older adults who have diabetes, osteoarthritis, arthritis, visual or hearing deficits, or do not comply with the required minimum of physical activity show a more significant presence of probable sarcopenia.

Study 2

Gait speed moderates the inverse relationship between high BMI and dependency. The cut-off point was established above 1.06 m / s, from which the detrimental effect on dependence could be alleviated.

Study 3

Handgrip strength moderated the adverse effect of excess central adiposity on the level of dependence. Our study found that in older adults who presented a handgrip strength above 0.62 kg/kg of body weight, the adverse effect of adiposity on dependence is mitigated or may even disappear.

Study 4

Blood glucose level mediated the adverse effect of excess adiposity on muscle strength.

Study 5

Gait speed and handgrip strength mediate the adverse effect of aging on cognitive function.

QUINTA PARTE

Perspectivas de futuro y recomendaciones

Estudio 1

Considerar la valoración de probable sarcopenia en adultos mayores ayudará a la detección de futuros eventos adversos asociados a la sarcopenia.

Se recomienda en futuros estudios el estudio de los factores asociados a la probable sarcopenia utilizando la metodología aportada por el grupo de expertos del EWGSOP.

En la prescripción de ejercicio físico en adultos mayores que presenten diabetes, osteoporosis, artritis, déficit visual o auditivo o no cumplan el mínimo requerido de actividad física, debería considerarse significativamente el entrenamiento de la fuerza muscular.

Estudio 2

En adultos mayores considerar la valoración de la velocidad de la marcha poniendo en valor la prescripción de ejercicio físico en aquellos que presenten sobrepeso u obesidad.

La velocidad de la marcha debería ser eje en los programas de ejercicio físico para adultos mayores alcanzando los mínimos establecidos de 1,06 m/s encontrados en este estudio, especialmente en sujetos con alto IMC.

Estudio 3

En futuros estudios examinar si los umbrales propuestos en este estudio son óptimos para el mantenimiento de la capacidad funcional en adultos mayores con exceso de adiposidad.

Incluir en los programas de ejercicio físico el entrenamiento de la fuerza muscular hasta alcanzar los mínimos encontrados en este estudio.

Estudio 4

En futuros programas para adultos mayores priorizar el ejercicio físico y una dieta saludable con el fin de reducir la acumulación de grasa y una glucosa elevada para evitar la pérdida de calidad y cantidad muscular.

Estudio 5

En estudios longitudinales sería conveniente estudiar la relación y momento temporal del declive de la velocidad de la marcha y la fuerza muscular con el comienzo del deterioro cognitivo.

A partir de los resultados encontrados destacamos las siguientes recomendaciones para un envejecimiento activo y saludable:

Recomendaciones para un envejecimiento saludable

1. **En líneas generales, la práctica de ejercicio físico, por adultos mayores, guiado por profesionales de la Ciencias del Deporte, debe ser obligatorio y no opcional para conseguir un envejecimiento saludable.**

2. **Incluir el entrenamiento de la velocidad de la marcha y de la fuerza muscular en futuros programas de ejercicio físico en adultos mayores para un envejecimiento saludable, teniendo como objetivo superar los umbrales propuestos en nuestros hallazgos.**

3. **Considerar tanto la velocidad de la marcha y como de la fuerza muscular como ingredientes activos ante cualquier tratamiento médico relacionado con comorbilidades típicas en adultos mayores.**

4. **Emplear la valoración de la probable sarcopenia en la práctica clínica como método de detección temprana de la sarcopenia.**

ANEXOS

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Original Study

High Prevalence of Probable Sarcopenia in a Representative Sample From Colombia: Implications for Geriatrics in Latin America

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Keywords:
Sarcopenia
associated factors
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A B S T R A C T

Objectives: The European Working Group on Sarcopenia in Older People 2 (EWGSOP2) recently defined the new concept of probable sarcopenia to help improve screening and prevent future sarcopenia. We investigated the prevalence of probable sarcopenia, defined as weak grip strength, in community-dwelling older Colombian adults, and examined the long-term associated conditions.
Design: Cross-sectional study.
Setting: Urban and rural Colombian older adults from the "Estudio Nacional de Salud, Bienestar y Envejecimiento (SABE) study".
Participants: 5237 Colombian older adults aged ≥60 years.
Measurements: Probable sarcopenia was assessed following the cut-off points for weak grip strength recommended by EWGSOP2 guidelines. Odds ratios (ORs) of the relationship between long-term conditions and probable sarcopenia were determined using logistic regression.
Results: The prevalence of probable sarcopenia defined as weak grip strength was 46.5% [95% confidence interval (CI), 45.1-47.8]. Physical inactivity (OR 1.35, 95% CI 1.14-1.59); diabetes (OR 1.32, 95% CI 1.11-1.56); and arthritis, osteoarthritis, and rheumatism (OR 1.44, 95% CI 1.25-1.67) were independently associated with probable sarcopenia.
Conclusions and Implications: We found that almost half of all the Colombian older adults in our sample had probable sarcopenia. Individuals with physical inactivity, diabetes, arthritis, or osteoarthritis and rheumatism had a higher prevalence of probable sarcopenia. Probable sarcopenia is clinically highly relevant, and several of the factors associated with this condition are potentially preventable, treatable, and reversible.

Sarcopenia is characterized by the progressive and generalized loss of muscle mass and function (strength and performance).[1] There is an extensive body of evidence for an association between sarcopenia and various health problems. Patients with sarcopenia have a poor quality of life and are more likely to have a higher incidence of falls, injuries, and hospitalizations than individuals with healthy muscle mass.[2] Sarcopenia is also associated with diabetes,[3] cardiovascular illness,[4] depression,[5] and greater dependency.[6] Accordingly, preventing sarcopenia or delaying its appearance is a clinical aspiration, as its prevalence presents a major challenge for public health.[7] Occurring commonly as an age-related process, the incidence of sarcopenia rises

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sharply after the age of 70 years, although the decline in physical performance starts decades before.

Recent studies have found that sarcopenia can be observed even in children and adolescents in association with health problems.[8,9] Recently, the European Working Group on Sarcopenia in Older People 2 (EWGSOP2) introduced the new concept of probable sarcopenia,[10] which is defined as low muscle strength based on poor performance in the grip strength test or chair rise test, or both, and arises from the need for a diagnosis when it is impossible to measure muscle mass. These new guidelines emphasize that, as indicated previously,[1] sarcopenia primarily is an age-related condition but can also occur at younger ages in combination with chronic conditions.

The prevalence of sarcopenia and its relationship with chronic conditions has been examined in detail, with several studies finding an inverse relationship between grip strength and the number of chronic health conditions.[11,12] However, comparatively little research has focused on the relationship between associated factors and probable sarcopenia. In Europe, Dodds et al[13] and Sousa-Santos[14] have analyzed the relationship between probable sarcopenia and multimorbidity in middle-aged and older adult populations. In Latin America, the English Longitudinal Study of Aging determined the prevalence and associated factors using the cut-off values recommended by the EWGSOP2 to screen for probable sarcopenia.[15] However, because the concept of probable sarcopenia is new and the literature regarding this syndrome is scarce, more studies are needed to determine the prevalence of probable sarcopenia and the factors associated with its development.

Using data from a national cross-sectional survey conducted in Colombia, the "Estudio Nacional de Salud, Bienestar y Envejecimiento (SABE) study,"[16] our aims were, first, to describe the prevalence of probable sarcopenia using the updated guidelines in a sample of older adults and, second, to investigate the relationship between probable sarcopenia and its associated factors.

Methods

Design, Setting, and Participants

Data were obtained from the SABE Colombia survey conducted in 2015 by the Epidemiological Office of the Ministry of Health and Social Protection of Colombia (https://www.minsalud.gov.co/). Details of the study have been published elsewhere.[16] The study included a sample of the Colombian population aged ≥60 years, residing in urban and rural households in all region of the country, who were non-institutionalized and Spanish speakers. Institutional review boards involved in developing the SABE-Colombia study (University of Caldas, ID protocol CBCS-021-14; and University of Valle, ID protocol 09–014 and O11–015) reviewed and approved the study protocol. The Human Subjects Committee at the Pontificia Universidad Javeriana approved the secondary analysis study protocol (ACTA ID 20/2017–2017/180, FM-CIE-0459- 17).

The estimated sample size was 24,553 individuals, assuming an 80% response of the target sample of 30,691 individuals.[16] The sample was probabilistic, clustered, stratified, and multistage. The sample size for these cities, 3500 individuals per city, was added to the national value by accumulating the sample values for the subregion, region, and country. The original sample size achieved (including 244 municipalities) was 23,694 elderly Colombians.[16] For this subsample analysis, 86 municipalities were selected, including the 4 large cities (Bogota, Cali, Medellin, and Barranquilla), for the application of functionality tests and muscle strength assessment. The same formula as for the subsample was used, assuming an expected proportion of 0.07, a design effect of 1.2, a relative standard error of 0.065, and a nonresponse percentage of 20%, obtaining a sample of 4525 people 60 years of age or older.[16] The selection of older adults was carried out using systematic sampling, by randomly selecting 2 of 5 individuals of the general sample. Flow-chart diagram is detailed in Figure 1.

Anthropometric Measurements

Trained personnel collected the data. Height and body weight were measured with a portable stadiometer (Seca 213; Seca, Hamburg, Germany) and an electronic scale (Kendall graduated platform scale). Body mass index[17] was calculated as weight (in kilograms) divided by height (in meters) squared and categorized following the Word Health Organization classification for Latin American populations.[18] Waist circumference measurements were taken at the end of a normal expiration to the nearest 0.1 cm, measuring from the middle point between the lower border of the rib cage and the iliac crest mid-axillary line.

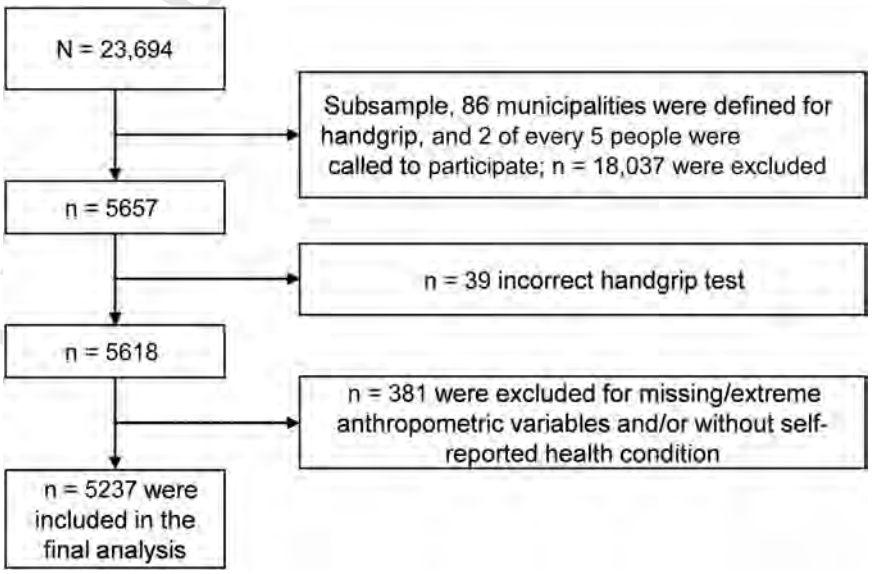

Fig. 1. Flow chart shows the study sample selection from the Colombian Health and Wellbeing and Aging Survey (SABE) 2015. All analyses presented here were based on 5237 surveyed participants, each with complete handgrip and long-term condition data.

Assessment of Probable Sarcopenia

The presence of probable sarcopenia was assessed following the cut-off points for weak grip strength recommended by the EWGSOP2 guidelines: <27 kg in men and <16 kg in women.[10,13,19] Grip strength was measured using a Takei dynamometer (Takei Scientific Instruments Co, Tokyo, Japan), which was calibrated before testing to ensure the accuracy of the results. Subjects were asked to perform the task (with elbow joint in full extension) while standing if possible and were given a practice trial to ensure comprehension of the procedure. The grip tests were performed 2 to 3 times on each hand, alternating hands between each trial, and the mean value was recorded. Testers ensured a total of 60 seconds of rest between trials on the same hand.

Potential Associated Factors

To develop the quantitative component, we included the following potential associated factors: socioeconomic data, including age, sex, ethnicity, socioeconomic status, urbanicity, as well as cognition, functionality, and medical and health conditions. For older adults, the questions were answered by a companion or caregiver when the score obtained by the test was lower than 13 points (Folstein Mini-Mental Test).[20,21] For lifestyle characteristics, personal habits regarding alcohol intake and cigarette smoking were also recorded. For the "proxy physical activity" report, the following questions were asked: (1) "Have you regularly exercised, such as jogging or dancing, or performed rigorous physical activity at least 3 times a week for the past year?" (2) "Do you walk at least 3 times a week between 9 and 20 blocks (1.6 km) without resting?" and (3) "Do you walk at least 3 times a week 8 blocks (0.5 km) without resting?" Participants were considered physically active if they responded affirmatively to 2 of the 3 questions.[22] Medical information including multimorbidity, as well as chronic conditions adapted from the original SABE study, was assessed by asking the participants if they had been medically diagnosed with hypertension, diabetes, chronic obstructive pulmonary disease, cardiovascular disease (heart attack, angina) stroke, cancer, arthritis, osteoporosis, cholesterol, triglycerides, and mental or sensory problems. Lastly, information on ethnicity (indigenous; black, "mulatto," or Afro-Colombian, white; and others), living area (rural or urban), and socioeconomic status (levels I and II: low; levels III and IV: middle; and levels V and VI: high) were obtained and used as covariables.

Statistical Analysis

Data were analyzed using JASP open-source software for statistical analysis (JASP Team 2020 v 0.12.2) for Windows. Continuous variables were expressed as mean ± standard deviation. Categorical variables were expressed as frequencies and percentages. The normality of the variables was verified using Kolmogorov-Smirnov tests and probability plots. The sample consisted of 2 groups: no sarcopenia (normal grip strength) or probable sarcopenia (weak grip strength). Mann-Whitney *U* tests were applied to identify significant differences in continuous variables, and chi-squared tests were used for categorical variables between groups.

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to explore the relationship between each category of associated factors and probable sarcopenia, adjusting for potential confounding variables such as age, sex, socioeconomic status, body mass index, and waist circumference.

Results

A total of 5237 participants had completed data for grip strength, anthropometric measures, and the presence of long-term conditions (see the flowchart in Figure 1). Of the total sample, 2434 individuals showed the presence of probable sarcopenia according to the EWGSOP2 definition, representing 46.5% (95% CI 45.1%-47.8%). By sex, 1041 men (47.9%, 95% CI 45.8%-50.0%) and 1393 women (45.4%, 95% CI 43.6%-47.2%) presented with probable sarcopenia (Table 1).

The mean age of the participants was 70.4 (7.8) years, and the majority (52%) were 60-69 years old. The distribution of probable sarcopenia across age groups was similar between the ages of 60-69 and 70-79 years. Most of the individuals in the no-sarcopenia (healthy muscular strength) group (65%) were 60-69 years old. Individuals in the lowest socioeconomic status group (levels I and II) had the highest prevalence of probable sarcopenia (76.2%). Finally, a high prevalence of probable sarcopenia was found in individuals of white ethnicity living in urbans areas.

According to anthropometric and lifestyle characteristics and long-term health conditions (Table 1), body mass index, waist circumference, and calf circumference were all slightly higher in nonsarcopenic individuals than in probable sarcopenic peers. As expected, similar results were obtained for muscular strength, with nonsarcopenic individuals showing better absolute and relative grip strength to body weight values. Regarding long-term health conditions, individuals with probable sarcopenia had a higher prevalence of diseases than nonsarcopenic individuals: hypertension 59.2%, diabetes 18.2%, arthritis 31.5%, cholesterol 47.7%, and altered triglycerides 36.3%. Finally, the probable sarcopenia group had a greater number of individuals who failed to achieve the minimum level of physical activity. Based on the data, physical inactivity was the most important modifiable risk factor, and hypertension was the most prevalent long-term illness in individuals with probable sarcopenia.

The results from logistic regression analyses are shown in Figure 2. Seven long-term health conditions were significantly related to probable sarcopenia. Specifically, individuals not accomplishing the minimum level of physical activity were more likely to have probable sarcopenia (OR 1.35, 95% CI 1.14-1.59). Similarly, those with diabetes (OR 1.32, 95% CI 1.11-1.56); mental disorders (OR 1.28, 95% CI 1.03-1.59); arthritis, osteoarthritis, and rheumatism (OR 1.44, 95% CI 1.25-1.67); osteoporosis (OR 1.27, 95% CI 1.05-1.67); vision (OR 1.24, 95% CI 1.07-1.42); and hearing problems (OR 1.22, 95% CI 1.06-1.42) were more likely to have probable sarcopenia. Other chronic long-term conditions related to cardiovascular health, triglycerides, cholesterol, or stroke were not significantly associated with probable sarcopenia.

Discussion

In the present study, we examined the prevalence of probable sarcopenia and its associated factors in a nationally representative sample of older adults. We found that probable sarcopenia has a high prevalence in Latin American older adults and is associated with several chronic conditions and physical inactivity. To our knowledge, this is the first study in a Latin American country to use the new diagnosis of probable sarcopenia and to assess its relationship with associated factors. Our findings highlight that the prevalence of probable sarcopenia is 46.5% (95% CI 45.1%-47.8%) in Colombian older adults and is associated with several risk factors such as physical inactivity, vision, hearing and mental disorders, and also osteoporosis, arthritis, and diabetes.

Several studies have reported the prevalence of probable sarcopenia in different countries using the handgrip strength cut-off points recommended by the EWGSOP2 guidelines (men <27 kg; women <16 kg). For instance, Dodds et al[13] found a prevalence of 5.3% in British adults aged 40-70 years, whereas Pal et al[23] found a prevalence of 14.6% in Indian adults aged ≥20 years (mean age 44 years). A study in Portugal[14] found a prevalence of probable sarcopenia of 36% in adults aged ≥65 years. Using data from the Brazilian Longitudinal Study of Aging, Borges[24] found a prevalence of 17.6% among men and

Table 1
Participants' Sociodemographic Characteristics; Anthropometric, Lifestyle, and Long-Term Conditions; and Probable Sarcopenia Status (n = 5237)

Characteristics	Total n (%)	Presence of Probable Sarcopenia, (n = 2434; 46.5%)	No Sarcopenia, (n = 2803; 53.5%)
Age, y	70.4 (7.8)	73.2 (8.4)	68.06 (6.3)
Age group			
60-69 y	2744 (52.4)	921 (37.8)	1823 (65.0)
70-79 y	1717 (32.8)	909 (37.3)	808 (28.8)
≥80 y	776 (14.8)	604 (24.8)	172 (6.1)
Sex			
Male	2172 (41.5)	1041 (42.8)	1131 (40.3)
Female	3065 (58.5)	1393 (57.2)	1672 (59.7)
Socioeconomic status			
Level I or II: low	3985 (76.1)	1855 (76.2)	2130 (76.0)
Level III or IV: middle	1207 (23.0)	565 (23.2)	642 (22.9)
Level V or VI: high	45 (0.9)	14 (0.6)	31 (1.1)
Living area			
Urban	4055 (77.4)	1897 (77.9)	2158 (77.0)
Rural	1182 (22.6)	537 (22.1)	645 (23.0)
Ethnicity			
Indigenous	313 (7.1)	135 (7.2)	178 (6.9)
Black or "mulatto"	428 (9.7)	165 (8.8)	263 (10.3)
White	1388 (31.3)	619 (33.0)	769 (30.0)
Others	2306 (52.0)	954 (50.9)	1352 (52.8)
BMI categories			
Underweight	101 (1.9)	57 (2.3)	44 (1.6)
Normal weight	1443 (27.6)	737 (30.3)	706 (25.2)
Overweight	1926 (36.8)	847 (34.8)	1079 (38.5)
Obese	1274 (24.3)	461 (18.9)	813 (29.0)
Missing	493 (9.4)	332 (13.6)	161 (5.7)
Anthropometric and muscle strength			
Waist circumference, cm	92.4 (11.1)	91.3 (11.1)	93.3 (10.9)
Calf circumference, cm	34.5 (3.8)	33.7 (3.7)	35.1 (3.8)
BMI	27.4 (5.01)	26.7 (4.9)	27.9 (4.9)
Grip strength, kg	20.8 (8.5)	15.2 (5.3)	25.7 (7.8)
Associated factors			
Smoke	548 (10.5)	237 (9.7)	311 (11.1)
Alcohol intake	645 (12.3)	250 (10.2)	395 (14.1)
Non-Physically active	4313 (82.5)	2095 (86.2)	2218 (79.2)
Hypertension	2929 (56.0)	1441 (59.2)	1488 (53.1)
Diabetes	868 (16.6)	442 (18.2)	426 (15.2)
History of cancer	259 (5.0)	124 (5.1)	135 (4.8)
Respiratory diseases Cardiovascular	568 (10.9)	302 (12.4)	266 (9.5)
Stroke	749 (14.3)	370 (15.2)	379 (13.5)
Arthritis, osteoarthritis, rheumatism	225 (4.3)	128 (5.3)	97 (3.5)
Osteoporosis	1458 (27.9)	766 (31.5)	692 (24.7)
Cholesterol	644 (12.4)	349 (14.3)	295 (10.5)
Triglycerides	2536 (48.7)	1161 (47.7)	1375 (49.1)
Mental	1952 (37.8)	884 (36.3)	1068 (38.1)
Hearing problems	465 (8.9)	238 (9.8)	227 (8.1)
Vision problems	1300 (24.9)	722 (29.7)	578 (20.6)
	2902 (65.5)	1276 (52.4)	1626 (58.0)

BMI, body mass index.
Data are expressed as frequencies and percentage.
*Frequencies in associated factors are reported as "yes."

17.7% among women in 8396 individuals aged ≥50 years. Lastly, a study in an Australian population aged ≥60 years[25] reported a mean prevalence of probable sarcopenia of 13.4% and 2.7% for men and women, respectively. It is clear that our results show a higher prevalence of probable sarcopenia than the aforementioned studies. Considering that decreases in muscular strength are closely related to age, the age range of individuals tested might explain this difference. Our study tested individuals aged ≥60 years, whereas the studies in the United Kingdom, India, and Brazil are based on a population aged ≥40 years. Also, our study is based on a nationally representative sample of older adults (n = 5237), and so our findings should be considered more robust.

Also worthy of note is the high proportion of overweight and obese older adults in our cohort. Latin Americans are more predisposed to overweight or obesity due to sociocultural, diet, or genetic factors.[26] Our findings are of clinical relevance, as obese individuals showed probable sarcopenia using a functional test based on handgrip strength. This points to the potential clinical utility of the handgrip test, now also to evaluate older adults or future sarcopenia. We found that physical inactivity and some chronic conditions might negatively influence the presence of probable sarcopenia. Physical inactivity seems to be the most damaging factor for muscle deterioration and consequent probable sarcopenia. Several studies have reported that physical inactivity is the primary risk factor for muscle loss and weakness,[27–29] whereas regular physical activity attenuates the aging effect on muscular health.[30] Accordingly, the Word Health Organization recommends at least 3 days per week of physical activity for adults and older people. As seen from our results, the proportion of individuals with probable sarcopenia and physical inactivity is relatively high, which could explain, in part, the higher prevalence of probable sarcopenia found in this study. Diabetes was also strongly associated with probable sarcopenia in our sample. Diabetes is known to increase the risk of developing sarcopenia in older people. In the Korean Sarcopenic Obesity Study, diabetes was found to be an

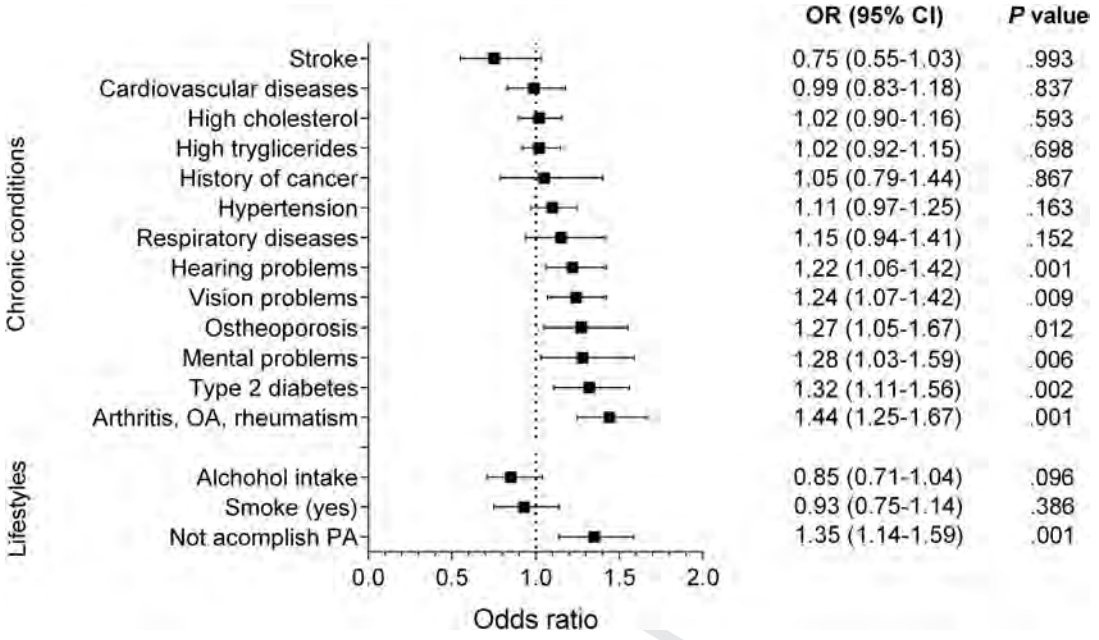

Fig. 2. Independent associations between probable sarcopenia and each category of chronic conditions. Odds ratios obtained through the logistic regression model showing an independent association between having +1 or more chronic condition in each category and probable sarcopenia. Analysis was adjusted for the following covariates: Sex, age, BMI, and WC. BMI, body mass index; OA, osteoarthritis; PA, physical activity; WC, waist circumference.

important predictor of sarcopenia, with more than twice the prevalence of sarcopenia in individuals with diabetes than in nondiabetic individuals.[31] Likewise, the English Longitudinal Study of Aging showed an increase in probable sarcopenia in men with diabetes but not women with diabetes 8 years later.[32] The main component involved in muscle strength deterioration in patients with diabetes (ie, diabetic myopathy) seems to be low-grade systemic inflammation.[33]

Osteoporosis, arthritis, osteoarthritis, and rheumatism were also factors associated with probable sarcopenia in our study. The evidence regarding these relationships is not clear. Until recently, the widely held view was that sarcopenia precedes osteoporosis, as reduction in muscle function (such as with sarcopenia or cachexia) leads to reductions in bone mass. However, during the last decade the concept of a "muscle-bone" unit has gained acceptance. Bone and muscle tissue comprise a unit of paracrine and endocrine exchange by adapting their response to loading, aging, and to additional factors such as adipose tissue,[34,35] and share interconnecting biochemical pathways.[34] Several studies have demonstrated that individuals show muscle weakness after hip fracture (reviewed in Yeung et al[36]). In a similar manner, the relationship between sarcopenia and osteoporosis cannot be understood without involving the cartilage and that a deterioration of the latter is also closely linked to sarcopenia and osteoporosis.[34,37] Accordingly, all 3 components are interrelated as a triad of cofactors.

We also found that sensory disorders were related to sarcopenia. Aging is associated with the development of hearing and visual deterioration,[38] leading to functional limitations, and often resulting in a complicated relationship with cognitive disturbance and mental health impairment.[38] Therefore, a reduction in input information may lead to decreases in proprioception and balance during walking, affecting mobility and, ultimately, physical activity. This might explain the probable sarcopenia in individuals with these characteristics. Also, the mean age of participants in our study was 70.4 years, and the prevalence of sensory impairment, mainly visual, was high.

Our findings confirm the importance of modifiable risk factors for controlling probable sarcopenia among older adults. Our data show that physical inactivity increases the odds of having probable sarcopenia. It is nevertheless remarkable that diabetes, osteoporosis, arthritis, and sensory problems significantly affect probable sarcopenia development. Early detection of muscle weakness using a simple clinical practice tool, such as handgrip strength, might help prevent or alleviate future risks in subjects with these health conditions. For example, sarcopenia is associated with functional dependence, one of the main factors affecting disability and quality of life.[39] Therefore, knowing the factors associated with probable sarcopenia would help health officials focus on screening for probable sarcopenia in older adults with chronic conditions.

Our study has several strengths, including the large sample size of older adults within a nationally representative proportion of persons aged ≥60 years, and the novelty of using a simple and practical method (handgrip) to screen for probable sarcopenia. However, several limitations should be considered. First, the work was based on baseline data from a cross-sectional study, and it is not possible to infer causality. Second, there were no objective body composition measures to compare the group with probable sarcopenia to the group with confirmed sarcopenia. Third, the associated factors were self-reported by participants, so different types of response biases may have been introduced.

Conclusions and Implications

There is a high prevalence of probable sarcopenia in older Latin American individuals that might be influenced by several factors. Older adults with diabetes, osteoporosis, arthrosis, and sensory disorders and those who do not accomplish the minimum of physical activity recommended have a higher prevalence of probable sarcopenia. Therefore, older adults with these characteristics should be the target of prevention strategies.

Uncited Table

Supplementary Table 1.

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Supplementary Table 1
Independent Associations Between Probable Sarcopenia and Sociodemographic Characteristics

	OR (95% CI)
Age group, y	
60-69	1
70-79	2.16 (1.89, 2.47)
≥80	6.33 (5.12, 7.81)
Sex	
Male	1
Female	0.95 (0.83, 1.00)
Socioeconomic status	
Level I or II: low	1
Level III or IV: middle	0.96 (0.83, 1.11)
Level V or VI: high	0.48 (0.23, 0.99)
Living area	
Urban	1
Rural	0.87 (0.75, 1.01)
Ethnicity	
Indigenous	1
Black or "mulatto"	0.80 (0.58, 1.12)
White	1.12 (0.84, 1.47)
Others	0.93 (0.75, 1.29)

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Gait speed moderates the adverse effect of obesity on dependency in older Colombian adult

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ABSTRACT

Introduction: Gait speed worsens with the presence of obesity, and is a powerful marker of functional dependence. Accordingly, gait speed could be a factor that improves or worsens the relationship between obesity and dependence in activities of daily living (ADL). However, to date this potential role has not been examined and the minimum gait speed threshold in the relationship between obesity and ADL is not known. The aim of this study was to determine whether speed moderates the association between obesity and dependence in ADL, and also define the gait speed threshold of this relationship.

Methods: A total of 20,507 community-dwelling older adults from a cross-sectional analysis of national survey data – the Colombian Health, Well-being and Aging study (SABE, 2015) – were surveyed. The research data were collected using structured questionnaires, including basic information, ADL measured using the Barthel Index, body mass index, and gait speed (3 m). The Johnson-Neyman technique was applied to determine the gait speed threshold adjusted for age, sex and comorbidities.

Results: Regression analysis showed a significant detrimental effect of obesity on dependence in ADL, which was moderated by gait speed ($\beta = 0.081$; 95%CI: 0.045 to 0.117; $p < 0.001$). Adjusted for major covariates, the Johnson-Neyman technique defined two gait speed thresholds: < 0.77 m/s, indicating an aggravated adverse effect; and > 1.06 m/s, indicating a positive effect.

Conclusions: The adverse effect of obesity on dependence in ADL is moderated by gait speed. Considering these thresholds, the distribution of older adults in each of the proposed areas of significance were: below 0.77 (m/s) = 14,324 (70.0%), above 1.06 (m/s) = 1553 older adults (7.5%) and between areas = 4630 older adults (22.5%).

1. Introduction

Obesity is the result of complex genetic and environmental interactions that lead to an excess of body fat, which has an unfavorable effect on health (Purnell, 2018) and increases the risk of several diseases including hyperlipidemia and type 2 diabetes mellitus (Maffetone et al., 2017), as well as morbidity and mortality (Abdelaal et al., 2017) among the elderly. Obesity in the elderly may also accelerate the decline of functional performance (Hardy et al., 2013) and can adversely affect activities of daily living (ADL) (Kumar et al., 2015), which is also related to high body mass index (BMI). In this context, gait speed, balance and muscle strength are central components of an individuals's functional ability to perform basic ADL (Cesari et al., 2018), and the assessment of gait speed is a valid and reliable method to detect cognitive impairment, functional independence, and health state (Garcia-Pinillos et al., 2016).

Abbreviations: ADL, activities of daily living; SABE, 2015, Colombian Health, Well-being and Aging study; BMI, body mass index; WHO, World Health Organization

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In recent years, there has been an increasing interest in gait speed as a measure of functional status in the elderly, as highlighted by some key findings. First, there is a strong association between obesity and decline in gait speed in older adults (Beavers et al., 2013; Mendes et al., 2018); second, gait speed predicts the reduction in dependency in ADL (Hong et al., 2016; López-Teros et al., 2014; Perera et al., 2016). Finally, gait speed is a predictor of mortality, cardiovascular disease and cancer (Veronese et al., 2018). In this line, a gait speed of 0.80 m/s is considered as the threshold to predict adverse health outcomes in older people (Abellan van Kan et al., 2009; Middleton et al., 2015). Furthermore, the assessment of gait speed is a valid and reliable method to detect cognitive impairment, functional independence, and health state (Garcia-Pinillos et al., 2016).

Disability in ADL is considered the most serious form of disability measure, and is defined as difficulty in undertaking activities in any areas of daily life because of a health or a physical condition (Portegijs et al., 2016). Evidence suggests that obese older adults typically have a reduced physical performance to body mass ratio compared with non-obese peers, particularly for tasks that require lower extremity strength, such as walking and rising from a chair (Cesari et al., 2018).

The interaction between obesity and physical disability has been the focus of investigation in both epidemiological and clinical contexts (Lv et al., 2018). In this sense, the subset of older adults with excess body fat appears to be at the greatest risk for physical disability, and data show that high body weight and BMI are associated with increased risk for functional impairment and disability (Alley and Chang, 2007; Berraho et al., 2010). Therefore, both obesity and functional impairment in ADL places older adults at high risk for adverse clinical outcomes including disability, hospitalization, and ultimately mortality (Al Snih et al., 2007; Lang et al., 2008; Wee et al., 2011).

Irrespective of how disability in ADL is measured (Lv et al., 2018), many studies have addressed the association between BMI and disability in ADL at older ages, and both cross-sectional (Alley and Chang, 2007; Berraho et al., 2010; Chen et al., 2002) and longitudinal studies (Al Snih et al., 2007; Lang et al., 2008; Wee et al., 2011) have consistently found that excess body fat is an independent risk factor for disability in ADL in older adults. Gait abnormalities due to excess body fat result in reduced gait speed, distance, and efficiency, leading to significantly limited functional performance and increase the energy cost (in over 30%) (Ko et al., 2010; Lai et al., 2008; Laroche et al., 2015; LaRoche et al., 2011). Also, the stability during the walk is weakens affecting to spatiotemporal adaptations, which can lead to falls and injuries (Forhan et al., 2013). When obesity is combined with increased disability or musculoskeletal disorders, the obesity cycle is perpetuated by encouraging sedentary behavior for prolonged periods. Therefore, excess body fat can affect to disability in the ADL being the gait performance the modulator of these effect.

Nonetheless, in these contexts, it is necessary to know under what circumstances a certain effect is produced or not. Against this background, moderation analysis can be used to test the relationship between two variables as a function of a third, moderator variable (Miller et al., 2013). Similarly, advanced statistical methods for example Johnson-Neyman procedures (Miller et al., 2013), can provide a region of significance or threshold of moderator values between a relationship. Little is known regarding the relationship between BMI and disability among the elderly and a "plausible" determinant of physical performance (gait speed). Based on prior research, we tested the moderation effect of gait speed between the adverse effect of BMI on functional dependence in ADL, and evaluated the gait speed thresholds that moderated negatively or positively that effect. This is particularly relevant for older adults, who have lower physical performance, greater adiposity and lower ADL functioning relative to their healthy counterparts.

Accordingly, the aim of this study was twofold: to first examine whether gait speed moderates the association between weight status and dependency in ADL; and secondly, to determine the gait speed threshold regarding this relationship.

2. Methods

2.1. Study design, setting, and participants

This study is part of the 2015 SABE study Survey on Health, Well-Being, and Aging in Latin America and the Caribbean, which is a multicenter project conducted by the Pan-American Health Organization and supported by the Epidemiological Office of the National Health Ministry in Bogotá, Colombia (https://www.minsalud.gov.co/). Details of the survey have been published elsewhere (Gomez et al., 2016).

Institutional review boards involved in developing the SABE-Colombia study (University of Caldas, ID protocol CBCS-021-14, and University of Valle, ID protocol 09–014 and O11–015) reviewed and approved the study protocol. Written informed consent was obtained from each individual before inclusion and completion of the first examination. Permissions and details are available at https://www.minsalud.gov.co/. The study protocol of the secondary analysis was approved by the Human Subjects Committee at the Pontificia Universidad Javeriana (ACTA ID 20/2017–2017/180, FM-CIE-0459-17).

This was a secondary analysis the SABE observational study. The estimated sample size was 24,553 individuals, assuming an 80% response of the target sample of 30,691 individuals (Gomez et al., 2016). The original sample size achieved (including 244 municipalities) was 23,694 elderly Colombians. A total of 20,507 remained in the present analysis after excluding participants with extreme values and outliers for gait speed (n = 2375), body mass index (n = 469), and Barthel index (n = 343) (see Fig. 1).

Data collection staff were trained by the research teams of the coordinating centers (Universities of Caldas and Valle) for face-to-face interviews and physical measurements. The target population for SABE-Colombia included all adults aged 60 years and above residing in households. Following conventional practice for population surveys, institutionalized persons (of prisons, jails, nursing homes, and long-term or dependent care facilities) were excluded.

2.2. Measures

Anthropometry measurements included height and body weight, which were measured with a portable stadiometer (SECA 213®, Hamburg, Germany) and an electronic scale (Kendall graduated platform scale), respectively. BMI (de Onis and Habicht, 1996) was

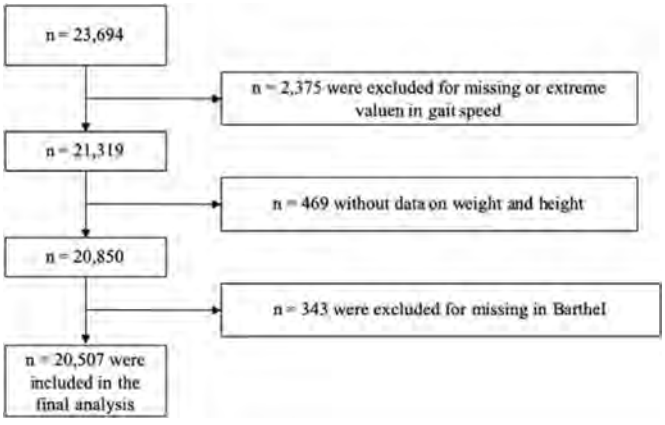

Fig. 1. Flow chart showing the selection of the study sample from the SABE 2015 Survey. All analyses presented in this paper are based on 20,507 participants with complete data on anthropometric, gait speed, Barthel index and covariables.

estimated in kg/m^2 from the measured weight and height. Underweight (BMI < 18.5 kg/m^2), healthy weight (18.5–24.9 kg/m^2), overweight (BMI ≥ 25 kg/m^2) and obese (BMI ≥ 30 kg/m^2) were defined according to the World Health Organization (WHO) recommendations for Latin-American populations (National Clinical Guideline Centre. Obesity Identification, assessment and management of overweight and obesity in children, young people and adults Partial update of CG43 Methods, evidence and recommendations Obesity (update) Contents, 2014). The self-reported comorbidities or medical conditions category was assessed by asking the participants if they had been diagnosed by a physician with hypertension, diabetes, respiratory diseases, cardiovascular diseases, cancer, osteoporosis, arthritis, auditive and vision problems. Drug use (intake > 3 medications) was evaluated with the following question: "Do you currently take or use any prescription medication"?. Gait speed was measured as the time taken to complete a 3 m distance. Participants were instructed to walk from a standing start at a pace that was normal and comfortable until they reached the end of the marked path, using an assistive device if needed. Speed of walking (m/s) was computed as distance (m) divided by time taken to cover the distance (seconds) (Ramírez-Vélez et al., 2019. The mean of the three measurements was used for analyses by a trained researcher. Functional impairment was assessed with an ADL evaluation using a Spanish-adapted version of the physical level ADL (Barthel Index). The scale is composed of 10 items and its total score ranges from 0 to 100 points. This index provides quantitative information about the level of dependency, measuring the execution of ten daily life activities. The items are weighted: a maximum score of 100 indicates independence, 91–99 minimal dependence, 75–90 mild dependence, 50–74 moderate dependence, 25–49 severe dependence, and 0–24 total dependence (Mlinac and Feng, 2016). The ADL showed an acceptable reliability (0.86–0.92). Socioeconomic status was determined based on the housing stratum (1 to 6), with level 1 being the highest poverty and level 6 the highest wealth. This classification is a measure developed by the National Government of Colombia that considers physical characteristics of the dwellings and their surroundings.

2.3. Statistical analysis

Descriptive statistics were calculated for the total sample on all variables through mean and standard deviation (SD) for continuous variables and frequencies and percentage for categorical variables. The Shapiro-Wilk test was used to assess conformity with a normal distribution. To test the distribution differences of main variables and covariables for participants by weight status Chi-squared and analysis of variance tests were applied. To explore the associations between predictor variable (BMI categories), gait speed as moderator variable (linear variable "W") and dependency (treated as categorical variable "Y", being "0" total dependency, "1" severe dependency, "2" moderate dependency, "3" mild dependency and "4" independency), moderation analysis was conducted. To explore whether gait speed moderated the adverse effect of high bodyweight status on dependency, interaction analysis was conducted. Additionally, the Johnson-Neyman technique was used to identify the point(s) at which the gait speed value (m/s) moderated the relationship between bodyweight status and Barthel categories. The Johnson-Neyman technique determines along the continuum of moderator values the region of significance for the relationship between independent and dependent variables (Hayes and Rockwood, 2016). All analysis was performed using the PROCESS macro for SPSS (IBM, version 24) with a bootstrap threshold of 5000 and 95% confidence intervals (CI) (Hayes, 2018).

3. Results

An overview of the sample characteristics is shown in Table 1. From a total of 20,507 participants, 55.9% were women. The mean age (SD) of the participants was 70 (7.6) years. In total, 97.0% of the participants were of a low-medium socioeconomic status. More than 50% presented high blood pressure and vision problems. The mean (SD) BMI of the participants was 27.0 (5.0).

Table 1
Study population (N = 20,507).

Sample characteristics	
Age	70 (7.6)
*Sex**	
Women	11,466 (55.9)
Men	9041 (44.1)
*Socio-economic status**	
Low to medium (1–3)	19,899 (97.0)
High (4–6)	608 (3.0)
*Self -reported comorbidities**	
High blood pressure	10,769 (52.5)
Diabetes mellitus	3324 (16.2)
COPD	1976 (9.6)
Coronary heart disease	2688 (13.1)
Stroke	789 (3.8)
Cancer	861 (4.2)
Auditive problems	4614 (22.5)
Vision problems	11,240 (54.8)
Intake > 3 medications	3176 (15.5)
Anthropometry	
Weight (kg)	64.8 (13.1)
Height (cm)	156.5 (8.8)
BMI (kg/m^2)	27.0 (5.0)

Data are reported as mean values (standard deviation, SD) or number (percentages)*. COPD: chronic obstructive pulmonary disease; BMI: body mass index.

Participant characteristics stratified by bodyweight status are shown in Table 2. The distribution of samples between weight status groups was widely in favor of the overweight group. The prevalence of obesity was 25.1%, and the prevalence of overweight was 39.0%. Moreover, significant differences ($p < 0.05$) were found in all health status categories, except for stroke and vision problems, with a higher prevalence of participants with clinical conditions in the overweight group. As shown in Table 2, the participants with higher BMI (overweight and obese) had high blood pressure (54.1% and 64.9%); vision problems (65.5% and 65.7%); and intake more than 3 medication (69.5% and 78.2%, respectively), as well as more prevalence of moderate and severe dependency in ADL. Also, gait speed was significantly different between groups. After posthoc analysis, we found that healthy weight older adults and overweighted have the same gait speed $p = 0.38$ (0.77 m/s). However there are significant differences between obese and the rest of the groups.

Table 3 shows the results from the moderation analysis executed through the PROCESS macro. Higher bodyweight status was found to have a significant adverse effect on dependency ($\beta = -0.070$; 95% confidence interval [CI]: −0.101 to −0.043; $p < 0.001$). The association between gait speed and dependency was positive since a higher gait speed was related to more independency ($\beta = 0.101$; 95% CI: 0.033 to 0.170; $p = 0.015$). Also, the covariables included in the model were significantly associated with dependence, that is, the presence of comorbidities worsened the dependency. Finally, to test the main hypothesis of our study, the interaction term, which establishes the possible indirect effect of the moderator variable in the relationship between bodyweight status and dependency, was statistically significant ($\beta = 0.081$; 95%CI: 0.045 to 0.117; $p < 0.001$). Moreover, the lower values in SE showed that the regression model is extremely precise and indicate that the observed values fit to the regression line.

These results are illustrated in Fig. 2, where the continuum values of moderator variable (gait speed) with 95% CI and the significant regions for the adverse effect of high bodyweight status on dependency level in ADL can be seen. In this regard, the Johnson-Neyman procedure revealed two-point estimates or thresholds. The first was at < 0.77 m/s,

Table 2
Sample characteristics stratified by nutritional status.

Sample characteristics (n / %)	Underweight (546 / 2.7)	Healthy Weight (6812 / 33.2)	Overweight (7998 / 39.0)	Obese (5151 / 25.1)	p value
Sex, n *(%)*					
Female	285 (52.2)	3111 (45.7)	4377 (54.7)	3693 (71.7)	< 0.001
Male	261 (47.8)	3701 (54.3)	3621 (45.3)	1458 (28.3)	< 0.001
Age group, n *(%)*					
60–64	106 (19.4)	1709 (25.1)	2439 (30.5)	1817 (35.3)	< 0.001
65–69	112 (20.5)	1579 (23.2)	1970 (24.6)	1385 (26.9)	< 0.001
70–74	90 (16.5)	1265 (18.6)	1533 (19.2)	946 (18.4)	< 0.001
75–79	86 (15.8)	1037 (15.2)	1133 (14.2)	588 (11.4)	< 0.001
80–84	89 (16.3)	714 (10.5)	590 (7.4)	275 (5.3)	< 0.001
85 +	63 (11.5)	508 (7.5)	333 (4.2)	140 (2.7)	< 0.001
Comorbidities, n *(%)*					
High blood pressure	194 (35.6)	2918 (42.9)	4316 (54.1)	3341 (64.9)	< 0.001
Diabetes mellitus	44 (8.1)	773 (11.4)	1400 (17.6)	1107 (21.6)	< 0.001
COPD	84 (15.4)	621 (9.1)	739 (9.3)	532 (10.4)	< 0.001
Coronary heart disease	59 (10.8)	767 (11.3)	1069 (13.4)	793 (15.4)	< 0.001
Stroke	21 (3.8)	257 (3.8)	322 (4.0)	189 (3.7)	0.749
Cancer	24 (4.4)	249 (3.7)	340 (4.3)	248 (4.8)	0.019
Auditive problems	129 (23.8)	1617 (23.8)	1784 (22.4)	1084 (21.1)	0.006
Vision problems	236 (65.4)	3523 (65.7)	4507 (65.5)	2974 (65.7)	0.994
Intake > 3 medications	330 (60.4)	4063 (59.6)	5555 (69.5)	4029 (78.2)	< 0.001
Dependency, n *(%)*					
Non-dependency	395 (72.3)	5648 (82.9)	6722 (84.0)	4140 (80.4)	< 0.001
Mild	70 (12.8)	600 (8.8)	716 (9.0)	554 (10.8)	< 0.001
Moderate	69 (12.6)	527 (7.7)	534 (6.7)	441 (8.6)	< 0.001
Severe	11 (12.4)	37 (0.5)	26 (0.3)	15 (0.3)	< 0.001
Total dependence	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	–
Gait speed (m/s)[a]	0.75 (0.28)	0.77 (0.25)	0.77 (0.25)	0.73 (0.23)	< 0.001

COPD: chronic obstructive pulmonary disease.
[a] Data are reported as mean values (standard deviation).

which indicates that in those subjects whose gait speed was lower than this threshold, the adverse effect of high bodyweight status (overweight or obesity) on dependency level is negatively moderated; that is, this relationship is aggravated with poor gait speed. The second threshold was established at 1.06 m/s, representing a beneficial effect of gait speed on the negative effect of high bodyweight status on dependency. Considering these thresholds, the distribution of older adults in each of the proposed areas of significance were: below 0.77 (m/s) = 14,324 (70.0%), above 1.06 (m/s) = 1553 older adults (7.5%) and between areas = 4630 older adults (22.5%).

4. Discussion

In the present study of 20,507 community-dwelling older-adults, we found a moderating effect of gait speed on the relationship between the detrimental effect of overweight or obesity and dependence in ADL, independently of age, sex and comorbidities. Our results show a significant link between higher bodyweight status and dependence, such that overweight or obese older adults present more dependence in ADL than older healthy weight adults. These findings are in line with a previous study performed in a similar population in which a relationship was found between high BMI and more prevalence in dependency in ADL (Kumar et al., 2015). A uniqueness of the present study was the significant association between gait speed, obesity and dependence in the elderly.

Similar to what has been reported in other studies (Hong et al., 2016; Perera et al., 2016), we found that a low gait speed has a negative impact on independence. Likewise, we found that overweight or obese older adults had a lower gait speed than healthy weight older adults, which is also similar to the results of previous studies (Beavers et al., 2013; Hardy et al., 2013; Mendes et al., 2018). Accordingly, our hypothesis on the regression model to test moderation – in which gait

Table 3
Adjusted model of regression for moderation analysis for variable Y (depedency).

Predictor	β	SE	p value	95% CIs
Body weight status (variable X)	−0.070	0.014	< 0.001	(−0.101 to −0.043)
Gait speed (moderator)	0.101	0.035	0.003	(0.033 to 0.170)
Interaction	0.081	0.018	< 0.001	(0.045 to 0.117)
Sex (covariable)	0.029	0.008	< 0.001	(0.013 to 0.044)
Age (covariable)	−0.011	0.000	< 0.001	(−0.012 to −0.010)
High blood pressure (covariable)	−0.031	0.007	< 0.001	(−0.046 to −0.015)
Diabetes mellitus (covariable)	−0.043	0.010	< 0.001	(−0.064 to −0.023)
Cancer (covariable)	−0.069	0.019	< 0.001	(−0.106 to −0.032)
COPD (covariable)	−0.117	0.013	< 0.001	(−0.143 to −0.092)
Coronary heart disease (covariable)	−0.033	0.011	0.003	(−0.056 to −0.011)
Stroke (covariable)	−0.054	0.015	< 0.001	(−0.025 to −0.084)
Artritis (covariable)	−0.100	0.009	< 0.001	(−0.118 to −0.082)
Osteoporosis (covariable)	−0.069	0.012	< 0.001	(−0.094 to −0.044)

SE: standard error; CI: confidence interval; COPD: chronic obstructive pulmonary disease.

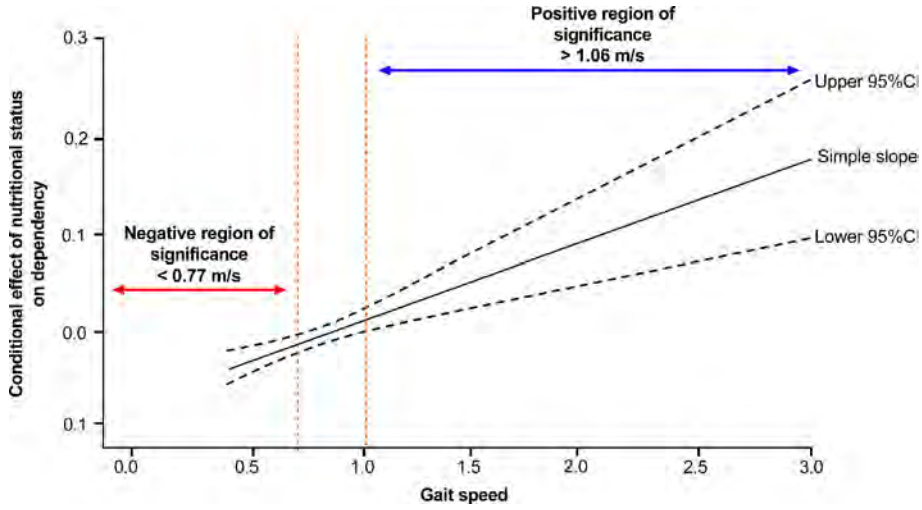

Fig. 2. Regression slope estimate and 95% confidence intervals for the relationship between moderator variable (gait speed) and adverse effect of bodyweight status and dependency level in ADL, based on the Johnson-Neyman procedure.

speed can be a moderator – was supported. Thus, our main finding was that gait speed could act as moderator of the relationship between obesity and dependence; namely, the negative effect of overweight or obese on dependency level in older adults was moderated positively or negatively by gait speed.

According to the literature, mobility impairment is defined as a gait speed ≤ 0.8 m/s, as this cut-off value can predict disability and reduced overall survival (Abellan van Kan et al., 2009; Middleton et al., 2015). This threshold is similar to our results, since we found that overweight or obese older adults with a gait speed below 0.77 m/s could have more dependence, whereas those with a gait speed above 1.06 m/s are likely to show lower dependence. This result has not previously been described, since the literature reports > 0.8 m/s as the recommended minimum gate speed to prevent disability. We also show that < 0.77 m/s would indicate that the negative effect of a high bodyweight status on dependence could increase, and a value > 1.06 m/s would indicate that the negative effect of a high bodyweight status on dependence could be reduced. Also, there is a non-significant region between ≥ 0.77 and ≤ 1.06 m/s in which the gait speed has no effect for the association studied.

To the best of our knowledge, this is the first time that the moderating effect of gait speed on the relationship between bodyweight status and dependency has been studied. However, there are related studies that support our findings. For example, a high BMI is associated with lower muscle quality (Barbat-Artigas et al., 2014; Tallis et al., 2017; Tomlinson et al., 2016) due to changes in contractile function (Akhmedov and Berdeaux, 2013), which impairs isometric, concentric and eccentric muscle force production (Bollinger, 2017; Tomlinson et al., 2016) and leads to alterations of kinematics and gait posture. Also, aging is related to a substantial decline in muscle strength, known as dynapenia (Manini and Clark, 2012), which is linked to a series of mechanisms such as a reduction in central activation, a decrease in motor unit number and size, as well as an alteration in the excitation-contraction cycle (Straight et al., 2015). Thus, neuromuscular deterioration could negatively influence gait speed (Clark et al., 2013). A third factor is a concurrence of fat accumulation and dynapenia during aging (Tallis et al., 2018). Finally, pro-inflammatory adipokines, which are related to fat accumulation and aging (Pararasa et al., 2015), seem also to be responsible for declinines in gait speed (Verghese et al., 2011). Therefore, these four factors feed a vicious cycle where the essential physical function affected is the gait speed. Accordingly, physical exercise focused to maintain an optimal gait speed (~1.06 m/s) could play a protector role against these factors to avoid a decline in ADL.

The strengths of the present research include the large population-based study with > 20,000 older adults. Also, the statistical procedures based on moderation analysis with the Johnson-Neyman procedure provide a better knowledge of thresholds, in our case of gait speed, in the relationship between obesity and dependence. As far as we know, this is the first study to explore the moderating effect of gait speed between overweight or obesity and dependence and also the first establishing a new threshold for this relationship based on the Johnson-Neyman procedure.

Our study has several limitations. Firstly, the cross-sectional design limits our ability to draw causal inferences. Secondly, BMI is not a perfect measure of actual adiposity and fat mass. Thirdly, the classification between independence-dependence categories was established through a self-reported index. Fourthly, we cannot entirely rule out the possibility of unmeasured or unknown confounding factors including behavioural habits, especially those related to nutrition, objective physical activity, and sleep in elders, which were not considered. However, the homogeneity of the study population and comprehensive data on the risk factors minimized potential confounding factors. Thus, we believe that our main findings will be broadly applicable.

5. Conclusions

The present results reveal that gait speed moderates the harmful effect of high bodyweight status on dependence in a large population-based study. Our results allow us to establish two thresholds: < 0.77 m/s, below which the detrimental effect of overweight or obesity on dependence could be aggravated; and > 1.06, above which the effect could be alleviated.

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Declaration of competing interest

No conflicts of interests, financial or otherwise are declared by the authors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.exger.2019.110732.

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Relative Handgrip Strength Diminishes the Negative Effects of Excess Adiposity on Dependence in Older Adults: A Moderation Analysis

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Abstract: The adverse effects of fat mass on functional dependence might be attenuated or worsened, depending on the level of muscular strength. The aim of this study was to determine (i) the detrimental effect of excess adiposity on dependence in activities of daily living (ADL), and (ii) whether relative handgrip strength (HGS) moderates the adverse effect of excess adiposity on dependence, and to provide the threshold of relative HGS from which the adverse effect could be improved or worsened. A total of 4169 participants (69.3 ± 7.0 years old) from 244 municipalities were selected following a multistage area probability sampling design. Measurements included anthropometric/adiposity markers (weight, height, body mass index, waist circumference, and waist-to-height ratio (WHtR)), HGS, sarcopenia "proxy" (calf circumference), and ADL (Barthel Index scale). Moderation analyses were performed to identify associations between the independent variable (WHtR) and outcomes (dependence), as well as to determine whether relative HGS moderates the relationship between excess adiposity and dependence. The present study demonstrated that (i) the adverse effect of having a higher WHtR level on dependence in ADL was moderated by relative HGS, and (ii) two moderation thresholds of relative HGS were estimated: 0.35, below which the adverse effect of WHtR levels on dependency is aggravated, and 0.62, above which the adverse effect of fat on dependency could be improved. Because muscular strength represents a critically important and modifiable predictor of ADL, and the increase in adiposity is inherent in aging, our results underscore the importance of an optimal level of relative HGS in the older adult population.

Keywords: fat mass; obesity; muscle strength; physical function; functional dependence

1. Introduction

Muscle strength and mass decline with aging [1]. The importance of preserving optimal muscle strength in middle- and older-age adults has been recently highlighted in epidemiological studies showing that muscle strength is an important predictor for all-cause [2] and cancer [3] mortality. Physical function in older adults declines with the loss of skeletal muscle [1,4], and a recent study reported that a non-weak handgrip strength (HGS) level (cut-off points ranged from 17.4 to 8.6 in men and 10.1 to 4.9 in women) is related to decreased odds of intrinsic capacity impairments (i.e., the interaction between the physical and mental capacity of an individual) among older adults [5].

Several studies have indicated that the aging process produces a series of changes in body composition, usually without affecting the body mass index or weight, but producing an accumulation of fat as individuals get older [6,7]. Beyond its corresponding effect on health, excess adiposity has a harmful impact on muscle quality and quantity [8]. Consequently, the convergence of aging and fat mass may create a perfect storm for skeletal muscle catabolism [9] and a decline in physical function [10].

Handgrip strength (HGS) is the most common index of muscle strength, owing to its ease of assessment, low cost, and simplicity, and it is considered a valid "proxy" of overall muscle strength for clinical and epidemiological studies [11]. Lower HGS correlates strongly with cardiovascular disease [2] and mortality [12], and several studies [13,14] have highlighted its protective role against activities of daily living (ADL) dependence in older adults. Thus, maintaining an optimum HGS is an effective determinant factor for healthy aging [5,15]. In this context, several studies have shown that aging is associated with a decline in handgrip strength, and several studies have highlighted the fact that an increase in fat mass contributes to a deterioration of HGS in older adults [8,16]. These aforementioned processes can be viewed as a cascade of events, beginning with aging, which are associated with greater muscle fat infiltration [17,18]. Aging and accumulation of infiltrating fat leads to a decline in muscle quality and quantity—therefore resulting in a poorer performance (lower muscle strength)—and, ultimately, affecting functional dependence in ADL [19,20].

This worsening of muscle strength can be explained several biological factors. First, fat infiltration induces changes in contractile function [21] in the different manifestations of strength (isometric, concentric, and eccentric) [22,23]. Second, aging and fat infiltration coexist in an environment marked by a loss of muscle strength and power, also known as dynapenia [24], which is related to a reduction in central activation, a decrease in motor unit number and size, and an alteration in the excitation–contraction cycle [25]. Finally, aging and dynapenia are related to a greater presence of proinflammatory activity, which seem to be responsible for the deterioration of muscular function (fat infiltration into muscle), and visceral fat increases and subcutaneous fat decreases with aging [26]. We therefore hypothesized that muscle strength could play a preventive role in this association.

The adverse effects of abdominal obesity on functional dependence, might be attenuated or worsened depending on the level of muscular strength. Additionally, relative handgrip strength is associated with functional dependence. Thus, central adiposity may have an effect between dependence status and relative handgrip strength after potential confounding variables such as age, gender, and/or lifestyle. Accordingly, describing the magnitude of these risk factors in older adults could be important for prioritizing prevention and public health efforts. Nevertheless, to our knowledge, no studies have examined the moderator role of muscle strength based on HGS between excess of central adiposity and functional dependence.

The aim of the present study was two-fold: (i) to examine the detrimental effect of abdominal obesity on functional dependence in ADL, and (ii) to discern whether relative HGS moderates the adverse effect of abdominal obesity on dependence, as well as to provide the threshold of relative HGS from which the adverse effect could be improved or worsened.

2. Materials and Methods

2.1. Study Design and Sample Population

The data for this secondary cross-sectional study were obtained from the Health and Well-being and Aging Survey in Colombia 2015 (SABE, from initials in Spanish: Salud, Bienestar y Envejecimiento, 2015), a multicenter project conducted from 2014 to 2015 by (in Spanish: Ministerio de Salud y la Protección Social de Colombia) [27]. The study included the Colombian population aged ≥60 years, and the indicators were disaggregated by age ranges, sex, ethnicity, and socioeconomic level.

A total of 23,694 surveys were conducted at the national level. A total of 6530 segments were planned to obtain the surveys (4928 urban and 1602 rural), with an expected average of 4.7 adults per segment. The standardized process for each home visit involved the identification of the participants, the registration of the demographic data, the signing of the informed consent, the application of the established filters and the selection criteria, the signing of assent when necessary, and the completion of the questionnaire by the interviewer. For this subsample, the calculation of the sample size was carried out, taking into account national representation. A total of 86 municipalities were selected, including the four large cities. For this analysis, we used data from 4169 participants included as a subsample with HGS measures. The rationale and detailed methodology of the SABE Colombia has been described in another document [28].

Institutional review boards involved in developing the SABE 2015 study (University of Caldas, ID protocol CBCS-021-14, and University of Valle, ID protocol 09-014 and O11-015) reviewed and approved the study protocol. The study protocol for the secondary analysis was approved by the Human Subjects Committee at the Pontificia Universidad Javeriana (ID protocol 20/2017-2017/180, FM-CIE-0459-17) in accordance with the Declaration of Helsinki of the World Medical Association and Resolution 8430 of 1993 of the then Ministry of Health of Colombia on technical, scientific, and administrative standards for conducting research with humans. All participants provided written informed consent.

2.2. Measurements

Data collection staff were trained by the research teams of the coordinating centers (University of Caldas, and University of Valle, from Colombia) for face-to-face interviews and physical measurements. Anthropometry measurements included height and body weight, which were measured with a portable stadiometer (SECA 213, Hamburg, Germany) and an electronic scale (Kendall graduated platform scale), respectively. Body mass index (BMI) was calculated in kilograms per square meter from the measured body weight and height. Waist circumference (WC) was measured over the midpoint between the lower border of the ribs and iliac crest in the midaxillary plane, at the end of normal expiration. The waist-to-height ratio (WHtR) was measured as the ratio of the waist circumference (in cm) to the height (in cm). We used WHtR as a measure for abdominal obesity because is a useful tool in clinical practice and has been shown to be a reliable parameter for predicting whole-body fat percentage and visceral adipose tissue [28]. The calf circumference was used for screening sarcopenia because it is a reliable, easy, and low-cost tool in clinical practice [4]. Following the recommendation of the WHO Expert Committee [29] and Rolland et al. [4], a cut-off of calf circumference ≤31 cm was considered as sarcopenia. HGS, including absolute and relative—HGS (kg)/body mass (kg)—were assessed with a Takei dynamometer (T.K.K., Takei Scientific Instruments Co., Ltd., Niigata, Japan), including the highest value (kg) from two attempts (both hands). This allowed us to be more accurate when comparing older adults with different body sizes and to focus on muscle quality rather than muscle quantity. The coefficients of variation for body weight, height, waist circumference, calf circumference, and HGS were 23.2%, 6.5%, 12.2%, 11.2%, and 42.2%, respectively.

Nutritional status was evaluated through Mini-Nutritional Assessment extended version [30]. Functional impairment was assessed with an ADL evaluation using a Spanish-adapted version of the physical level ADL (Barthel Index), recommended for epidemiological studies in older adults [31].

The Barthel Index scores are in multiples of five, ranging from 0 (completely dependent) to 100 (independent in basic). The Barthel index scores are classified as follows: 100 means independence, 91–99 low-level dependency, 75–90 mild dependency, 50–74 moderate dependency, 25–49 severe dependency, and 0–24 total dependency [32].

For lifestyle characteristics, personal habits regarding alcohol intake (participants were categorized as those who do not drink and those who drink less than 1 day per week, 2 to 6 days a week, or every day) and cigarette smoking (participants were categorized as those who do not smoke and those who have never-smoked, those who currently smoke, or those who previously smoked) were recorded. A "proxy physical activity" report was conducted by the following questions: (i) "Have you regularly exercised, such as jogging or dancing, or performed rigorous physical activity at least three times a week for the past year?"; (ii) "Walk, at least three times a week, between 9 and 20 blocks (0.6 to 1.2 km) without resting?"; (iii) "Walk, at least three times a week, eight blocks (0.5 km) without resting?". Participants were considered physically active if they responded affirmatively to two of the three questions. Medical information including multimorbidity, as well as chronic conditions adapted from the original SABE study, were assessed by asking the participants if they had been diagnosed, by a physician, with hypertension, type 2 diabetes mellitus, chronic obstructive pulmonary disease, cardiovascular diseases (heart attack, angina), stroke, cancer, arthritis, osteoporosis, or sensory impairments (vision and hearing loss). Medication use was evaluated with the question "do you currently take or use any prescription medication?".

Race/ethnicity grouped as indigenous (people belonging to various indigenous groups, such as Ika, Kankuamo, Emberá, Misak, Nasa, Wayuu, Awuá, Mokane), black "mulato" or Afro-Colombian, white, and others (mestizo, gypsy, etc.) was assessed by self-reporting. Socioeconomic status (SES) was determined on the basis of the housing stratum (1 to 6), with level 1 being the highest poverty and level 6 the highest wealth. This classification is a measure developed by the National Government of Colombia that considers physical characteristics of the dwellings and their surroundings. The classification in any of the six strata approximated the hierarchical socioeconomic difference from poverty to wealth and vice versa.

2.3. Statistical Analysis

Descriptive analyses using mean ± standard deviation (SD) for the continuous variables and frequency distribution for categorical variables were used to obtain the characteristics of the sample. The normality of the data was examined by the Kolmogorov–Smirnoff test. Significant differences between men and women were analyzed using Student's *t*-test or the chi-square (χ^2) post-hoc test.

The PROCESS macro in the SPSS statistical software package, version 24.0 (IBM, Chicago, IL, USA) for Windows, was used to conduct a moderation analysis. Preliminary analysis showed no significant interactions between gender and abdominal obesity in relation to functional dependence ($p = 0.814$); therefore, all analyses were performed with men and women together. Moderation analysis was conducted to examine whether WHtR levels were related to increased dependence and to determine whether this negative effect was moderated by relative HGS. This relationship used ordinary least squares regression analysis when predicting continuous variables (WHtR and relative HGS in the study). A simple slope plot was used to visualize the effect of the moderator. The Johnson–Neyman approach was used to test the point in which the relative HGS value moderated the relationship between WHtR levels and dependence. The Johnson–Neyman technique determined, along a continuum of moderator values (relative HGS), the region of significance on the relationship between the independent and dependent variables [33]. All tests were adjusted for sex, age, alcohol, smoking status, and physical activity habits.

3. Results

Of the 4169 study participants, 56.2% were female and 43.8% were male (Table 1). Anthropometric data, including BMI, waist circumference, and WHtR, described the principal characteristics of the

sample, such as overweight or obesity and an excess of fat mass. The differences between sex for these variables were significant ($p < 0.05$), with the exception of calf circumference. Regarding performance outcomes—computed from absolute HGS and relative HGS—men showed a significantly higher performance than women. Additionally, the ethnic distribution was dissimilar between sexes, except for the Afro-Colombian ethnic group. We observed a major proportion of white and other ethnic groups (mestizo, gypsy, etc.). A major proportion of participants were found to be in SES level 2 and significant differences were observed between sexes in all SES levels except level 1.

Likewise, there were significant differences between sexes regarding lifestyle habits including smoking, alcohol consumption, and physical activity "proxy" recommendations. According to self-report comorbidities presented by participants, there was a prevalence of visual problems (57.7%) and high blood pressure (53.7%) in both sexes. Regarding the distribution difference between males and females, we found significant differences in hearing problems, high blood pressure, type 2 diabetes mellitus, arthritis, and osteoporosis. In addition, there were significant differences in medication use and nutritional status. Finally, the prevalence of dependency was 8.1% and 4.3% for mild and moderate dependency, respectively. However, when we combined all three levels of dependency (mild, moderate, and severe) this rose to 12.5%, with 522 older adults dependent in ADL.

Figure 1 shows the results from the regression model, where it shows the moderation analysis based on ordinary least squares regression, in which there is an inverse relationship between the excess of adiposity, measured via WHtR, on functional dependence in older adults. This path known as direct effect ($\beta = -0.11$ (-0.23, -0.01)) was moderated by relative HGS. Therefore, the adverse effect of excess adiposity on functional dependence was moderated by relative HGS ($\beta = 19.08$ (8.49, 29.66)).

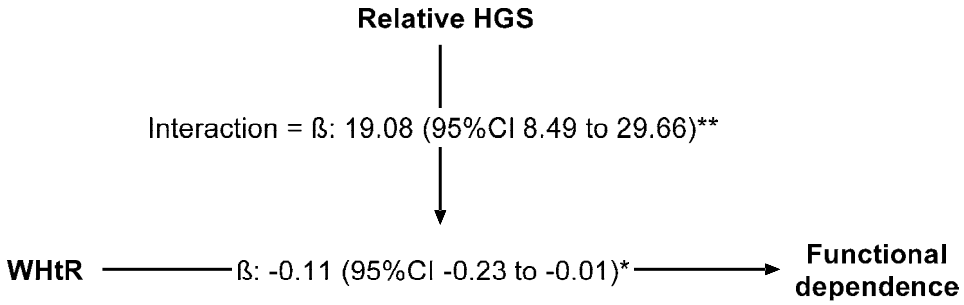

Figure 1. Moderation models. Beta expressed as unstandardized regression coefficients and 95% confidence interval. Because there was substantial covariance between strength capacity and body mass—and, moreover, the links between muscle strength and both physical function and chronic health were mediated by the proportion of strength relative to body mass—grip strength (HGS) was relative as strength per body mass (i.e., (HGS in kilograms)/(body mass in kilograms)). Moderation analysis in which relative handgrip strength moderate the relationship between waist-to-height ratio (WHtR) and functional dependence, adjusted by age, gender, and lifestyle (alcohol intake, smoking, and physical activity "proxy"); * $p < 0.01$; ** $p < 0.001$.

To elucidate a possible estimate point from which the moderator value has a moderator effect, the Johnson–Neyman statistical approach was used. The result is shown in Figure 2. The slope shows the continuum of the moderator (relative HGS expressed as kilogram per kilogram of body weight) and the different regions of significance. The first region was found to be less than 0.35, denoting that the adverse effect of excess adiposity, based on WHtR, on dependence could be aggravated for those in this region. Secondly, a significant positive region was found from 0.62, indicating that the adverse effect of WHtR could be ameliorated for those who were above this point. Lastly, a "black" region was observed, which indicated that the adverse effect did not improve or worsen in those with an HGS between the lower and upper thresholds.

Table 1. Characteristics of the study participants.

Characteristics	Men (n = 1825, 43.8%)	Women (n = 2344, 56.2%)	Overall (n = 4169)	P for Gender
Anthropometric, mean ± SD				
Age (years)	69.9 ± 7.2	68.9 ± 6.9	69.3 ± 7.0	<0.0001
Height (cm)	163.1 ± 6.7	151.1 ± 6.2	156.4 ± 8.7	<0.0001
Body weight (kg)	68.1 ± 11.8	63.3 ± 11.9	65.4 ± 12.1	<0.0001
BMI (kg/m^2)	26.1 ± 3.9	28.3 ± 4.9	27.3 ± 4.6	<0.0001
Waist circumference (cm)	93.2 ± 10.7	91.6 ± 10.9	92.3 ± 10.8	<0.0001
Waist-to-height ratio	0.57 ± 0.1	0.60 ± 0.1	0.59 ± 0.1	<0.0001
Calf circumference (cm)	34.7 ± 3.3	34.7 ± 3.8	34.7 ± 3.6	0.807
Functional performance, mean ± SD				
Absolute HGS (kg)	27.5 ± 8.0	17.3 ± 5.3	21.8 ± 8.3	<0.0001
Relative HGS/body weight (kg/kg)	0.41 ± 0.1	0.27 ± 0.1	0.33 ± 0.1	<0.0001
Race/ethnic group, n (%)				
Indigenous	149 (9.1)	103 (5.0)	252 (6.8)	0.004
Black "mulato" or Afro-Colombian	173 (10.6)	181 (8.7)	354 (9.6)	0.671
White	478 (29.3)	696 (33.6)	1174 (31.7)	<0.0001
Others *	831 (51.0)	1092 (52.7)	1923 (51.9)	<0.0001
Missing	194	272	466	-
Socioeconomic status, n (%)				
Level I	689 (37.8)	752 (32.1)	1441 (34.6)	0.097
Level II	755 (41.4)	987 (42.1)	1742 (41.8)	<0.0001
Level III	345 (18.9)	511 (21.8)	856 (20.5)	<0.0001
Level IV	27 (1.5)	67 (2.9)	94 (2.3)	<0.0001
Level V–VI	9 (0.5)	27 (1.2)	36 (0.9)	0.003
Lifestyle outcomes, n (%)				
Alcohol intake	451 (24.7)	122 (5.2)	573 (13.7)	<0.0001
Smoking	287 (15.7)	171 (7.3)	458 (11.0)	<0.0001
Physical activity "proxy"	1375 (75.3)	1965 (83.8)	3340 (80.1)	<0.0001
Multimorbidity/chronic conditions, n (%)				
Hearing loss	492 (26.9)	463 (19.7)	955 (22.9)	<0.0001
Visual loss	1029 (56.3)	1378 (58.7)	2407 (57.7)	0.029
High blood pressure	844 (46.2)	1395 (59.5)	2239 (53.7)	<0.0001
Diabetes mellitus 2	258 (14.1)	410 (17.5)	668 (16.0)	0.004
Chronic pulmonary disease	168 (9.2)	244 (10.4)	412 (9.9)	0.195
Coronary heart disease	235 (12.8)	326 (13.9)	561 (13.4)	0.340
Stroke	73 (4.0)	78 (3.3)	151 (3.6)	0.267
Cancer	74 (4.1)	124 (5.3)	198 (4.7)	0.062
Arthritis	285 (15.6)	822 (35.1)	1107 (26.5)	<0.0001
Osteoporosis	82 (4.5)	378 (16.1)	460 (11.0)	<0.0001
Medication use, n (%)	451 (24.7)	122 (5.2)	573 (13.7)	<0.0001
Nutritional status				
Malnutrition	31 (1.9)	66 (3.2)	97 (2.7)	<0.0001
Risk of malnutrition	502 (31.3)	718 (35.0)	1220 (33.4)	<0.0001
Normal nutritional status	1073 (66.8)	1267 (61.8)	2340 (64.0)	<0.0001
Missing	219	293	512	-
Functional dependence, n (%)				
Severe dependency	0 (0.0)	3 (0.1)	3 (0.1)	-
Moderate dependency	68 (3.7)	113 (4.8)	181 (4.3)	<0.0001
Mild dependency	101 (5.5)	237 (10.1)	338 (8.1)	<0.0001
Non-dependency	1656 (90.7)	1991 (84.9)	3647 (87.5)	<0.0001

Data are presented as mean ± SD or number (percentage) of participants. Significant differences between the men and women groups were analyzed by Student's t-test or χ^2 test. BMI: body mass index. * Others (mestizo, gypsy, etc.).

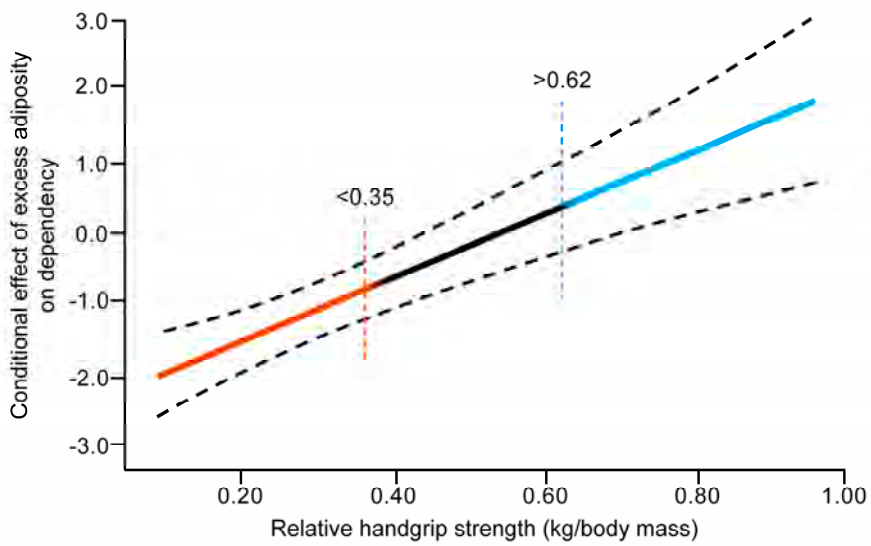

Figure 2. Regression slope estimate and 95% confidence intervals for the relationship between moderator variable (relative HGS) and adverse effect of WHtR levels on dependency level in activities of daily living (ADL), based on the Johnson–Neyman procedure. Red line indicates negative region of significance at moderator value (<0.35 of relative HGS). Blue line indicates the positive region of significance at moderator value (>0.62 of relative HGS). Black line represents neutral region of significance.

4. Discussion

The present study investigated the moderator role of HGS on the adverse effect of WHtR on dependency in older Colombian adults. The major finding of the study was that the adverse effects of high WHtR levels on dependency were found to be moderated by relative HGS. Two moderation thresholds of relative HGS were estimated: 0.35, below which the adverse effect of WHtR levels on dependency was aggravated, and 0.62, above which the adverse effect of fat on dependency improved. Accordingly, our results indicated that older adults with higher WHtR could experience more dependence in ADL than older adults with lower WHtR; however, this unfavorable effect was moderated by relative HGS. Consequently, older adults with high relative HGS levels could attenuate the negative effect of adiposity. Therefore, age-related declines in muscle mass and strength are often detected by reductions in HGS.

The findings of the present study are supported by several previous studies. For example, de Carvalho et al. [8] found that abdominal obesity is associated with lower HGS, accelerating the decline of muscle strength. A possible explanation for this phenomenon is that excessive adiposity can downregulate the anabolic actions of testosterone [34], growth hormones [35], and insulin [36], which may contribute to a progressive loss of muscle mass and associated function in both sexes. Additionally, excessive adipose tissue can induce a proinflammatory state by the action of several cytokines (e.g., higher plasma concentrations of tumor necrosis factor-alpha and interleukin-6), which is associated with lower muscle strength [37] and disability in older adults [38].

No previous studies have reported a moderator role of HGS on the relationships studied here. We found that higher relative HGS could attenuate the adverse effect of abdominal obesity on functional dependence in older adults. Our findings show that higher central obesity has an adverse effect on functional independence. It is therefore likely that functional independence in ADL will be reduced in those older adults with abdominal obesity. However, this negative effect could be moderated by relative HGS. Consequently, the adverse effect may worsen, improve, or even disappear, depending on the relative HGS of older adults. Our findings indicate that muscle strength relative to body weight can play a crucial role between WHtR levels and dependency. Specifically, if older adults have a high WHtR value and a relative HGS above 0.62, the adverse effect on dependency could be mitigated or

even disappear. Conversely, if older adults have a high WHtR value and a relative HGS below 0.35, it could worsen the adverse effect on dependency.

Biomechanical and neuromuscular scientific evidence could justify the moderator role of HGS between excess of central adiposity and functional dependence. For example, it is well reported that abdominal obesity is related to a greater body weight, and consequently walking more slowly might help to keep the dynamic balance between steps, as well as to maintain shorter the cadence and length of steps to optimize gait pattern [39]. Another plausible reason might be neuromuscular deterioration, as there is an association between obesity/high-fat mass content and poor muscle quality [23,40–42], with an impairment of force production relative to body weight [22,23]. Conversely, abdominal obesity may be linked to reduced HGS, as every 10 cm increase in WC has been shown to be associated with a 3.56 kg lower HGS in middle-aged and older men [24]. Additionally, every 1 kg increase in HGS for older women was associated with a 0.13 s decrease in the timed up-and-go test, 0.03 s decrease in 3 m walk time, and 1% decrease in chair rise time [43]. With regard to ADL, McGrath et al. [44] determined that high baseline grip strength decreased the odds ratio (OR) of developing disability in ADL (OR 0.95) and instrumental ADL (OR 0.92) among older Mexican Americans. These findings suggest that a minimum level of strength is a prerequisite for physical function and that, when strength is above the minimum required level, it may serve as reserve capacity, which is beneficial in preventing functional limitation in the future [45]. Accordingly, maintaining muscle strength is an important factor for maintaining function during the aging process [2,3]. Future research should expand upon the longitudinal associations between HGS and clinically relevant health outcomes that are mediated (e.g., in both instrumental activities and ADL) or moderated (e.g., obesity) by other factors [45].

The strengths of the study include the large population-based study in older, Latin-American adults. Additionally, we carried out complex statistical analyses to determine the role of muscle strength to circumvent the detrimental effect of excess adiposity on dependence. As well as this, through the Johnson–Neyman statistical approach, we provided two thresholds of relative HGS, which we believe will add to the knowledge base to improve clinical practice and exercise programs in this population.

There are some limitations of the study design that need to be considered. First, the cross-sectional design limits drawing any causal inferences. Second, the assessment of excess adiposity can result in bias because of the proxy method (i.e., WHtR levels), and therefore, standardized measures of body composition should be used. Third, the classification of dependency was based on a self-report questionnaire. Thus, we are unable to say whether low grip strength (with or without excess adiposity) leads to higher risk of neuromuscular/ADL abnormalities, or conversely, whether poor neuromuscular/dependency profiles lead to declines in grip strength (i.e., reverse causation). Future research is needed to better describe the age- and sex-specific trajectories of HGS as a predictor of comorbidities across the lifespan, and perhaps, just as importantly, to apply robust analyses that can compartmentalize risk into hierarchical categories. Finally, the thresholds for HGS are open to discussion and the values may vary depending on the comorbidities that individuals present with.

5. Conclusions

In summary, older adults with excess adiposity have major dependency in ADL. However, this adverse effect can be moderated by relative HGS. Our findings bring two thresholds of relative HGS as moderators of the adverse effect: <0.35, in which the adverse effect of abdominal obesity on dependence could worsen, and >0.62, in which the detrimental effect could be improved or even disappear. Because muscle strength represents a critically important and modifiable predictor of ADL [13,14,43], and an increase in body fat is inherent in aging [46], our results underscore the importance of an optimal level of relative HGS among the older adult population. Thus, this study provides support for the importance of considering both HGS and WHtR as contributors to diagnostic functional disability/dependence, and healthcare professionals should encourage participation in physical activity to improve muscular fitness in old age [47].

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Conflicts of Interest: The authors declare no conflict of interest.

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Glucose Levels as a Mediator of the Detrimental Effect of Abdominal Obesity on Relative Handgrip Strength in Older Adults

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Abstract: Excess central adiposity accelerates the decline of muscle strength in older people. Additionally, hyperglycemia, independent of associated comorbidities, is related to the loss of muscle mass and strength, and contributes to functional impairment in older adults. We studied the mediation effect of glucose levels, in the relationship between abdominal obesity and relative handgrip strength (HGS). A total of 1571 participants (60.0% women, mean age 69.1 ± 7.0 years) from 86 municipalities were selected following a multistage area probability sampling design. Measurements included demographic and anthropometric/adiposity markers (weight, height, body mass index, and waist circumference). HGS was measured using a digital dynamometer for three sets and the mean value was recorded. The values were normalized to body weight (relative HGS). Fasting glucose was analyzed by enzymatic colorimetric methods. Mediation analyses were performed to identify associations between the independent variable (abdominal obesity) and outcomes (relative HGS), as well as to determine whether fasting glucose levels mediated the relationship between excess adiposity and relative HGS. A total of 1239 (78.8%) had abdominal obesity. Abdominal obesity had a negative effect on fasting glucose (β = 9.04, 95% CI = 5.87 to 12.21); while fasting glucose to relative HGS was inversely related (β = −0.003, 95% CI = −0.005 to −0.001), $p < 0.001$. The direct effect of abdominal obesity on relative HGS was statistically significant (β = −0.069, 95% CI = −0.082 to −0.057), $p < 0.001$. Lastly, fasting glucose levels mediates the detrimental effect of abdominal obesity on relative HGS (indirect effect β = −0.002, 95% CI = −0.004 to −0.001), $p < 0.001$. Our results suggest that the glucose level could worsen the association between abdominal obesity status and lower HGS. Thus, it is plausible to consider fasting glucose levels when assessing older adults with excess adiposity and/or suspected loss of muscle mass.

Keywords: fat mass; obesity; muscle strength; physical function; diabetes

1. Introduction

Aging is related to a progressive unfavorable change in body composition, particularly abdominal fat accumulation and loss of lean mass [1,2]. Abdominal obesity, measured by waist circumference (WC) [3], is associated with systemic inflammation, hyperlipidemia, cardiovascular diseases, impaired fasting glucose, prediabetes, insulin resistance, hyperinsulinemia, and type 2 diabetes (T2DM) [4–14]. Specifically, hyperglycemia, independent of associated comorbidities, is related to the loss of muscle mass and strength, and contributes to functional impairment in older adults [9–13]. Lower muscle mass is positively associated with central adiposity and an increased risk of developing T2DM [8]. Hyperglycemia and the presence of insulin resistance may increase autophagy, muscle protein degradation, and mitochondrial dysfunction, which may negatively impact skeletal muscle function [6]. Therefore, the coexistence of aging and abdominal obesity creates the harmful environment for the deterioration of muscle mass. On the other hand, it has been suggested that excessive and naturally occurring deposition of adipose tissue in the abdomen may increase the risk of hyperinsulinemia, metabolic syndrome, and type 2 T2DM [6–8].

Handgrip strength (HGS) is a simple and reliable tool for measuring body function and has been suggested as a biomarker for older adults [15]. In the past decade, the majority of studies have used the HGS normalized to body weight or body mass index, since has been recommended in the research of muscle health [16,17]. In this sense, some evidence that relative handgrip strength is associated with persistent hyperglycemia [18,19]. Joule et al. [20] found that upper muscle strength (measured by bench press) was weaker in patients with T2DM than in healthy controls, and similarly, Mee-Ri et al. [21] recently found an inverse relationship between T2DM and HGS. In older adults (>65 years), hyperinsulinemia increases the risk of falls, dementia, depression, and vision and hearing loss [22], and is associated with a substantial burden of cardiovascular disease [23], and brain abnormalities [24], with significant long-term morbidity and mortality [13]. It seems to be that higher level on glucose also affects skeletal musculature (diabetic myopathy), involving contractile weakness, mitochondrial dysfunction, fiber-type changes, slow-to-fast muscle transitions, and decreased oxidative activity [25,26]. In addition to this, it has a negative impact on muscular strength and quality in older adults. Park et al. [27,28] found a decline in muscle strength in the lower body in older adults with T2DM. However, these and other studies have not examined muscular strength in lower or upper extremities in individuals with disorders of glucose tolerance [29,30].

Overall, these findings indicate the coexistence of two vectors negatively affecting muscle strength–excess central adiposity and higher level of glucose. However, the exact biological mechanisms are poorly understood. Nevertheless, changes in body composition, particularly declines in lean body mass and the concurrent fat accumulation, coupled with impairment glucose metabolism have been proposed as potential mediators contributing to the declines in muscle strength and quality. Because an increase in body weight (adiposity) typically precedes the development of T2DM, research examining the relationship between HGS and body weight is desirable to know more about how relative HGS is associated with central adiposity, and to test whether fasting glucose has an effect on the relationship between central adiposity and relative HGS. To date, the potential role of fasting glucose in attenuating or modifying the relationship between central adiposity and hepatic relative HGS remains unknown and, to the best of our knowledge, has not been examined in older subjects.

The interplay between sarcopenia and excess adiposity in an ageing population has now emerged as an important public health concern in older populations. Considering the increasing number of obese older adults occurring in parallel with a greater prevalence of declines in muscle strength and quality, this study aimed to investigate the possible mediation effect of fasting glucose on the relationship between central adiposity and relative HGS, in community-dwelling older adults.

2. Materials and Methods

2.1. Study Design and Sample Population

We used the database from the "Health and Well-being and Aging Survey in Colombia, 2015" (SABE, from initials in Spanish: SAlud, Bienestar & Envejecimiento, 2015), a cross-sectional study supported by the Epidemiological Office of the Ministry of Health and Social Protection of Colombia (https://www.minsalud.gov.co/) of a nationally representative sample of Colombian older adults. The sampling design in the SABE study consists of a multistage probability sampling design for participant selection according to the existing municipal cartography as municipalities, urban, rural segments, homes or sidewalks, homes, and people. Therefore, it constitutes 99% of the population residing in private homes in the urban and rural strata of the sample. The study protocol was approved by the Human Subjects Committee for this secondary analysis at the Pontificia Universidad Javeriana (ID protocol 20/2017–2017/180, FM-CIE-0459-17) following the tenets of the Declaration of Helsinki of the World Medical Association and Resolution 8430 of 1993 of the then Ministry of Health of Colombia on technical, scientific and administrative standards for human research. All participants provided written informed consent. Details of the survey have been published [31].

The SABE assessed 23,694 elderly people from 246 municipalities across all departments of the country. For this subsample, we selected 86 municipalities, including the four large cities. The sample size calculation was carried out, selecting two out of five individuals of the general sample, obtaining a sample of 1571 participants (60.0% women) aged 60 years and over. We included individuals who completed the handgrip strength test and who had available anthropometric/biological data to establish relative handgrip strength (Figure 1).

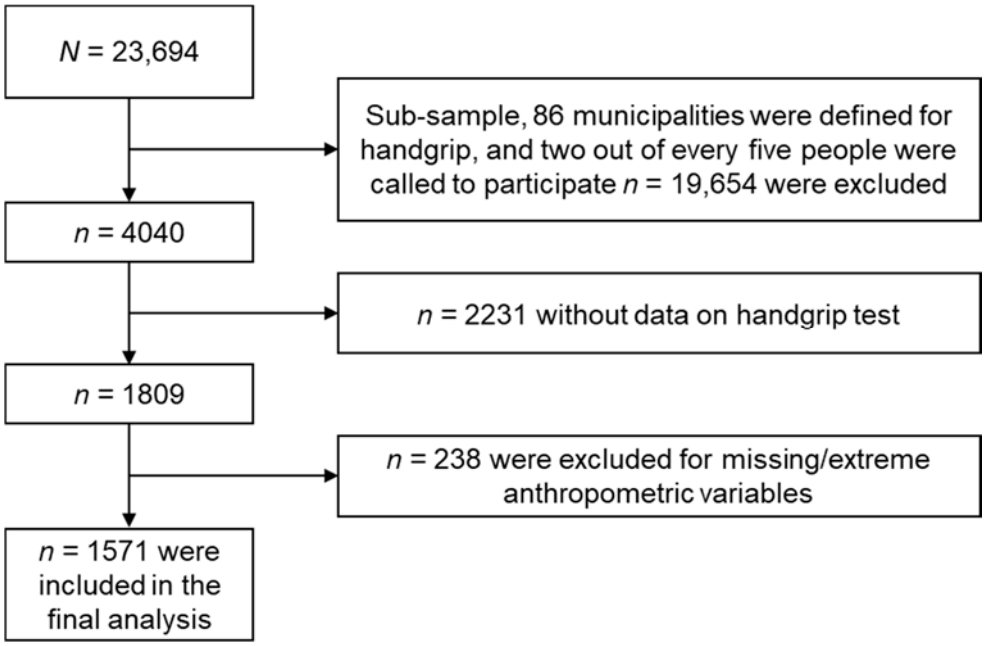

Figure 1. Flow chart showing the selection of the study sample from the Colombian Health and Wellbeing and Aging Survey (SABE) 2015. All analyses presented in this paper are based on 1571 surveyed participants, each with complete anthropometric, blood-based, and covariable data.

2.2. Measurements

Trained staff investigators carried out the physical examination, and medical laboratory technicians performed the blood samples and laboratory tests. With the aim to minimize the error, all analysis were performed by the Universities of Caldas and Valle, Colombia. Height and body weight were measured with a portable stadiometer (SECA 213, Hamburg, Germany) and an electronic scale (Kendall graduated

platform scale). BMI was calculated in kg/m^2 from the measured body weight and height. WC was measured over the midpoint between the lower border of the ribs and iliac crest in the midaxillary plane, at the end of normal expiration. We used WC as proxy measures of central adiposity since they are useful tools in clinical practice, and are reliable predictors of T2DM and visceral adiposity [32]. The HGS of both hands was measured with a digital hand dynamometer (Takei; Scientific Instruments Co., Ltd., Tokyo, Japan). Each participant completed the 3-trial for each hand, and the final estimate of HGS was the average of all measurements. The values were normalized to body weight (relative HGS). After an overnight fast, blood samples were obtained in the morning. Plasma glucose was analyzed by enzymatic colorimetric methods (Dinamica Laboratories, Bogotá, Colombia).

The following detailed demographics were recorded: age, sex, ethnicity, socioeconomic status (for lifestyle characteristics), alcohol intake (participants were categorized as those who do not drink and those who drink less than 1 day per week, 2 to 6 days a week, or every day), and cigarette smoking (participants were categorized as those who do not smoke and those who have never-smoked, those who currently smoke, or those who previously smoked) were recorded. A "proxy physical activity" report was conducted using questions: (i) "Have you regularly exercised, such as jogging or dancing, or performed rigorous physical activity at least three times a week for the past year?"; (ii) "Do you walk, at least three times a week, between 9 and 20 blocks (0.6 to 1.2 km) without resting?"; (iii) "Do you walk, at least three times a week eight blocks (0.5 km) without resting?". Participants were considered physically active if they responded affirmatively to two of the three questions. Demographics such as sex, age, socioeconomic status (low, middle, and high), ethnicity (people belonging to various indigenous groups, i.e., Ika, Kankuamo, Emberá, Misak, Nasa, Wayuu, Awuá, Mokane, etc., black "mulato" or Afro-Colombian, white and others, i.e., mestizo, gypsy, etc.), and urbanicity (urban, rural) were obtained by structured interview.

2.3. Statistical Analysis

Descriptive analyses of the study population characteristics were performed through mean ± standard deviation (SD) for the continuous variables and frequency distribution for categorical variables. The normality of the data was examined by the Kolmogorov–Smirnov test. Significant differences between men and women were analyzed using Student's *t*-test or the chi-square (χ^2) post-hoc test. To elucidate the differences after controlling confounder variables like sex, age, lifestyle, and sociodemographic characteristics, we performed an analysis of covariance (ANCOVA). Differences were interpreted through Cohen's effect size indices as small ($d = 0.2$), medium ($d = 0.5$), or large ($d = 0.8$) based on benchmarks suggested by Cohen [33]. Mediation analysis was conducted to determine the indirect effect of fasting glucose levels on the relationship between abdominal obesity by WC and relative HGS (see Figure 2).

In this order, we obtained the direct effect from variable X (categorized as 0 = healthy vs. 1 = abdominal obesity) to Y (relative HGS). Fasting glucose levels were used to know whether it played a mediator role. That is, to know if the detrimental effect of being abdominal obese on poorer muscle health is mediated by fasting glucose. Note that mediator in this case would be understood as the harmful ingredient for such a damaging relationship between abdominal obesity status and muscle health to take place. The analyses were conducted using the PROCESS macro for SPSS, version 3.4.1, developed by Hayes [34]. This method provided an estimation of both the direct (Path c) and indirect (Path c') pathways, resulting in the calculation of 95% confidence intervals (CI) for both direct and indirect effects (see Figure 2 for model depiction). The regression coefficients are displayed in unstandardized form, as the bootstrapped CI's correspond to the unstandardized effects rather than the standardized effects (β). Mediation results are considered significant if the CI's do not contain 0. A p-value < 0.05 was interpreted as statistically significant.

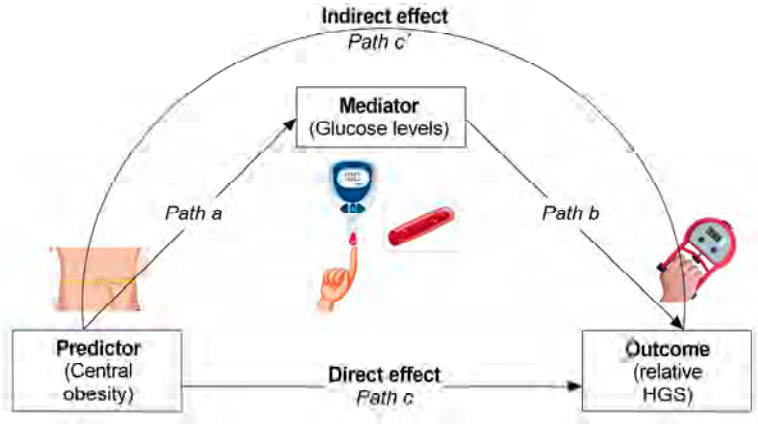

Figure 2. Mediation analysis tests a hypothetical causal chain where one variable X (abdominal obesity status) affects a second variable M (fasting glucose levels) and, in turn, that variable affects a third variable Y (HGS, relative handgrip strength).

3. Results

Of the 1571 subjects included in the sample, 1239 (78.8%) had abdominal obesity and 331 were healthy (22.2%). Healthy individuals presented a mean age of 70.5 (8.1) years and abdominal obese individuals 69.6 (7.3) years (see Table 1). Statistical differences ($p < 0.05$) between groups were found for all anthropometric characteristics and glucose level with higher values for older adults with central obesity. Healthy individuals presented better performance in muscular strength than obese individuals. Also, statistical differences were found between healthy and obese individuals on ethnicity, socioeconomic status, lifestyle outcomes and urbanicity, $p < 0.05$.

Table 1. Characteristics of the study participants (n = 1571).

Characteristics	Full Sample (n = 1571)	Healthy (n = 331)	Abdominal Obesity (n = 1239)	p-Value
Age, years	69.6 (7.3)	70.5 (8.1)	69.6 (7.3)	0.052
Sex, n (%)				
Females	943 (60.0)	108 (32.6)	835 (67.3)	<0.001
Clinical outcomes, mean (SD)				
Body mass, kg	68.3 (11.5)	55.2 (8.4)	68.3 (11.5)	<0.001
Height, m	1.55 (0.08)	1.59 (0.08)	1.55 (0.07)	<0.001
BMI, Kg/m^2	28.9 (4.3)	22.5 (2.7)	28.9 (4.3)	<0.001
Waist circumference, cm	96.1 (9.1)	79.3 (6.6)	96.1 (9.1)	<0.001
Glucose fasting, mg/dL	100.1 (26.3)	90.4 (18.0)	100.1 (26.3)	<0.001
Muscular strength, mean (SD)				
HGS (kg)	21.1 (8.4)	22.9 (8.6)	20.6 (8.2)	<0.001
Relative HGS (kg/kg body mass)	0.32 (0.12)	0.41 (0.13)	0.30 (0.1)	<0.001
Race/ethnic group, n (%)				
Indigenous	79 (5.0)	21 (6.3)	58 (4.7)	<0.001
Black "mulato" or Afro-Colombian	125 (8.0)	32 (9.7)	93 (7.5)	<0.001
White	414 (26.4)	70 (21.1)	344 (27.7)	<0.001
Others *	753 (47.9)	153 (46.2)	600 (48.4)	<0.001
Missing date	200 (12.7)	55 (16.6)	145 (11.7)	—
Socioeconomic status, n (%)				
Level I-II (low)	1138 (72.4)	247 (74.6)	891 (71.9)	<0.001
Level III-IV (middle)	424 (27.0)	83 (25.1)	341 (27.5)	<0.001
Level V-VI (high)	9 (0.6)	1 (0.3)	8 (0.6)	0.020
Lifestyle outcomes, n (%)				
Smoking	152 (9.7)	56 (16.9)	96 (7.7)	0.001
Alcohol intake	203 (12.9)	59 (17.9)	144 (11.6)	<0.001
Physical activity "proxy"	1278 (81.3)	261 (78.9)	1017 (82.2)	<0.001
Urbanicity, n (%)				
Urban	1311 (83.5)	247 (74.6)	1064 (85.8)	<0.001
Rural	260 (16.5)	84 (25.4)	176 (14.2)	<0.001

Data are presented as mean ± SD or number (percentage) of participants. Significant differences between groups were analyzed by Student's t-test or χ^2 test. BMI: body mass index; * Others (mestizo, gypsy, etc.).

Thus, to clarify the differences between central obesity status ("healthy" vs. "abdominal obesity") adjusted by the confounder variables we performed analysis of covariance, Table 2. The ANCOVA shows that differences in glucose levels and relative HGS parameters between older adults with and without abdominal obesity were independent after adjusting for sex and age ($p < 0.001$, Model 1), sex, age, and lifestyle ($p < 0.001$, Model 2), and ANCOVA Model 2 was additionally adjusted with socioeconomic status, ethnicity, and urbanicity ($p < 0.001$, Model 3).

Table 2. Comparison of the marginal mean values of fasting glucose levels and relative HSG according to central obesity status.

Variables	Model 1			Model 2			Model 3		
	Healthy	Abdominal Obesity	*d*	Healthy	Abdominal Obesity	*d*	Healthy	Abdominal Obesity	*d*
Glucose levels (mg/dl)	90.5 (87.8; 93.3)	100.0 (98.6; 101.4)	0.38 *	90.9 (88.1; 93.7)	99.9 (98.5; 101.3)	0.36 *	90.9 (87.8; 94.0)	100.1 (98.5; 101.5)	0.36 *
Relative HSG (kg/kg)	0.38 (0.37; 0.39)	0.30 (0.29; 0.31)	0.65 *	0.38 (0.37; 0.39)	0.31 (0.30; 0.32)	0.63 *	0.38 (0.37; 0.39)	0.31 (0.30; 0.32)	0.62 *

Data are presented as mean and (95% CI), *d* = Cohen's effect size, * $p < 0.001$.

Figure 3 shows the results of mediation analysis to test whether the fasting glucose could be a mediator of the relationship between abdominal obesity and relative HGS. Path a indicated that central obesity status had a statistical significant negative effect on fasting glucose (β= 9.04, 95% CI = 5.87 to 12.21), $p < 0.001$; the *path b* from fasting glucose to relative handgrip strength was inversely related (β= −0.003, 95% CI −0.005 to −0.001), $p < 0.001$. The direct effect of abdominal obesity on relative HGS was statistically significant (β= −0.069, 95% CI = −0.082 to −0.057), $p < 0.001$. Besides, there was a significant indirect effect since the CI did not include zero. Finally, fasting glucose mediates the detrimental effect of abdominal obesity on relative HGS (β= −0.002, 95% CI = −0.004 to −0.001), $p < 0.001$.

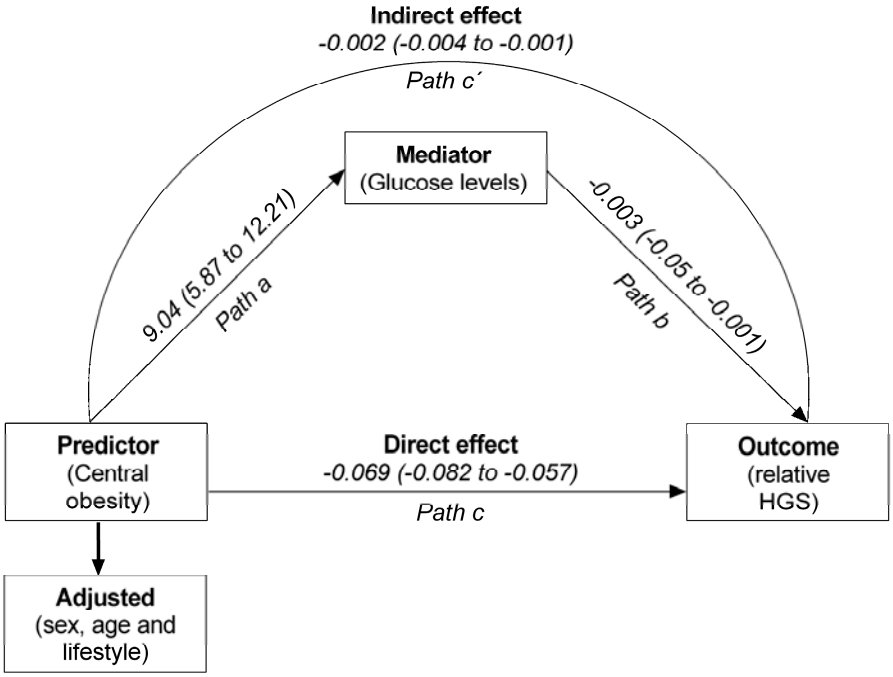

Figure 3. The direct effect of abdominal obesity status (healthy versus unhealthy) on relative HGS gives through fasting glucose level. In the model, abdominal obesity has an inverse relationship with relative HGS. This relationship is mediated by fasting glucose level as the active ingredient (in this case, harmful ingredient). The indirect effect is statistically significant at the 95% confidence interval (CI) when the CI does not include zero.

4. Discussion

In a cross-sectional study of community-dwelling older adults, we found that central obesity was inversely associated with relative HGS, as a measure of muscular strength, in older Colombian adults. This association was mediated by fasting glucose levels. In the same line, we also showed that the abdominal obesity was associated with higher fasting glucose levels. As far as we know, this is the first study to have examined the mediation role of fasting glucose level for the relationship between abdominal obesity and relative HGS. Our results suggest that the glucose level could worsen the association between abdominal obesity status and lower relative HGS. Also, our results provide novel insight into the mechanisms underlying this relationship.

In this study, WC were used as proxy measures for abdominal obesity which have been widely used in older adults for identification of central obesity in older adults [35]. According to the IDF guidelines cutoff point of WC for abdominal obesity, presents a reliable measure of visceral fat [3] in Latin-American people and is strongly associated with metabolic syndrome. Our findings clearly showed that abdominal obesity is associated with a low level of relative HGS. Our results are consistent with previous literature showing that obesity, particularly central adiposity, is inversely associated with strength and/or muscle quality in older adults [8]. Also, we found the relationship between WC and impaired fasting glucose, which is in agreement with previous research showing that central adiposity measured by WC is strongly related to more incidents of T2DM [8,35,36].

In a review study, Freemantle et al. [36] found that WC was strongly associated with T2DM, and Wang et al. [37] also found that WC was a better predictor of T2DM than BMI, even in non-obese individuals. Likewise, Son et al. [38] found a strong association between waist-to-height ratio (another proxy marker for central obesity dysfunction) and hyperglycemia. Overall, these findings support a clinically relevant issue which, through a simple measure of central adiposity, could help to screen for chronic metabolic disorder.

In our study, also showed that higher level of fasting glucose was inversely associated with relative HGS. According to the Guidelines on Integrated Care for Older People, handgrip strength is considered a reliable tool for measuring muscular fitness in older adults [39]. Low relative HGS is an indicator of poor physical performance [40], and it is clear that low levels of physical fitness are related to a lower level of muscle mass [41]. Our results are consistent with previous research which found an inverse association between muscle strength and impaired fasting glucose [21,42,43].

The key finding of this study was that fasting glucose plays a mediator role in the relationship between abdominal obesity and relative HGS. To the best of our knowledge, this is the first study investigating this hypothesis in older adults. Other studies show that fatness is a mediator of muscular fitness and metabolic syndrome [44] in adolescents and, similarly, Brand et al. [45] and Bailey et al. [46] found that body fat mediated the relationship between cardiorespiratory fitness and cardiovascular risk factors. Also, it has been shown that patients with T2DM and with visceral fat accumulation have low muscle quality [47]. Although we did not perform measures of muscle quality per se, previous evidence is suggestive that total and regional adiposity is associated with inter- and intramuscular adipose tissue infiltration, which is considered to be an important anatomical correlation of poor muscle quality [48]. Additionally, the aging effect since age is linked to increased body fat accumulation, insulin resistance, and muscle strength decline [48]. Several epidemiological studies have previously reported that skeletal muscle fat infiltration with age is associated with a decrease in muscle density, loss of muscle quality, poor lower body extremity performance, and falls risk [16–19]. In the same line, higher level of fasting glucose mediating detrimental effect of abdominal obesity on muscle strength, might be the result of a greater content of glucose causing muscle atrophy [49,50]. Skeletal muscle seems to be a protector against diabetes [51]. Mechanistically, this might involve better insulin clearance by muscle myocytes. In this line, it has been shown that an insulin molecule activated by an insulin receptor in the muscle offers 2.1- to 3.1-times higher glucose uptake (removal) than the same insulin molecule activated by an insulin receptor in an adipocyte [52]. Another protector role of muscle mass is better glycolysis by increased glucose transport via GLUT-4 expression from intracellular

pools to the surface cell membrane [53,54]. Therefore, individuals who are fit display higher insulin sensitivity than unfit, obese, or sarcopenic individuals [55].

As indicated above, an increase in intramuscular fat could lead to insulin resistance due to the presence of adipocytes, which worsens glucose clearance [52]. Additionally, this effect leads to a worsening of the intramuscular mitochondrial function since the concomitant atrophy reduces the oxidative and phosphorylation activity of muscle mitochondria [56]. Furthermore, the underlying functions of cytokines and myokines might come into play in this environment. It has been shown that the production of proinflammatory cytokines may be one of the crucial mechanisms for T2DM development as, without good muscle health, the anti-inflammatory myokines cannot prevent systemic inflammation and development of T2DM [57,58].

The attributable risk for chronic metabolic disorder associated with low HGS has been previously reported from populations with varying ethnic backgrounds in different settings within one region or country [20,59,60]. In this line, our findings are consistent with prior reports in the literature as a number of previous studies have emphasized that HGS is inversely associated with plasma glucose after adjusting for age, sex, and BMI [61]. Peterson et al. [43] reported that every 0.05 kg decrease in the relative HGS was independently associated with a 1.49 (95% CI: 1.42–1.56) and 1.17 (95% CI: 1.11–1.23) odds for T2DM in American and Chinese adults, respectively, while among older Mexican Americans, muscle weakness was associated with T2DM (hazard ratio: 1.05; 95% CI: 1.02–1.09) [19]. Notably, we found that glucose fasting plays a mediator role in the negative effect of abdominal obesity on relative HGS in Colombian older adults. However, since this research used a cross-sectional design, casual relationships cannot be inferred. The precise mechanisms for the observed associations must be examined in future studies.

Therefore, primary care strategies should be developed to prevent the loss of muscle mass and muscular strength [62]. Also, maintaining low body fat could help to avoid the deterioration of muscular health associated with insulin resistance or pre-diabetes. These findings can help guide physical exercise programs for coaches, sports technicians or health agents, and nutritionists, prioritizing physical exercise and diet to reduce the accumulation of fat.

Our study has several limitations, including its cross-sectional design, which prevents us from making causal inferences [50]. However, the strengths of this study are the mediation analysis that, to our knowledge, is the first to study the role of glucose levels in the relationship between central adiposity and muscular strength in Latin-American older adults. Also, our results are comparable with other health surveys since both muscle strength and abdominal adiposity were measured using simple and reliable tools for clinical practice. Therefore, the results of this study can provide a foundation for developing hypotheses for longitudinal studies.

5. Conclusions

In summary, fasting glucose level mediates the association between abdominal obesity status and relative HGS in Colombian older adults. Our findings illustrate the importance of glucose control and healthy habits for the prevention of insulin resistance in older with abdominal obesity and the relevance of optimum muscular strength. Longitudinal studies are required in the future to further clarify the influence of glucose levels on this relationship in community-dwelling older adults.

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Role for Physical Fitness in the Association between Age and Cognitive Function in Older Adults: A Mediation Analysis of the SABE Colombia Study

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Abstract: *Objectives.* We investigated the association between physical fitness and cognitive status. Further, we examined whether physical fitness mediates the association between cognitive functioning and aging. *Design.* Cross-sectional study. *Setting.* Urban and rural Colombian older adults. *Methods.* 4416 participants from the SABE study were included in the current analysis. Physical fitness was assessed with the handgrip test and the usual gait speed test. Cognitive status was evaluated through the Folstein Mini-Mental State Examination. A parallel mediation path was used to test the possible mediator role of physical fitness between aging and cognitive functioning. *Results.* Older adults with lower handgrip strength (HGS) were more likely to have mild-cognitive status than older adults with healthy HGS (OR = 1.53, 95% CI = 1.15; 2.02). In addition, older adults with a slower gait speed were more likely to have mild cognitive impairment (OR = 2.05, 95% CI = 1.54; 2.78). Age had an inverse relationship with cognitive function (β = −0.110, 95% CI = −0.130; −0.100) and it was also inversely associated with HGS (β = −0.003, 95% CI = −0.005; −0.002) and gait speed (β = −0.010, 95% CI = −0.011; −0.009). The indirect effects, which indicate that the effect of age on cognitive function is transmitted through mediators, showed that both gait speed (β = −0.028, 95% CI = −0.036; −0.020) and HGS (β = −0.014, 95% CI = −0.024; −0.005) were independent mediators of the detrimental effect of aging on cognitive function. *Conclusions.* Physical fitness mediates the effects of aging on cognitive functioning. Our findings suggest that physical activity can be a key factor to prevent cognitive deterioration during aging process.

Keywords: aging; physical function; cognitive status

1. Introduction

The Latin-American population is aging fast, and it has been projected that by 2050 the number of people older than 65 will double [1]. Aging is associated with several non-communicable diseases, including mobility disability [2] and cognitive decline [3]. In Colombia (South America), the prevalence of mild cognitive impairment is increasing and currently stands at 5.6% [4]. Mild cognitive impairment in older adults leads

to deficits in activities of daily living and quality of life [5], and its progression to more serious cognitive problems (e.g., dementia) is associated with early mortality [6]. Accordingly, identifying risk factors that can help mitigate or delay the appearance of cognitive impairment is a key challenge for health care systems.

Maintenance of physical fitness through the adoption of a physically active lifestyle is known to promote healthy aging [7]. Physical fitness can be defined as a set of measurable attributes that people achieve through physical activity and that are associated with physical and mental well-being [8]. In older adults, physical fitness is typically assessed through specific tests, including handgrip, balance, and gait speed [8], which provide an overview of motor and muscle strength competence.

Physical fitness can decrease dramatically with age, and numerous studies have highlighted the deterioration in muscular strength, balance, gait speed, mobility, and cardiorespiratory performance in men and women aged >60 years of age [9–11]. A better physical fitness status is associated with better health and quality of life [12,13].

Accumulating evidence indicates that a relationship between physical fitness and cognition exists and that a decline in physical performance precedes the deterioration of cognitive ability. For example, A recent study based on the UK Biobank study (2007–2010) of 476,559 participants highlighted that muscle strength measured by a handgrip test was positively and prospectively associated with memory and processing speed [14]. A similar study with 6874 older adults found that physical activity level and lower-limb muscle strength predicted a lower cognitive function [5]. Conversely, other studies have found the opposite: cognitive decline leads to a lower physical performance. For example, in a longitudinal study of over 3500 participants from The Netherlands, Stijntjes et al. [15] found that a poorer executive function was associated with a steeper decline in gait speed in people aged 55–90 years. Likewise, in the Baltimore Longitudinal Study of Aging (412 participants aged $\geq$60 years), Tian et al. [16] found that the relationship between usual gait speed and executive function was unidirectional, such as a slower walking speed predicted future declines in executive function and memory but not vice versa. Finally, a prospective study of 2876 well-functioning older adults (70–79 years) from the US found that early declines in gait speed predicted a decline in orientation, attention, calculation, language and short-term memory, but the association between early declines in cognition and later declines in gait speed was weaker [17]. Thus, the empirical evidence connecting the two phenomena is rather inconclusive.

Regarding the potential beneficial relationship between exercise training and cognitive functioning, Baker et al. used a rigorously controlled methodology to examine aerobic exercise's effects on cognition in 33 adults (mean age 70 years) with mild cognitive impairment. The authors of the former study found an improvement of executive function through aerobic exercise in older women but not men [18]. Likewise, Zhihui et al. [19] reported in a systematic review of randomized clinical trials on the beneficial effects of resistance training on cognitive function in older adults. Exercise-induced changes in cognitive status could be explained by modifications to brain characteristics and functioning, as exercise induces cognitive plasticity [20], improves cerebral perfusion [21] and cerebrovascular reactivity [22], and reverses hippocampal volume loss, thereby improving memory [23].

While it is clear that aging is associated with cognitive decline and changes to cognitive functioning, to our knowledge, no studies have examined the potential mediating role of physical fitness measured through gait speed and HGS on the association between aging and cognitive decline. Consequently, the present study was designed to evaluate the association between physical fitness and cognitive status and to examine whether physical fitness mediates the decline in cognitive functioning associated with aging.

2. Methods

2.1. Design, Setting and Participants

We analyzed data from the "Estudio Nacional de **Sa**lud, **B**ienestar y **E**nvejecimiento" (SABE) Colombia survey. SABE is a nationwide, population-based, cross-sectional study

that was conducted in 2015 by the Epidemiological Office of the Ministry of Health and Social Protection of Colombia (https://www.minsalud.gov.co/). Data were obtained using a probabilistic sampling scheme by clusters (housing segments) with block stratification. The estimated sample size was 24,553 adults aged 60 years and above, assuming an 80% response; the target sample was 30,691 individuals [24]. Nonetheless, because of variations in the application of strategies to achieve a response rate of 70% across regions and civil settings (i.e., urban/rural distributions), the final sample size included 23,694 from 244 municipalities across all departments. More details about the study design and protocol can be consulted in the research published by Gomez et al. [24].

For this subsample analysis, 86 municipalities were selected, including the 4 large cities (Bogota, Cali, Medellin and Barranquilla), for the application of functionality tests and muscle strength assessment, obtaining a sample of 5657 people 60 years of age or older. Of these participants, 4146 subjects were selected for this study. We excluded those with missing data of HGS, gait speed tests and/or anthropometric variables and/or without self-reported health condition (see Figure 1). All participants (or their proxy respondent) provided written informed consent for their data to be used in the study.

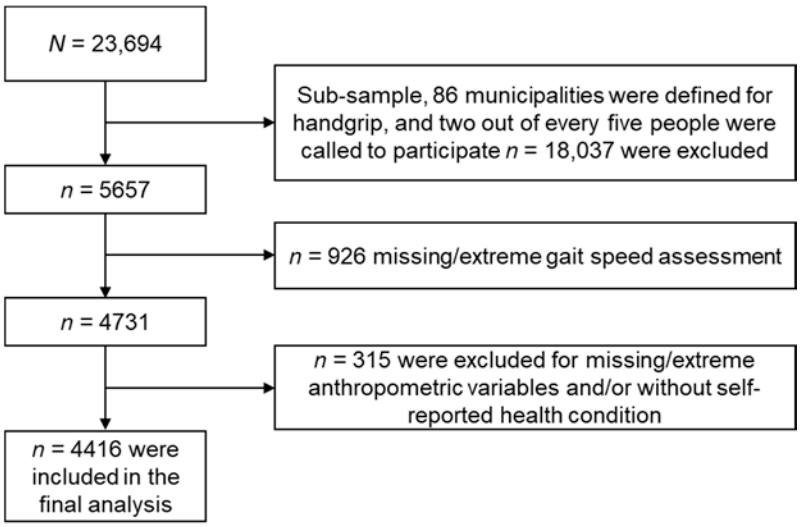

Figure 1. The flow chart shows the study sample selection from the Colombian Health and Wellbeing and Aging Survey (SABE) 2015. All analyses presented here were based on 4416 surveyed participants, each with complete HGS and long-term condition data.

2.2. Data Collection

The health survey included medical history examination, physical fitness examination and questionnaires on health disorders history, lifestyle data and anthropometric variables. Physical tests were performed by technical, medical staff following the standardized protocol for the SABE study [24].

2.2.1. Sociodemographic, Health Disorders History and Lifestyle Data

Participants were asked about sociodemographic factors, including ethnic group (indigenous, black "Mulatto" or Afro-Colombian, white, others and non-ethnic), living area (rural or urban), and socioeconomic status (SES): level I–II: low; level II–III: middle; and level V–VI: high. Three lifestyle variables were included in the survey. Alcohol consumption was assessed using the question: "In the last three months, on average, how many days of the week have you had alcoholic beverages?" Responses were divided into four categories: (1) no alcohol consumption, (2) 1–2 glasses per day, (3) 3–5 glasses per day, (4) more than 5 glasses per day. The variable was then dichotomized by grouping categories 2–4 as alcohol consumption, and category 1 as no alcohol consumption.

Smoking was assessed by asking individuals if they were currently smoking or had ever smoked. Answers were divided into four categories: (1) never smoked, (2) former smoker, (3) smokes less than 5 cigarettes per day, (4) smokes more than 5 cigarettes per day. This variable was also dichotomized by grouping categories 1 and 2 as not smokers and 3 and 4 as smokers. The following questions were used to assessed a "proxy" for physical activity: (1) "Have you regularly exercised, such as jogging or dancing, or performed rigorous physical activity at least three times a week for the past year?"; (2) "do you walk at least three times a week between nine and 20 blocks (1.6 km) without resting?"; (3) "do you walk at least three times a week eight blocks (0.5 km) without resting?". Participants were considered physically active if they responded affirmatively to two of the three questions [25].

Medical information including multimorbidity, as well as chronic condition adapted from the original SABE study [24], was assessed by asking the participants if they had been medically diagnosed with hypertension, diabetes, chronic obstructive pulmonary disease, CVD (heart attack, angina), stroke, different types of cancer, arthritis, osteoporosis, cholesterol, triglycerides, mental or sensory problems.

2.2.2. Anthropometrics Measurement

Height and body weight were measured by a portable stadiometer (SECA 213, Hamburg, Germany) and an electronic scale (Kendall graduated platform scale). BMI was calculated as weight in kilograms divided by the square of height in meters.

2.2.3. Physical Fitness Tests

HGS was used to measure the muscle force profile of the upper limb. For this, we used the Takei dynamometer (Takei Scientific Instruments Co., Tokyo, Japan). Prior to the assessment, the dynamometer was calibrated to ensure proper usage and accuracy. Subjects were asked to perform the assessment (with the elbow joint in full extension) while standing if possible and were given a practice trial to ensure comprehension of the procedure. The grip tests were performed three times on each hand, alternating hands between each trial, and the mean value was recorded as the final score of the test. Testers ensured a total of 60 s of rest between trials on the same hand. The values were normalized to body weight (relative HGS).

Usual gait speed (meters/second) was measured by 3 m walking. The participants had to walk two times at the usual pace starting from a standing position.

2.2.4. Cognitive Function

Cognitive status was assessed using the revised version of the Folstein Mini-Mental State Examination (MMSE), a validated international scale translated to Spanish [26]. The modified version ranges from 0 to 19, with a higher score representing better cognitive function.

2.3. Statistical Analysis

At first, univariate analysis was used to explore extreme values and Kolmogorov Smirnov was used to examine data distribution. Categorical variables are presented using frequencies and percentages, and continuous variables are presented using means and standard deviations. We applied covariance analysis adjusted by sex, age, lifestyle and comorbidities variables to explore the physical fitness differences between cognitive status groups. Unadjusted and adjusted logistic regressions controlling for age, sex, lifestyle and comorbidities were employed to assess the likelihood of having cognitive impairment based on physical fitness level. According to the literature, the covariates included in the adjusted analyses were based on the conceptual model [14–17]. For this purpose, we used the European Working Group on Sarcopenia in Older People 2 (EWGSOP2) guidelines and criteria to determine sarcopenia from the assessment of gait speed (<0.80 m/s) and HGS (<27 kg in men and <16 kg in women) [27].

To test for the possible mediator role of physical fitness between aging and cognitive status, we designed a parallel mediation path analysis (see Figure 2). The mediation model indicated through estimation of indirect effects, what physical fitness components (handgrip strength or/and gait speed) were mediators between the detrimental impact of age on cognitive function as assessed by the MMSE test [26]. To perform the analysis, we used the PROCESS macro for SPSS (IBM, Chicago, IL, USA) [28]. The mediation hypothesis was tested using the bias-corrected bootstrap method with 5000 samples to calculate confidence intervals (95%). The point estimate was considered significant when the confidence interval did not cross zero. In addition, we used the test included in the PROCESS macro to compare indirect effects. Significance was set at the $p \leq 0.05$ level.

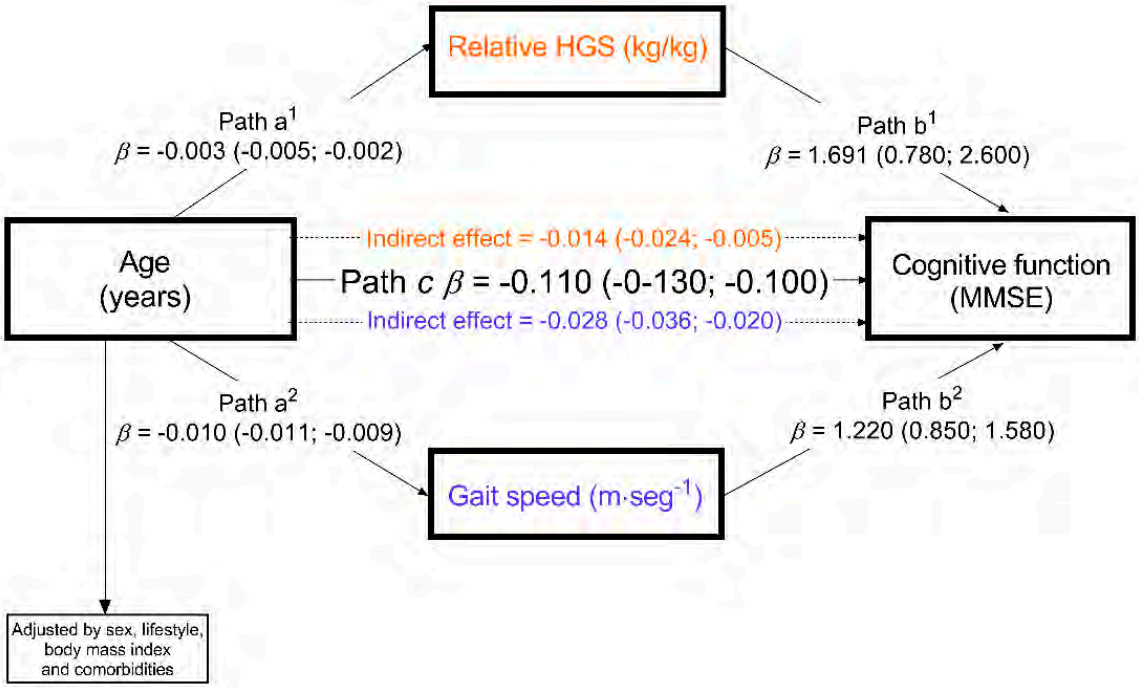

Figure 2. Parallel mediation analysis of aging effects on cognition (MMSE) score through relative HGS (kg) and gait speed ($m \cdot seg^{-1}$), adjusted by sex, lifestyle, body mass index and comorbidities. Number of bootstrap samples = 5000. The indirect effect is statistically significant at the 95% confidence interval (CI) when the CI does not include 0. Betas (β) are reported as the product of simultaneous regression with bootstrap replacement Path a^1 & a^2 = association between age and relative HGS and gait speed, respectively; Path b^1 & b^2 = association between relative HGS and gait speed with cognitive function; Path c = direct effect; orange and blue associations = indirect effect by relative HGS and gait speed, respectively.

3. Results

The descriptive characteristics of participants are presented in Table 1. The mean age of participants was 69.5 ± 7.1 years. The distribution by sex in the overall sample was 57.3% for females and 42.7% for males. Of the 4416 participants included in the study, 510 (11.5%) showed mild cognitive impairment. Regarding the distribution across the different SES levels, the majority of participants fit in the lowest SES level (level I–II). The lifestyle outcomes showed that the proportion of individuals drinking alcohol and smoking was low, 13.5% and 11.0%, respectively. A significant proportion of older adults (80.6%) did not accomplish the minimum required daily physical activity "proxy". Regarding comorbidities, visual problems, high blood pressure and cholesterol had the highest percentage of incidence. There were significant differences between healthy individuals and individuals with cognitive impairment for all variables tested.

Table 1. Sample characteristics stratified by cognitive status.

Sociodemographic Characteristics	Overall	No Cognitive Impairment n = 3906 (88.5%)	Cognitive Impairment n = 510 (11.5%)	p-Value
Sex (female), n (%)	2531 (57.3)	2224 (56.9)	307 (60.2)	0.001
Sex (male), n (%)	1885 (42.7)	1682 (43.1)	203 (39.8)	
Age group, n (%)				
60–69	2512 (56.9)	2366 (60.6)	146 (28.6)	0.001
70–79	1431 (32.4)	1234 (31.6)	197 (38.6)	
80+	473 (10.7)	306 (7.8)	167 (32.7)	
Nutritional status, n (%)				
Underweight	83 (1.9)	73 (1.9)	10 (2.0)	0.001
Normal weight	1344 (30.4)	1141 (29.2)	203 (39.8)	
Overweight	1809 (41.0)	1628 (41.7)	181 (35.5)	
Obese	1180 (26.7)	1064 (27.2)	116 (22.7)	
Socioeconomic status, n (%)				
Level I–II (low)	3371 (76.3)	2934 (75.3)	428 (83.9)	0.001
Level III–IV (medium)	1007 (22.8)	926 (23.7)	81 (15.9)	
Level V–VI (high)	38 (0.8)	37 (0.9)	1 (0.2)	—
Ethnic group, n (%)				
Indigenous	267 (6.0)	267 (6.8)	0 (0.0)	—
Black	369 (8.4)	369 (9.4)	0 (0.0)	—
White	1234 (27.9)	1234 (31.6)	0 (0.0)	—
Others	2036 (46.1)	2036 (52.1)	0 (0.0)	—
Non-ethnic	510 (11.5)	0 (0.0)	510 (11.5)	—
Living area, n (%)				
Urban	3406 (77.1)	3060 (78.3)	346 (67.8)	0.001
Rural	1010 (22.9)	846 (21.7)	164 (32.2)	
Lifestyle outcomes, n (%)				
Alcohol	594 (13.5)	559 (14.3)	35 (6.9)	0.001
Smoking	487 (11.0)	422 (10.8)	65 (12.8)	
Non-physically active	3555 (80.6)	3098 (79.3)	457 (89.8)	
Comorbid chronic diseases, n (%)				
HBP	2374 (53.9)	2077 (53.3)	297 (58.3)	0.001
High cholesterol	2159 (49.1)	1930 (49.6)	229 (45.5)	
Diabetes	715 (16.2)	635 (16.3)	80 (15.7)	
Cancer (any type)	210 (4.8)	195 (5.0)	15 (2.9)	
COPD	443 (10.0)	375 (9.6)	68 (13.4)	
CVD	600 (13.6)	520 (13.3)	80 (15.7)	
Stroke	167 (3.8)	138 (3.5)	29 (5.7)	
Arthritis	1192 (27.1)	1075 (27.6)	117 (23.1)	
Osteoporosis	499 (11.4)	446 (11.5)	53 (10.4)	

Categorical variables are reported as numbers and percentages in brackets. Significant between-cognition status differences χ^2. Comorbidities are reported as "presence/yes". HBP: high blood pressure; COPD: chronic obstructive pulmonary disease; CVD: cardiovascular disease.

Table 2 shows the performance and differences in physical fitness according to cognitive status. Statistically significant differences in HGS relative to body weight were found between older healthy adults and their peers with cognitive impairment after adjusting for sex, age, lifestyle characteristics and comorbidities. The best performance was 0.34 kg/kg *versus* 0.30 kg/kg in healthy older adults *versus* peers with poor cognitive functioning. Similar results were observed for gait speed, with older adults without cognitive impairment showing better functioning than those with poor cognition. Analysis of covariance revealed statistically significant differences ($p < 0.001$) after adjusting for sex, age, lifestyle outcomes and comorbidities.

Table 2. Physical fitness performance in Colombian older adults according to cognitive status.

Variables	No Cognitive Impairment	Cognitive Impairment	Model 1 *p*-Value	Model 2 *p*-Value	Model 3 *p*-Value
Absolute HGS (kg)	22.08	18.50	<0.001	<0.001	<0.001
Relative HGS (kg/kg)	0.34	0.30	<0.001	<0.001	<0.001
Gait speed ($m \cdot s^{-1}$)	0.77	0.63	<0.001	<0.001	<0.001

Note: Model 1: adjusted by sex and age; Model 2: adjusted by Model 1, ethnicity, urbanicity, socioeconomic status and lifestyle; Model 3: adjusted by Model 2 and comorbidities.

Table 3 shows the associations in odds ratios between low HGS and low gait speed according to the EWGSOP2 cut-off and mild cognitive impairment. Older adults with low HGS were more likely to have mild-cognitive impairment than older adults with healthy muscle strength after adjusting for age, sex, lifestyle characteristics and comorbidities (OR = 1.55, 95% CI = 1.16; 2.03). In addition, older adults with slow gait speed were more likely to have mild cognitive impairment (OR = 2.08, 95% CI = 1.56; 2.80).

Table 3. Physical fitness association with cognitive function in Colombian older adults.

	Model 1			Model 2			Model 3		
	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value
Lower HGS	1.45	(1.11; 1.90)	0.006	1.47	(1.11; 1.93)	0.006	1.55	(1.16; 2.03)	0.002
Lower Gait speed	2.12	(1.61; 2.79)	0.007	2.06	(1.55; 2.72)	<0.001	2.08	(1.56; 2.80)	<0.001

Note: Lower HGS and gait speed are defined according to EWGSOP2 guidelines (<0.80 m/s for gait speed) (<27 kg in men and <16 kg in women for HGS). Model 1: adjusted by sex and age; Model 2: adjusted by Model 1, ethnicity, urbanicity, socioeconomic status and lifestyle; Model 3: adjusted by Model 2 and comorbidities.

As shown in the mediation model (Figure 2), we found that the independent variable (age) had an inverse relationship with cognitive function (β = −0.110, 95% CI = −0.130; −0.100). Age was inversely associated with HGS (β = −0.003, 95% CI = −0.005; −0.002) and gait speed (β = −0.010, 95% CI = −0.011; −0.009). The indirect effects showed that both gait speed (β = −0.028, 95% CI = −0.036; −0.020) and HGS (β = −0.014, 95% CI = −0.024; −0.005) were independent mediators of the detrimental effect of aging on cognitive function.

4. Discussion

The present study analyzed a representative sample of Colombian older adults from a National Survey (SABE). We examined the association between low HGS (men <27 kg, women <16 kg) and low gait speed (<0.80 m/s) and cognitive impairment. We also studied the relationship between age and cognitive functioning and whether this relationship was mediated by physical fitness measured through gait speed and HGS.

This study's main finding was the mediator role of gait speed and HGS between aging and cognitive impairment using a parallel mediation model. Our findings suggest that the association between age and cognition is mediated by the level of HGS and gait speed. Accordingly, the loss in cognitive function associated with age could depend on the individual level of physical fitness. For example, older adults with poorer HGS or/and gait speed would show an accelerated loss in cognitive impairment, and the opposite would be seen in peers with a better performance on HGS or/and gait speed. The findings indicate that gait speed and HGS mediate the deterioration of the cognitive status associated with aging, and thus are active components of the aging effects on cognitive status. To the best of our knowledge, this is the first study examining the mediating role of physical fitness in the relationship between age and cognition. Our findings are consistent with the idea that physical fitness contributes to better cognitive functioning [14,29].

The mediator effect of physical fitness could be explained by the benefits that physical exercise has on cognitive health. For example, Xu et al. [30] found an improvement in cerebral perfusion in older women (but not men) after one session per week of resistance

training. Strength training also leads to beneficial changes in white matter atrophy and neuroplasticity [31]. The results from two systematic reviews [31,32] revealed that older adults who participated in a resistance training program maintained or improved their neuroplasticity and brain atrophy. The hippocampus is known to shrink in late adulthood, and exercise training has been shown to increase the hippocampal volume, including high-intensity interval training [33] and strength exercise [34]. Similarly, a multicomponent exercise program, including strength, aerobic and balance exercises, was found to reduce whole brain cortical atrophy in older patients with mild cognitive impairment compared with a control group [35], resulting in improved cognitive function. A possible underlying mechanism for these beneficial changes in brain characteristics and functioning is the increase in production and secretion of brain-derived neurotrophic factor [36–38].

Another finding showed that Colombian older adults with a poor performance in HGS and gait speed were 1.53 and 2.05 times more likely, respectively, to experience mild cognitive impairment. Our findings are supported by prior research showing that a decline in cognition is led by lower physical fitness performance. For example, it was shown that lower HGS was associated with a poorer performance in memory and processing speed [14]. Likewise, gait speed was shown to predict cognitive impairment and dementia [39]. However, other studies indicate the opposite, with several showing that the relationship between physical fitness and cognition is bidirectional or that cognitive decline precedes poor HGS and gait speed [15–17]. From our perspective, the deterioration in cognitive function is preceded by low physical activity and, consequently, by poor physical fitness. This is based on the beneficial effects that exercise has on cognitive health, as shown in previous studies [40,41]. With this in mind, the main objective of the present study was to assess whether physical fitness mediates the inverse relationship between age and cognition.

The present study has several strengths. It is based on a large sample size of older adults within a nationally representative proportion of persons aged $\geq$60 years. In addition, we used a direct measure of physical fitness, a far more reliable and valid measure than self-report questionnaires. HGS and gait speed also are the two most used measures of physical fitness levels used in older adults [42–44]. Moreover, the novelty of examining the mediator role of physical fitness comparing HGS and gait speed should also be considered a strength. Thus, there should be more emphasis on physical fitness in subsequent iterations of the mental health act of Colombia as part of a policy to improve cognitive status across the life course.

Our study does have several limitations. First, the cross-sectional design limits the ability to draw on causal associations. Second, even though we adjusted for potential confounding factors such as sex, lifestyle variables and comorbidities, the population was heterogeneous, especially regarding ethnicity. Some variables were self-reported and are subject to biases. In addition, cognitive status was assessed by a unique self-reported questionnaire, but it is not a clinical diagnosis of cognitive impairment. It would thus be advisable in future studies to combine several questionnaires to avoid bias.

Our finding offers insight into the potential role of fitness on cognitive decline in older adults. Specifically, it is clear that both gait speed and muscle strength must be addressed in future anti-aging programs. Specifically, and following the EWGSOP2 [27] recommendations, the HGS should be above 27 kg for men and 16 kg for women, and gait speed should be >0.80 m/s.

5. Conclusions

Physical fitness, measured by gait speed and HGS, mediates the relationship of aging on cognitive functioning in older adults in Colombia and elsewhere in Latin America & the Caribbean. Our findings suggest the need to maintain gait speed and HGS in older adults to avoid cognitive function loss.

Author Contributions: Formal analysis, M.Á.P.-S. and P.R.O.; investigation, C.A.C.-G.; methodology, C.A.C.-G., M.I. and R.R.-V.; supervision, M.I. and R.R.-V.; writing—original draft, M.Á.P.-S. and J.d.P.-C.; writing—review & editing, P.R.O., C.A.C.-G., M.I. and R.R.-V. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was approved by the Institutional review boards involved in developing the SABE-Colombia study (University of Caldas, ID protocol CBCS-021-14, and University of Valle, ID protocol 09–014 and O11–015) reviewed and approved the study protocol. Permissions and details are available at https://www.minsalud.gov.co/. The Human Subjects Committee approved the secondary analysis study protocol at the University of Javeriana [ACTA ID 20/2017–2017/180, FM-CIE-0459-17].

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The current study used data from the Ministerio de Salud y la Protección Social de Colombia (https://www.minsalud.gov.co), and legal constraints do not permit public sharing of the data. The Ministerio de Salud y la Protección Social de Colombia, however, is open to all qualified researchers anywhere in the world. Thus, the data used in this communication can be easily and directly accessed by applying through the Ministerio de Salud y la Protección Social de Colombia Management System (https://www.sispro.gov.co/pisis/Pages/pisis-plataformade-integraci%C3%B3n-de-SISPRO.aspx).

Conflicts of Interest: The authors declare no conflict of interest.

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