FATORES SOCIODEMOGRÁFICOS, CLÍNICOS E PRÁTICA DE ATIVIDADE FÍSICA SOBRE A CAPACIDADE FUNCIONAL NO ENVELHECIMENTO

TESE

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"It would not be much of a universe if it wasn't home to the people you love."

Stephen Hawking

SUMÁRIO

LISTA DE ABREVIATURAS E SIGLAS

1RM - one repetition maximum

30-s chair - Teste de sentar e levantar da cadeira durante 30 segundos

6MWT - 6-minute-walk test

BMI - Body Mass Index

HbA1c - Glycated Hemoglobin

HbA1c - Hemoglobina Glicada

HR% - Heart Rate

HR_{max} - Maximum Heart Rate

HR_{peak} - Peak Heart Rate

HRR - Heart Rate Reserve

IMC - Índice de Massa Corporal

METs - Equivalentes Metabólicos da Tarefa

MVC - Maximum Voluntary Contraction

NRS - Non-randomized Controlled Studies

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analysis

PRISMA-P - Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols

PROSPERO - International Prospective Register of Systematic Reviews

QoL - Quality of Life

RCTs - randomized controlled trials

RM - Repetitions Maximum

RPE - Rating of Perceived Exertion

TC6 - Teste de Caminhada de 6 minutos

TUG - Timed Up and Go test

VO_{2max} - Maximal Oxygen Consumption

$VO_{2máx.}$ - Consumo Máximo de Oxigênio

VO_{2peak} - Peak Oxygen Consumption

VO_{2pico} - Consumo de Oxigênio de Pico

RESUMO

É relevante estimar a contribuição de determinantes sociais de saúde e clínicos na capacidade funcional e avaliar os efeitos do treinamento físico sobre resultados funcionais. O presente volume inicia com uma revisão de literatura sobre o impacto do envelhecimento e de variáveis clínicas e sociodemográficas na capacidade funcional. Adicionalmente, dois estudos são apresentados, sendo estes: (1) artigo com análise de estudo transversal, explorando a associação de variáveis clínicas e sociodemográficas com o desempenho funcional em idosos, e (2) revisão sistemática e meta-análise avaliando o efeito do exercício físico em parâmetros funcionais. Os desfechos em estudo nesta tese abrangem diversas medidas de aptidão e função física. O estudo 1 demonstra que o desempenho em testes funcionais está associado com idade, sexo, índice de massa corporal e qualidade de vida em idosos. O estudo 2 demonstra que o treinamento físico está associado a uma melhora na capacidade funcional em pacientes com diabetes tipo 2.

Palavras-chave: Envelhecimento; Exercício Físico; Diabetes Tipo 2; Revisão Sistemática; Estudos Transversais.

ABSTRACT

It is relevant to estimate the contribution of social and clinical determinants of health to functional capacity and to assess the effects of physical training on functional outcomes. This volume begins with a literature review on the impact of aging and clinical and sociodemographic variables on functional capacity. Additionally, two studies are presented, namely: (1) article with cross-sectional study analysis, exploring the association of clinical and sociodemographic variables with the functional performance in the older, and (2) systematic review and meta-analysis evaluating the effect of physical exercise on functional parameters. The outcomes studied in this thesis cover several measures of fitness and physical function. Study 1 demonstrates that performance on functional tests is associated with age, sex, body mass index, and quality of life in the older. Study 2 demonstrates that exercise training is associated with an improvement in functional capacity in patients with type 2 diabetes.

Keywords: Aging; Exercise; Diabetes Mellitus, Type 2; Systematic Review; Cross-Sectional Studies.

1. INTRODUÇÃO

O envelhecimento possui diversos fatores explicativos que podem interagir entre si e diferir em suas etiologias, dentre os quais incluem-se características genéticas, ambientais, comportamentais e demográficas (1). Essas interações modificam os sistemas fisiológicos, com aparentes efeitos sobre o sistema neuromuscular. Mesmo na ausência de qualquer doença crônica, o processo de envelhecimento está associado a uma variedade de alterações biológicas que podem diminuir a massa musculoesquelética, força muscular e a função física geral (2).

O curso natural do processo de envelhecimento causa alterações neuromusculares como sarcopenia - declínio progressivo da massa muscular esquelética (3,4) e a dinapenia, que está ligada à diminuição da força muscular (5). Além disso, ocorrem alterações na força máxima, tempo de reação muscular e diminuição de potência muscular (6), somados ao declínio da aptidão cardiorrespiratória (7). O envelhecimento também aumenta o risco de desenvolvimento de diabetes, especialmente para o tipo 2 (8), sendo os adultos mais velhos os maiores representantes do crescimento acelerado nos números da doença (9). Essas alterações somadas têm grande relação com o decréscimo da capacidade funcional.

A sarcopenia tem prevalência estimada de 10% em adultos com mais de 60 anos (10), e está correlacionada com declínio funcional e incapacidade física (3,11,12). A dinapenia tem relação com o aumento no risco de incapacidade física e limitações funcionais (13,14) e baixo desempenho físico (15–17). Por sua vez, a diminuição da potência muscular promove prejuízos na realização de atividades da vida diária (18), sendo uma valência importante para a funcionalidade em idosos (19,20).

Em diabéticos, a função neuromuscular sofre declínio ainda maior do que em seus pares saudáveis (21–24), a doença parece ter um efeito direto no músculo ocasionando comprometimento muscular, dessa forma influenciando na capacidade functional. Além disso, ocorre declínio acentuado de massa (23), força (25) e potência muscular, sendo esta, considerada essencial na manutenção da capacidade funcional básica, como caminhar (22). Em relação à capacidade cardiorrespiratória, valores basais nas medidas de capacidade aeróbica máxima podem influenciar em risco futuro de limitações funcionais (26), sendo que a perda da aptidão cardiorrespiratória e da tolerância ao exercício também são mais acentuadas em pessoas com diabetes tipo 2, em comparação com não diabéticos (27–30).

Interações entre condições clínicas e sociodemográficas também podem ter uma parcela de influência na capacidade funcional. Vários indicadores que contribuem para a identificação do declínio funcional em idosos têm sido relatados, incluindo condição médica e dados demográficos (31). A idade, sexo e massa corporal estão associados a resultados funcionais, como teste de caminhada e força de preensão manual e tem sido consistentemente descritos na literatura (32–37). Outros fatores (i.e. renda, uso de medicamentos, diabetes, qualidade de vida e depressão), não tão explorados como os anteriores, também podem apresentar essa relação (38–42).

Um dos fatores clínicos que merece destaque, é o diabetes tipo 2, considerado um forte fator relacionado à limitação funcional, potencial fator de risco para incapacidade física futura e perda de independência, especialmente em pessoas mais velhas (43). A tendência de incapacidade física pelo diabetes aumenta progressivamente com a idade (44,45) e o risco de incapacidade física (mobilidade e atividades instrumentais da vida diária) para pessoas com diabetes aumenta cerca de 50% a 80% em comparação com aqueles sem a doença (46). Em comparação a idosos saudáveis, aqueles que possuem diabetes tipo 2 têm maior redução da função neuromuscular (23,47), apresentam maior declínio no estado funcional (48), bem como pior desempenho em testes funcionais (23,47).

Além do envelhecimento e de todas as condições discutidas anteriormente, a inatividade física também está relacionada ao prejuízo na capacidade de realizar as atividades diárias e viver de forma independente (49). Porém, na presença de níveis adequados de atividade física esses efeitos deletérios podem ser substancialmente atenuados (49), contribuindo dessa forma para um envelhecimento saudável, definido como o processo de desenvolvimento e manutenção da capacidade funcional (50). Indivíduos com diabetes são menos propensos a praticar exercícios físicos regulares, mesmo que este seja um dos pilares do manejo da doença (51). Ensaios clínicos como o Look AHEAD Study (52) e o Italian Diabetes and Exercise Study (53) demonstraram que as intervenções de atividade física que compõem os programas de estilo de vida aumentaram o desempenho físico em pacientes com diabetes tipo 2 (52–55). No entanto, esses achados ainda são inconsistentes em outros ensaios de exercícios (56–58). Esses resultados divergentes podem ser parcialmente afetados por vários desfechos utilizados para mensurar a capacidade funcional e na especificidade de cada tipo de treinamento, levando a um grau variável de preparação para o teste funcional real.

Sabe-se que diversos fatores e mecanismos interferem na capacidade funcional, no entanto, ainda não se tem clareza de como todos estão envolvidos e qual o grau de influencia nesses desfechos funcionais. Além da divergência quanto aos resultados em desfechos funcionais nos estudos primários, existe uma tensão enorme para desfechos de controle glicêmico nos estudos anteriores de síntese e não identificamos nenhum estudo prévio sintetizando desfechos de capacidade funcional na população com diabetes tipo 2, mesmo que os desfechos funcionais sejam importantes para essa população. Por isso, julga-se importante estimar e explorar fatores que influenciam a capacidade funcional, bem como abranger os diversos desfechos utilizados para medir a capacidade funcional e quantificar a mudança que o treinamento físico pode promover. Um dos objetivos desta tese foi explorar e identificar a contribuição de determinantes sociais de saúde e determinantes clínicos na capacidade funcional (capacidade de caminhada e força de preensão manual), em uma amostra de base populacional de idosos. O outro objetivo foi sintetizar, por meio de uma revisão sistemática e meta-análise, o efeito de diferentes modalidades de exercício físico em pacientes com diabetes tipo 2, em diversos resultados utilizados para medir a capacidade funcional.

2. REVISÃO DA LITERATURA

2.1 Epidemiologia e fisiopatologia do diabetes tipo 2

Diabetes mellitus é um grupo heterogêneo de distúrbios metabólicos que se caracteriza clinicamente pelo quadro de hiperglicemia, resultante de defeitos na ação da insulina, na secreção de insulina ou em ambas, caracterizando aumento nos níveis de glicose sanguínea (59). Deste modo, podemos caracterizar o diabetes mellitus do tipo 1 como ausência de produção endógena de insulina e o diabetes mellitus do tipo 2 como resistência dos tecidos-alvo à ação da insulina associada à hiperprodução endógena de glicose (60,61).

Considerada uma doença crônico-degenerativa e um problema crescente em saúde pública, a doença vem tomando proporções cada vez maiores na população mundial, principalmente em países de baixa e média renda, nos quais tanto o número de casos quanto à prevalência da doença têm aumentado constantemente (62). No ano de 2019, a Federação Internacional de Diabetes (IDF) (63) estimou que 1 em cada 11 adultos da população mundial com idade entre 20 e 79 anos vivia com diabetes. Além do crescente número de casos da doença, o diabetes causou 1,5 milhão de mortes no ano de 2012 (62). Os custos com a doença são altos, tanto para os pacientes, como para os serviços de saúde (62), de modo que os valores estimados demonstraram que 75% das despesas globais em saúde com a doença no ano de 2015 foram com pessoas de 50 a 79 anos (64).

O diabetes tipo 2 é a forma mais comum da doença, presente em 90% a 95% dos casos (61). O quadro geral é descrito como um conjunto de vários fatores retroalimentáveis desencadeados pela resistência dos tecidos-alvo à ação da insulina (60), na qual a lipotoxicidade (65), herança genética (66) e a queda na função mitocondrial (67) são considerados potenciais candidatos para as suas causas ao início da doença. Para o desenvolvimento de diabetes tipo 2, idade - envelhecimento e aumento da expectativa de vida - sobrepeso, perfil lipídico, hipertensão e inatividade física são fatores de risco (8), também frequentemente associados à predisposição genética ou histórico familiar em parentes de primeiro grau (61).

O envelhecimento da população mundial é considerado como um dos principais contribuintes para essa epidemia, sendo os adultos mais velhos os maiores representantes do crescimento acelerado nos números da doença (9). Em geral, 20%

dos idosos têm diagnóstico da doença, além de uma proporção semelhante não diagnosticada (68). É comum após os 40 anos de idade, (59) com maior prevalência em adultos acima de 65 anos do que em outras faixas etárias (69).

Além do envelhecimento, elementos socioeconômicos e comportamentais podem ter associação com o desenvolvimento e manutenção da doença. Estudos sugerem uma ligação entre o nível socioeconômico e a prevalência de diabetes tipo 2 (70–72). Em países desenvolvidos, a prevalência da doença é maior em indivíduos materialmente e socialmente carentes (73). O baixo nível de escolaridade também está associado a maior prevalência da doença (74), bem como a ocupação e renda estão relacionadas com a incidência do diabetes (75). Esses efeitos são relacionados ao longo do curso de vida e a posição socioeconômica nos diferentes estágios de vida pode influenciar no risco para doenças crônicas (76). Por exemplo, associações entre a posição socioeconômica na infância, a educação e a incidência de diabetes (75,77) indicam existir uma associação de longo prazo entre a posição socioeconômica e o desenvolvimento do diabetes. Fatores psicossociais, como sintomas depressivos elevados, falta de controle sobre a vida e relações sociais mais precárias, também têm sido relacionados à doença e ao seu controle (78,79); atividade física e índice de massa corporal (IMC) também são relevantes (80–82). Em resumo, uma revisão narrativa abrangente da literatura existente sobre os fatores de risco do diabetes tipo 2, com maior foco em adultos de países europeus, apresentou resultados com ênfase nos fatores sociodemográficos, incluindo idade, etnia, história familiar, baixo nível socioeconômico, obesidade e comportamentos de estilo de vida pouco saudáveis (como baixos níveis de atividade física, tempo sedentário e dieta pobre em nutrientes) (83).

Atualmente, pessoas com diabetes possuem expectativa de vida mais elevada devido aos recursos terapêuticos disponíveis, no entanto, o manejo clínico da doença em adultos mais velhos pode ser complicado por comorbidades (9). Embora as taxas de complicações relacionadas ao diabetes tenham diminuído na população em geral, a doença em adultos mais velhos está relacionada à maior mortalidade, redução do estado funcional e aumento do risco de institucionalização (84).

2.2 Envelhecimento, diabetes tipo 2 e alterações na capacidade funcional

Considerado como um fenômeno multidimensional, o envelhecimento se manifesta diferentemente entre os indivíduos e depende de interações entre características genéticas, ambientais, comportamentais e demográficas (1). É um processo multifatorial, em que vários aspectos interagem simultaneamente, ocasionando alterações em diversos sistemas corporais (e.g. sistema neuromuscular, composição corporal e metabolismo). Os níveis elevados de marcadores pró-inflamatórios detectados com frequência em indivíduos mais velhos, predizem o risco de doenças cardiovasculares, fragilidade, multimorbidade e declínio da função física e cognitiva (85). Mesmo na ausência de doença crônica, o envelhecimento está associado a uma variedade de alterações biológicas que podem contribuir para a diminuição da massa, força e função musculoesquelética, levando a diminuição na capacidade de tolerar e se recuperar de estressores externos, conhecido como resiliência fisiológica (2). Esta por sua vez, quando diminuída pelo processo do envelhecimento, pode levar à incapacidade física, comprometimento da mobilidade, quedas, diminuição da independência e qualidade de vida (86).

2.2.1 Alterações na função neuromuscular

Entre tantas alterações, o envelhecimento está associado também às alterações na função neuromuscular. Ocorre um declínio progressivo na massa muscular, conhecido como sarcopenia, o qual afeta a produção de força muscular de maneira direta (87). A sarcopenia tem prevalência estimada de 10% em adultos com mais de 60 anos (10), aumentando para valores acima de 50% em adultos com mais de 80 anos (88). Diminuições progressivas da massa muscular ocorrem em uma taxa anual de 1% a 2% após os 30 anos de idade, 1,5% a 3% após os 60 anos de idade e quedas mais aceleradas após os 75 anos de idade (89), com valores maiores de perda nos membros inferiores do que superiores (90,91). Uma redução de aproximadamente 30% na massa muscular e cerca de 20% na área de secção transversa do músculo pode ocorrer na faixa etária de 20 a 80 anos (6), ocorrendo em função do declínio no tamanho e no número das fibras musculares (92). A sarcopenia está correlacionada com declínio funcional e incapacidade física (3,11,12) e também foi associada ao aumento da mortalidade (93). Além disso, é um fator de risco independente para diabetes (94,95).

O grupo *The European Working Group on Sarcopenia in Older People* (EWGSOP) recomenda a avaliação de domínios primários de desempenho físico, força muscular e massa muscular, para identificar a sarcopenia em adultos mais velhos (96). Outro grupo de estudos em sarcopenia, *International Working Group on Sarcopenia* (97) indica condições que devem ser consideradas para iniciar a avaliação de sarcopenia em um paciente, deve ser observado declínio notável na função, força, estado de saúde; dificuldade autorreferida relacionada à mobilidade; histórico de quedas recorrentes; perda recente de peso não intencional; pós-hospitalização e outras condições crônicas (por exemplo: diabetes tipo 2, insuficiência cardíaca crônica, câncer). O diagnóstico de sarcopenia é consistente quando é identificado incapacidade funcional (e.g. estar acamado, não ser capaz de se levantar de uma cadeira de forma independente ou apresentar velocidade de marcha de menos de 1 $m \cdot s^{-1}$), apresentar baixa massa muscular medida de maneira objetiva (absorciometria de raios-X de dupla energia), com pontos de corte de ≤ 7,23 kg/m^2 em mulheres e ≤ 5,67 kg/m^2 em homens, levando em consideração a massa apendicular relativa a $altura^2$ (97).

No entanto, a perda de força ao longo do tempo é maior do que a perda de massa muscular. A dinapenia é definida como a perda de força muscular associada à idade, independente de perdas morfológicas (98) e apresenta taxas de declínio de 2 a 5 vezes maiores (99), sendo a força dos membros inferiores perdida mais rapidamente do que a dos membros superiores (6). Em um estudo longitudinal com 1.678 idosos acompanhados por 5 anos, os homens perderam 16% da força extensora do joelho e apenas 5% da massa muscular da coxa, enquanto as mulheres perderam 13% da força, mas apenas 3% da massa muscular (99). A dinapenia tem relação com o aumento no risco de incapacidade física e limitações funcionais (13,14), baixo desempenho físico (15,17,100) e mortalidade total dentro de acompanhamentos médios de 4,9 anos, 5 anos e 9 anos (101–103).

Os mecanismos responsáveis por um aumento ou diminuição da força podem surgir de duas grandes categorias, de fatores neurológicos e musculoesqueléticos (104). Diferente do que se pensava, o tamanho do músculo não é a principal causa da dinapenia, inclusive desempenha um papel relativamente pequeno neste processo (99,105), no entanto, déficits em estruturas e mudanças na função neurológica e/ou deficiências nas propriedades geradoras de força intrínseca do músculo esquelético contribuem para a fraqueza muscular e disfunção motora (105,106). Um modelo conceitual de como as deficiências do sistema nervoso e muscular levam à dinapenia foi apresentado por Clark & Manini (2012) (5), no qual os autores descrevem que o comprometimento do sistema muscular ocasiona diminuição da produção de força do músculo esquelético e da ativação muscular voluntária, levando ao quadro de dinapenia, que ocasiona limitação funcional e que acaba por gerar incapacidade física.

Ainda ocorrem alterações na força máxima, tempo de reação muscular, principalmente de membros inferiores e diminuição de potência muscular (6). Como comentado acima, ocorre a dissociação entre a diminuição da força e da massa muscular com o envelhecimento, do mesmo modo, ocorre com a força e potência muscular, sendo que a potência diminui em taxa mais acelerada que a força máxima (107). Em idosos com idades entre 65-89 anos, enquanto a força máxima de extensores de joelho diminuiu em torno de 1% a 2% por ano, a potência máxima diminuiu aproximadamente 3,5% ao ano (108). Dados indicam queda da potência muscular de aproximadamente 2,9% por ano em idosos com idade entre 70 e 85 anos (109) e declínio na potência de extensão de joelho de aproximadamente 9,0% por década (110). A diminuição da potência muscular prejudica a realização de atividades da vida diária, tais como caminhar, subir escadas e levantar de uma cadeira (18). Declínios na potência muscular demonstram ser mais importantes do que a força na capacidade de realizar atividades diárias (111,112), sendo a potência muscular dos membros inferiores uma valência importante para a funcionalidade em idosos (19,20).

No entanto, em diabéticos a função neuromuscular sofre declínio ainda maior do que em seus pares saudáveis (21–24). Park e cols. (2009) (23) identificaram declínio de massa muscular em idosos com diabetes tipo 2, especialmente nos casos ainda não identificados, sugerindo que o efeito da doença na massa muscular se manifesta até mesmo nos estágios iniciais. Após seis anos de acompanhamento, a massa muscular da coxa declinou duas vezes mais rápido em mulheres idosas com diabetes do que em mulheres não diabéticas (23). Em um estudo coreano com 414 participantes com idade igual ou superior a 65 anos, o diabetes tipo 2 foi associado a um risco duas a quatro vezes maior de baixa massa muscular em comparação aos indivíduos controle (113). Outros estudos também mostraram declínio acelerado da massa magra (pernas), força muscular e capacidade funcional, incluindo a velocidade da marcha em pessoas idosas diabéticas em comparação com aquelas sem diabetes (22,47,114). Em resultados encontrados por Guerrero e cols. (2016) (21) foi demonstrado que existe deterioração prematura da massa e função muscular em pacientes adultos com diabetes tipo 2, com idade inferior a 60 anos, associada ao quadro da doença, independente do tempo de doença, controle metabólico e complicações microvasculares características dessa condição.

Em relação à força muscular, o estudo *Health, Aging, and Body Composition Study* documentou perda acelerada de força e qualidade de membros inferiores em idosos com diabetes após três anos de acompanhamento em comparação com aqueles sem a doença (25). Idosos com diabetes tipo 2 demonstraram 30% de declínio na força muscular comparados aos saudáveis (25). Pacientes diabéticos tipo 2 e controles pareados por sexo, idade, peso, altura e nível de atividade física, foram avaliados para força de membros superiores e inferiores. Os participantes com diabetes tipo 2 tiveram uma redução de 17% da força dos flexores do tornozelo e 14% nos extensores do tornozelo, a força dos extensores e flexores de joelho foi reduzida em 7% e 14%, respectivamente, e a fraqueza muscular foi relacionada à presença e gravidade de neuropatia periférica (24). Em um estudo transversal (115), foram avaliados 1.391 participantes, com idades entre 60 e 70 anos, no qual verificou-se que o diabetes tipo 2 foi associado a uma força de preensão manual significativamente mais baixa, principalmente em homens, esse grupo realizou em média 3 quilograma-força a menos de força no teste, do que o grupo que apresentou tolerância normal à glicose. Em pacientes com diabetes tipo 2 com e sem polineuropatia, a força muscular máxima dos membros inferiores é reduzida em até 50% em relação a comparadores saudáveis, bem como mobilidade prejudicada (116). A potência muscular também decai em proporção maior em indivíduos com diabetes tipo 2 em comparação com seus pares sem a doença, e é considerada essencial na manutenção da capacidade funcional básica, como caminhar (22).

2.2.2 Prejuízos na capacidade funcional

O consumo máximo de oxigênio reduzido é um marcador padrão com valor prognóstico negativo sólido do estado de saúde na população geral (117). Níveis mais altos de aptidão cardiorrespiratória associam-se com menor risco de eventos clínicos, como morbidade e mortalidade cardiovascular, e mortalidade por todas as causas (118–122). Com o avanço da idade, é observado declínio não-linear na aptidão cardiorrespiratória quando não acompanhada por um programa de exercícios regulares, com uma taxa de declínio acelerado maior de 20% a cada 10 anos em pessoas com 70 anos ou mais (7). O incremento nas medidas de capacidade aeróbica máxima ($VO_{2máx,}$ VO_{2pico}) e desempenho neuromuscular esquelético são importantes determinantes da tolerância ao exercício (123) e habilidades funcionais (124) entre adultos mais velhos. Os valores basais em homens e mulheres de meia idade podem influenciar em risco futuro de limitações funcionais (26), doenças crônicas e morte (125).

O diabetes tipo 2 resulta em perda da aptidão cardiorrespiratória e da tolerância ao exercício (27,28), com evidências de que a capacidade aeróbica máxima desses pacientes é reduzida em comparação com não diabéticos (29,30), tendo desempenho submáximo e máximo de exercício prejudicados, independente de obesidade, com comprometimento presente mesmo na ausência de doença cardiovascular (126). Green e cols. (2015) (27) revisaram resultados de participantes com diabetes tipo 2 de curta duração (~3-5 anos), com idades entre 40-60 anos, e observaram que a doença reduziu o VO_{2pico} de 12% a 15% e contribuiu para desaceleração da resposta dinâmica pulmonar durante o exercício submáximo, sendo os valores de tolerância ao exercício (tempo de exercício) também menores (27). Uma revisão de literatura, relatou que o diabetes tipo 2 estabelecido (> 5 anos de duração) está associado à aptidão cardiorrespiratória prejudicada (i.e. tolerância reduzida ao exercício) e redução de 20-30% do VO_{2pico} em comparação com não diabéticos, pareados em relação ao sexo, idade, sedentarismo e obesidade (127). Essas alterações na capacidade funcional do sistema cardiovascular significam um comprometimento da capacidade de exercício em pessoas com diabetes tipo 2. Consequências clínicas relevantes podem ser associadas a isso, como redução da independência em atividades diárias, aumento do risco de mortalidade por doenças cardiovasculares (120). Em uma coorte com pacientes com diabetes tipo 2, foi demonstrada associação inversa entre equivalentes metabólicos da tarefa (METs) alcançados na capacidade de exercício e mortalidade por todas as causas, na faixa etária de 50-65 anos, o acréscimo de 1 METs foi associado a redução de risco de 27%, e 16% naqueles com mais de 65 anos (128).

O desempenho do exercício é prejudicado nessa população, pois parâmetros metabólicos e cardiovasculares podem ser gravemente afetados, de maneira que a função cardíaca e a oferta sistêmica de oxigênio possam ter relação com este cenário (129). Em indivíduos com diabetes tipo 2, sobrepeso e obesidade, fatores como idade, circunferência da cintura, IMC, duração da doença, níveis elevados de HbA1c, história de doença cardiovascular, síndrome metabólica, uso de beta bloqueadores e etnia afro-americana podem ter relação com a diminuição na capacidade de exercício (130). Considerando que durante o exercício ocorre interação delicada de múltiplas funções fisiológicas (como ventilação pulmonar, débito cardíaco, distribuição e difusão do sangue muscular, capacidade aeróbica, força musculoesquelética), ainda não se sabe quais destes parâmetros, isolados ou em conjunto, devem ser considerados como determinantes principais do decréscimo da capacidade de exercício nesta população (127).

Os modelos do processo de incapacidade física são de natureza longitudinal e pressupõem que as interações entre o indivíduo e seus ambientes sociais, psicológicos e físicos são elementos fundamentais no desenvolvimento de limitações funcionais ao longo da vida (131,132). Podem existir múltiplos fatores biopsicossociais que afetam os resultados de saúde na população idosa. Uma estrutura conceitual apresenta alguns fatores conhecidos por influenciar negativamente os resultados de saúde (limitações funcionais e bem-estar emocional diminuído), tanto física quanto mental em adultos mais velhos, as quais sejam: etnia, sexo, idade, estressores ambientais como pobreza do bairro, quantidade e tipo de atividade física, doenças crônicas e adaptação a estressores físicos e emocionais (133). A idade, sexo e massa corporal estão associados a resultados funcionais (i.e. teste de caminhada prejudicada e força de preensão manual) e são consistentemente descritos na literatura (32–37), bem como outros fatores tais como renda, uso de medicamentos, diabetes, qualidade de vida e depressão (38–42).

Entre os fatores que influenciam a capacidade funcional, o diabetes tipo 2 tem sido relatado como um forte fator relacionado à limitação funcional, potencial fator de risco para incapacidade física futura e perda de independência, especialmente em idades mais avançadas (43). A tendência de incapacidade física pelo diabetes aumenta constantemente com a idade (44,45), visto que, além das complicações macrovasculares e microvasculares, as síndromes geriátricas também ocorrem com maior frequência nessa população (134). O risco de incapacidade física para pessoas com diabetes aumenta em cerca de 50% a 80% em comparação com aqueles sem a doença, esta revisão sistemática, incluindo 26 estudos, demonstrou que a doença aumentou o risco de incapacidade para mobilidade e atividades instrumentais da vida diária (46). Até 70% dos idosos com diabetes têm dificuldades em realizar atividades de vida diária, apresentando limitações de mobilidade, principalmente de membros inferiores (48). Em comparação a idosos saudáveis, aqueles que possuem diabetes tipo 2 têm maior redução da função neuromuscular (23,47), apresentam maior declínio no estado funcional (48), bem como pior desempenho em testes funcionais (23,47). Com o desempenho afetado em suas atividades diárias (47,114), diminuem o seu nível de atividade física, consequentemente, reduzindo a qualidade de vida (135). Menos se sabe sobre a ligação entre diabetes e incapacidade física na meia-idade, onde o impacto das complicações associadas à doença também é menos conhecido. No entanto, evidências exploratórias indicam que a doença pode explicar, em pequena extensão, a deficiência física na meia idade (136), da mesma forma, a doença contribui para explicar a variação na trajetória idade e incapacidade física (137).

A maior prevalência de limitação funcional e incapacidade física em adultos mais velhos com diabetes pode ser o resultado de um processo multifatorial (coexistem processo de envelhecimento - alterações neuromusculares e de capacidade de exercício - complicações tradicionais micro e macrovasculares relacionadas ao diabetes, comorbidades associadas) e essa etiologia ainda não está completamente entendida. Por exemplo, condições crônicas (i.e., doenças cardiovasculares, doença arterial periférica, neuropatia periférica, sobrepeso, depressão e deficiência visual) explicam <60% do risco de limitação na caminhada, relacionado ao diabetes, enquanto foi explicado 85% do risco de incapacidade nas atividades básicas (138). Informações semelhantes foram apresentadas no estudo *National Health and Nutrition Examination*

Survey (NHANES), em que comorbidades como doenças cardiovasculares, obesidade, úlceras, doença renal crônica, deficiência visual, deficiência auditiva, problemas de memória, fratura de quadril, artrite, doença pulmonar obstrutiva crônica, câncer e nível de controle glicêmico, foram associados com até 72% das chances de inaptidão em atividades básicas e atividades instrumentais da vida diária (139). Além disso, a doença parece ter um efeito direto no músculo. A resistência à insulina, a hiperglicemia, neuropatia periférica e infiltração de gordura intramuscular são consideradas mecanismos que levam ao comprometimento muscular, influenciando na capacidade funcional (140).

Além do envelhecimento e de todas as condições discutidas anteriormente, o sedentarismo também está relacionado ao prejuízo na capacidade de realizar as atividades diárias e viver de forma independente, porém, este pode ser substancialmente atenuado na presença de níveis adequados de atividade física (49), contribuindo dessa forma para um envelhecimento saudável, definido como o processo de desenvolvimento e manutenção da capacidade funcional (50). A partir dos pontos discutidos nesse tópico principal, podemos enfatizar a importância da avaliação rotineira do estado funcional em pessoas idosas, da forma mais completa e abrangente possível, para assim possibilitar a promoção de intervenções precoces voltadas à manutenção da capacidade funcional, além de compreender os fatores que podem influenciar positiva ou negativamente na capacidade funcional de idosos.

2.3 Efeitos do exercício físico na capacidade funcional

O exercício físico é um subconjunto planejado, estruturado e repetitivo da atividade física que visa melhorar um ou mais parâmetros da aptidão física (141). Diferente do exercício físico, a atividade física é definida como qualquer movimento corporal produzido por contrações do músculo esquelético, resultando em aumento do gasto de energia (142). As diretrizes da Organização Mundial da Saúde de 2020 (143) para prática de atividade física para adultos, orientam que volumes semanais de atividade física aeróbica e de fortalecimento muscular sejam alcançados (150-300 minutos de intensidade moderada ou 75-150 minutos de intensidade vigorosa) para que benefícios sejam conferidos, além de diminuir comportamento sedentário. Além disso, é recomendado que idosos realizem atividades de componentes variados (combinações de força, equilíbrio, marcha e treinamento de função física) três ou mais dias por semana, com o objetivo de aumentar a capacidade funcional e prevenir quedas. Na população adulta (18-64 anos), os benefícios da atividade física estão relacionados à resultados de saúde, como mortalidade por todas as causas e por doenças cardiovasculares, hipertensão arterial, diabetes tipo 2, saúde mental e saúde cognitiva, entre outros aspectos. Em adultos mais velhos, além dos benefícios citados, a atividade física também ajuda a prevenir quedas, declínios na saúde óssea e incapacidade funcional (143).

Para pessoas com diabetes tipo 2, as diretrizes atuais (144) recomendam que seja realizado pelo menos 150 minutos por semana de exercícios aeróbicos de intensidade moderada a vigorosa e 2 a 3 vezes por semana exercícios de força, além de diminuir a quantidade de tempo sedentário. Ainda, os pacientes idosos devem realizar treinamento de flexibilidade e equilíbrio, sendo o exercício, juntamente com as intervenções dietéticas e farmacológicas, a base do controle do diabetes (144). Uma síntese de evidências demonstrou, a partir de 16 artigos primários e 11 revisões sistemáticas com meta-análise, que a atividade física/exercício se associa com redução de até 51% da incidência de diabetes tipo 2, além de melhorar a sensibilidade à insulina, força muscular, consumo de oxigênio e capacidade aeróbica (145). Um dos benefícios do exercício físico para o controle do diabetes é o controle glicêmico, desfecho importante para o manejo clínico da doença. Resultados de uma meta-análise (146) demonstraram que o treinamento físico (incluindo exercícios aeróbicos, de força ou combinados), se associou com redução de HbA1c em aproximadamente 0,6%, quando comparado a grupos controle sem treinamento. Além disso, os benefícios do exercício físico também podem ser manifestados pela melhora da capacidade funcional nesta população.

Ensaios experimentais notáveis como o *Look AHEAD Study* (52) e o *Italian Diabetes and Exercise Study* (IDES) (53) levaram em consideração desfechos de função física e demonstraram que o exercício/atividade física em programas de estilo de vida pode melhorar o desempenho físico em pacientes com diabetes tipo 2 (52–55). A literatura dispõe um número limitado de ensaios com intervenções estruturadas em pessoas com diabetes tipo 2, que avaliaram como objetivo principal, desfechos funcionais e utilizaram grupos controles sem outras intervenções (147–149). Um deles, em idosos, demonstrou que a força máxima de membros inferiores e superiores aumentou significativamente (até 65% de aumento) para o grupo intervenção em comparação ao grupo controle, após 16 semanas de treinamento de força (147). Em outro dos estudos citados, (149) após 8 semanas de treinamento combinado na água, em indivíduos com média de idade de 62,5 anos, a capacidade aeróbica (VO_{2pico}) melhorou em 16%. Ainda, a força muscular geral (dados de teste de força somados) melhorou significativamente com o treinamento em comparação ao controle, de maneira que os resultados da força muscular da parte inferior do corpo melhoraram significativamente em 13% com o treinamento. Entretanto, a força superior do corpo não sofreu alterações significativas. O terceiro destes estudos demonstrou que um treinamento de força utilizando faixas elásticas em idosos, durante 48 semanas, melhorou apenas a força de extensão de joelhos, tendo os valores de preensão manual e velocidade na marcha não alterados (148).

Ensaios que não utilizaram desfechos primários de capacidade funcional e com grupo controle sem intervenção, também apresentam resultados variados. Balducci e cols. (2010) (150), com o objetivo de investigar o efeito de 12 semanas de diferentes modalidades de exercício sobre os níveis de marcadores inflamatórios em adultos com média de idade de 62 anos, avaliaram como desfecho secundário, entre outros, a aptidão cardiorrespiratória ($VO_{2máx.}$), que aumentou significativamente apenas nos grupos de exercício aeróbico e combinado. Homens e mulheres (n=49), com idades entre 60 e 69 anos, realizaram treinamento aeróbico durante 16 semanas, com diversos desfechos funcionais avaliados. Tanto as mulheres quanto os homens aumentaram o $VO_{2máx.}$, o número de repetições no teste 30-s *chair* (sentar e levantar da cadeira durante 30 segundos) e a distância percorrida no teste de caminhada de 6 minutos (TC6) após o treinamento, enquanto outras mudanças substanciais não foram encontradas nos demais desfechos avaliados e no grupo controle (151). Uma intervenção de 12 semanas utilizando plataforma vibratória, com 39 participantes e idade média de 69 anos, apresentou apenas uma tendência de melhora no teste Timed Up and Go (TUG) para os participantes do grupo. Já para os testes TC6 e de 30-s *chair*, o grupo que realizou o treinamento melhorou significativamente seus resultados, quando comparados ao grupo controle (152). Em uma intervenção com exercício combinado de 24 semanas, com amostra de 208 participantes (80 homens, 128 mulheres) e idade média de 61 anos, foi avaliada a resistência muscular, a flexibilidade e a distância percorrida no TC6. No grupo intervenção, nos testes de rosca direta do braço direito e esquerdo, 30-s chair e no TC6, houve melhora; nos demais testes não foram observadas mudanças significativas, sendo que, no grupo controle, os mesmos valores diminuíram. Já os valores dos testes de flexibilidade aumentaram no grupo controle (153).

Em relação a estudos com intervenções de exercício físico, mas com grupos controle ativos, as intervenções, desfechos funcionais avaliados e resultados, continuam variados. Um estudo em idosos com diabetes tipo 2, idade entre 61-88 anos que realizaram uma intervenção de 12 semanas de treinamento de potência muscular, enquanto o grupo controle realizou alongamento muscular, diversos desfechos de capacidade funcional foram avaliados. Os autores identificaram que houve aumento no escore total da bateria de testes *Short Physical Performance Battery* para ambos os grupos e, quando os testes foram desmembrados, o grupo de potência muscular melhorou o tempo de realização do teste de marcha em 4 m e ambos os grupos melhoraram o desempenho no teste de sentar e levantar cinco vezes. Quanto ao equilíbrio, o equilíbrio dinâmico avaliado pelo teste de alcance funcional mostrou que o grupo intervenção melhorou o desempenho em relação ao controle. Não houve mudança no equilíbrio estático para nenhum dos grupos. Potência e força dinâmica máxima aumentaram significativamente para o grupo intervenção em comparação ao controle (58). Na mesma linha, 44 idosos com idade média de 69,7 anos, realizaram uma intervenção de treinamento de força muscular ou fizeram parte de um grupo controle ativo com aulas de alongamento, durante 12 semanas. Desfechos de capacidade funcional foram avaliados e apenas a força dinâmica máxima dos extensores do joelho melhorou significativamente em comparação ao controle. Força rápida de extensores de joelho, teste de sentar e levantar, TUG e teste de subir escadas não apresentaram melhoras para nenhum dos grupos (57).

Conforme demonstramos ao longo desta revisão de literatura, diversos mecanismos têm influencia sobre a capacidade funcional de idosos, entre eles fatores clínicos e sociodemográficos. No entanto, ainda não se tem clareza de como todos esses fatores estão envolvidos e qual o grau de influência em desfechos de capacidade funcional, por isso, é relevante explorar e conhecer mais sobre quais desses fatores podem estar associados ao desempenho em testes funcionais. Para isso, realizamos um estudo transversal exploratório com o objetivo de explorar e identificar a contribuição de determinantes sociais de saúde e determinantes clínicos na capacidade funcional (capacidade de caminhada e força de preensão manual), em uma amostra de base populacional de idosos.

Também demonstramos a importância de preservar e/ou melhorar a capacidade funcional na população idosa, especialmente em idosos com diabetes tipo 2. Observa-se grande variabilidade nos tipos de intervenções utilizados, nos desfechos avaliados e nos resultados encontrados. Não havendo consistência na literatura, nem diretrizes específicas sobre esse tema para a população com diabetes tipo 2. É importante ressaltar que a força da relação entre o exercício e o desempenho funcional varia, possivelmente, dependendo das medidas específicas realizadas e do método de treinamento selecionado em cada estudo. Além da divergência quanto aos resultados encontrados nos estudos primários, existe uma grande tensão para desfechos de controle glicêmico nos estudos anteriores de síntese e não identificamos nenhum estudo prévio sintetizando desfechos de capacidade funcional na população com diabetes tipo 2. Para isso realizamos uma revisão sistemática e meta-análise, objetivando sintetizar o efeito de diferentes modalidades de exercício físico em pacientes com diabetes tipo 2, em diversos resultados utilizados para medir a capacidade funcional.

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4. ARTIGO I

Correlates of functional physical capacity in physically active older adults: a conceptual-framework-based cross-sectional analysis of social determinants of health and clinical parameters

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Correlates of functional physical capacity in physically active older adults: a conceptual-framework-based cross-sectional analysis of social determinants of health and clinical parameters

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Abstract

The objective of this study was to estimate the extent of the contribution of social determinants of health and health/clinical determinants in functional physical capacity (walking capacity and the hand-derived force) in a population-based sample of older adults. A total of 327 older adults (69±7 years; 83.5% women) were analyzed. A multivariate linear regression model was performed, age (-4.05m; -5.3 to -2.8), male sex (71.40m; 50.5 to 92.3), body mass index (-3.88m; -5.6 to -2.1) and quality of life (18.48m; 6.3 to 30.6) remained as predictive variables for walking capacity (R^2 30.8%). In the final model for the dominant handgrip test, age (-0.6% $Kg.F^{-1}$; 0.89 to 0.2) and male sex (65.2% $Kg.F^{-1}$; 55.3 to 75.8) were the predictive variables. Performance in functional physical capacity tests is positively and negatively affected by age, sex, body mass index and quality of life and, for handgrip, age and sex.

Keywords: Aged, Physical function, Sociodemographic factors.

INTRODUCTION

Aging is associated with several biological changes that can decrease musculoskeletal mass, muscle strength and physical fitness, leading to a potential decrease in the tolerance and recovery against environmental stressors (Lally & Crome, 2007). Whenever triggered during the aging process, impaired body mobility, balance, independence for daily activities and quality of life can simultaneously appear (Webber et al., 2010).

Several indicators that are correlated and associated with a functional decline in older adults have been reported, including clinical status, physical fitness and social determinants of health prevalence (Beaton et al., 2015). For example, one well-established correlate to a decline in functional capacity and disability is the sarcopenia process - the progressive decline in skeletal muscle mass (Janssen et al., 2002; Landi et al., 2012). Similarly, dynapenia, which relates to the loss in muscle strength independently of changes in muscle mass. In its presence, dynapenia has relevant consequences in functional capacity and is also an independent predictor of overall mortality (Clark & Manini, 2012). Claiming for potential musculoskeletal-determinants of functional capacity, muscle power in lower limbs (Frontera et al., 2000), which is, generally, impaired by the aging may cause a detrimental effect on functionality and daily activity performance (Aagaard et al., 2010; Foldvari et al., 2000; Suzuki et al., 2001). Nonetheless, handgrip and lower limb muscle strength, and ambulatory gait speed are indexes of physical fitness and may predict adverse events in older adults, such as declines in cognition, mobility, functional status (Rijk et al., 2016), disability, (Donoghue et al., 2014; Shimada et al., 2015), hospitalization (Cesari et al., 2009) and all-cause mortality (De Buyser et al., 2013; Rantanen et al., 2003; Rijk et al., 2016; Studenski et al., 2011). Importantly, greater physical activity levels may counteract these deleterious effects (Izquierdo et al., 2021), which may be achieved through engagement in a physical activity program. Both structured exercise and general physical activity perform important preventive roles for chronic diseases, thus optimizing the maintenance of functional capacity during aging, thus, they should be prescribed based on the result to be achieved (eg, improvement of functional status or prevention primary) like any other treatment (Izquierdo et al., 2021).

In a whole context, as close as to the vast majority of health-related events, the functional decline in older adults is potentially influenced by a combination of social determinants of health and also health/clinical-related determinants then. Age, sex and body mass have a solid association with ambulatory functional outcomes (i.e., impaired walking test and handgrip strength) (ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories, 2002; Casanova et al., 2011; Corrêa et al., 2020; V. Z. Dourado, 2011; Gale et al., 2007; Lu et al., 2020; Salbach et al., 2015; Tveter et al., 2014) and are frequently in trials as surrogate outcomes because of the ease of obtaining it (V. Z. Dourado, 2011); income, use of medications, diabetes, quality of life and depression are, likewise, associated (Enright et al., 2003; Kuziemski et al., 2019; Liang et al., 2020; Ling et al., 2010; Love et al., 2020; Serra et al., 2015), although not explored as far as the other potential predictors aforementioned. The variability in results of functional tests can be explained through a myriad of factors (standards of the tests, color, ethnicity and geographic locations, even in the same country), which make the inter and intra-test comparability inappropriate to other populations.

We perform out the first exploratory study from a sample initially evaluated in a cross-sectional descriptive study carried out previously (F. M. Dourado et al., 2021). We aimed to estimate, in a representative sample of older adults engaged in a municipal program of physical activity, the extent of the contribution of social and clinical health determinants in functional physical capacity, here defined as the ambulatory walking capacity and the handgrip force. As this is an exploratory study, we do not present a directional hypothesis.

METHODS

Study setting

This is a secondary analysis and the first exploratory study within the descriptive cross-sectional study, entitled: *"Health profile of elderly users of a town public program of physical activity: a cross-sectional study",* which evaluated the health profile and social determinants of health of older adults enrolled in a public lifestyle program composed of several lifestyle items, including a physical activity program, in the city of Porto Alegre, Brazil. Modalities such as gymnastics, resistance training, rhythms and/or recreational sports were often offered to participants. The majority of them took place twice a week lasting one hour of duration (F. M. Dourado et al., 2021). The study protocol is publicly available at https://osf.io/q4r69/ and was approved by the Institutional Review board of the Hospital de Clínicas de Porto Alegre (GPPG 2018-0100; CAAE 84093317600005327) and of the City Health Department of Porto Alegre. The procedures followed the resolution number 466/2012, of the Conselho Nacional de Saúde (Brazil). All participants read and signed the informed consent before starting their enrollment in the study. The reporting of this manuscript is based on the STROBE Statement recommendations (Strengthening the reporting of observational studies in epidemiology) in its extension for cross-sectional studies (von Elm et al., 2007). Study data are also available in a public repository for independent researchers (https://zenodo.org/record/4341443#.X9u61thKhPY; doi: 10.5281/zenodo.4341443).

Participants and eligibility criteria

The inclusion and exclusion criteria defined in the previous descriptive study were: being 60 years old or older and regularly attending the physical activity programs of the municipal community centers. Exclusion criteria were defined as the impossibility of moving to the assessment sites and/or any musculoskeletal injury which put the patient at risk in any setting. All participants included in the previous study were considered for inclusion in this study provided they had complete assessment data.

Sampling and sample size calculation

The sample size calculation was performed for the previous descriptive study, totaling 443 participants. Detailed information is described in the previous study (F. M. Dourado et al., 2021).

Data collection

The recruitment and data collection were carried forward between April 2018 and February 2019. Data were collected in two moments - the visit 1 occurred at 11 different sites attended by the participants. In visit 1, we collected all questionnaire-based variables and also applied the 6-minute walking test (6MWT). The questionnaires were self-applied but, whenever needed, the research staff team provided help without intervening in the answers. The visit 2 took place at the Hospital de Clínicas de Porto Alegre, Clinical Research Center, undergoing anthropometric measurements and handgrip testing. The complete procedure for collecting all variables is described in the previous manuscript (F. M. Dourado et al., 2021).

The researchers received training in the standardization of procedures; some of the measurements were routinely performed by the research team for other studies (Umpierre et al., 2019), based on a manual of standard operating procedures. This was done in order to minimize measurement bias, since different researchers were involved in the measurements and procedures in different centers visited.

Study Variables

Social determinants of health and clinical/health related variables

Information on age, sex, color, number of medications, diabetes diagnosis self-reported and family income were collected through questionnaire. 62 questions were applied based on social determinants, risk factors, biological risk factors, lifestyle, morbidity and perception of health, applied during visit 1. Sex was categorized into men and women; the number of medications in four categories (none, up to 3 medications, 4 to 6 and 7 or more); diabetes as yes, no, or gestational; family income in four minimum wages (MW) categories (up to 2 MW, 2 to 4 MW, 4 to 10 MW, 10 to 20 MW).

Body mass (kg) and height (cm) were measured on a scale and stadiometer (Líder, P-200 C, Brazil). From the values of body mass and height, the body mass index (BMI) in kg/m2 was calculated.

Quality of life was assessed using the Short Form 6 Dimension (SF-6D) questionnaire. Six questions, in a self-applied character, with six domains, namely: functional capacity, physical and emotional aspects, social aspects, pain, mental health and vitality. The questionnaire generates a score between 0.29 - 1.00, with 1 being a full quality of life state.

Depressive symptoms were assessed or appraised by the Geriatric Depression Scale (GDS-15), which consists of 15 questions, in which each positive answer associated with depression represents a point, generating scores from 0 to 15, where scores of 6 or higher were used as suggestive of depression (Krishnamoorthy et al., 2020). Using this cutoff point (score 6), the variable was categorized into presence or absence of depression.

Functional Capacity

6MWT

The 6MWT is used to indirectly assess the cardiorespiratory fitness (estimations) and also ambulatory functional capacity. It considers the distance covered during a 6-minute period, in a 30-meter delimited pathway. The subjects should be encouraged, however, in a standardized manner, according to the (ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories, 2002).

Hand Grip Test

The handgrip strength test is used to measure the strength generated by the muscles of the hand and forearm, and assess the physical condition of the upper limb, an important proxy of health status. Three measurements were taken using a dynamometer (Jamar, model 2A, Asimow Engineering Co., Santa Monica, USA), at a standing position of participants, and the elbow at 90 degrees. We took a series of measurements for both hands and intervals of one minute were given between each attempt. For the purpose of this study, the highest value reached in $Kg.F^{-1}$ was considered the dominant hand.

Statistical methods

Continuous variables are described as mean and standard deviation and categorical variables as prevalences whenever necessary. Components of functional capacity were defined as dependent variables for this study in two separate models. Variables were maintained in the way they were collected, whenever possible, however, some of them were categorized (i.e., sex, number of medications, diabetes diagnosis, family income, and depression). We evaluated probabilities' distributions visually and statistically - the first through a visual inspection of histograms and Kolmogorov-Smirnov tests which assume normality of the data as H0.

For inferential analysis, we regressed independent variables in a multivariable linear regression model to predict dependent variables. The handgrip data had, by nature, a Poisson-like distribution, whereas 6WMT a Gaussian distribution. To maintain similarities between analyses and preserve the natural units of the coefficients, we then transformed the handgrip observations into log-10 observations, which generated a Gaussian distribution and allowed us to carry on a linear regression model. Then, we regressed both handgrip strength and 6WMT by linear multivariable regression analysis using a Gaussian distribution for the outcome and an identity function as linkage, in a two-step manner (model 1 and model 2 - the last one adjusted to more variables based in our conceptual framework model).

In regression analyses, we diagnosed the basic assumptions of multivariable linear regressions (i.e., normality of the distribution of the outcome and its residual, multicollinearity and constant variance of residuals), the adequacy of the chosen model predictors the model's effect. We plotted adjusted outcomes against residuals (i.e., Pearson residual for the generalized linear model/generalized least squares estimation - GLM and GLS) and independent variables against residuals, as well as tested correlation between them and assumption of homoscedasticity through ANOVA tables. Normality of residuals and outcomes was visually inspecting through quantiles-quantiles graphs ("*qqplots"* - i.e., a normal probability of residuals graph) and supported by statistical significance tests for normal distributions assumptions.

We found evidence of inconsistency of variances when exploring, mostly due to observations in BMI. Then, a complementary analysis by a density plot of Pearson's residuals was done, and, to test inter-correlation assumption, a scatterplot of predicted values against Pearson's residuals was generated, fitted by a locally weighted smoothing line (i.e., loess) and its 95% confidence interval, and the same was done with BMI and handgrip strength. Based on this, we carried out a linear model for 6WMT and a GLM for handgrip strength, maintaining BMI as a continuous predictor. The GLM allows the fit of models with heterogeneity on variances and to handle with a certain degree of correlation of predictors to the residuals, and implies in the generalized least squares estimation model. We then conducted an analysis of deviance, estimated by a likelihood ratio, of the model in two situations, for handgrip strength - BMI continuous and as categorical and in both models - which supported us to maintain BMI in its current form (continuous).

The variables included in the multivariable linear regression model were defined *a priori* based on a causal conceptual framework. Distal and proximal variables were inserted according to their *a priori* probability for causality. We chose the conceptual framework method because stepwise models may have limitations if no causal relationship is considered. These models may have limited power to select important predictors and correlates in small datasets and may result in a bias regarding the estimated regression coefficients (Steyerberg et al., 1999). Statistical significance is not always the best criterion for deciding which variables should be included or excluded from a regression model, for this reason, different methods can be used to determine them (Bagherzadeh-Khiabani et al., 2016). Therefore, our variable selection model for inclusion in the regression model is based on the authors' knowledge of direct evidence of a possible association and physiologically plausible relationship of the influence of covariates. Considering that model 1 of the regression was composed of the proximal variables, which were loaded into model 2 (distal variables) only when they reached a correlation with the dependent variable (P=0.05).

No data imputation was done. In this analysis model, only the complete data of all variables present in the regression model remained, that is, any participants that presented missing data were excluded. To claim statistical significance, we assumed a threshold of 0.05. Analyses were performed in the software SPSS (Statistical Package for the Social Sciences) version 18.0 and R (R Core Team 2020, version 4.0.3). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. R Packages used were tidyverse, magrittr, nlme, emmeans.

RESULTS

In total, 327 participants were included in the current study. Participants had a mean age of 69±7 years (min to max 60 up to 91 years old), and 83.5% of them were female (**Table 1**). The mean BMI was 27±3 kg/m^2 and 47.4% of the participants were classified as "overweight". The prevalence of self-reported diabetes (any type) was 12.5%. Potential depression, as classified by the depression scores of the GDS-15 instrument, had a prevalence of 18%; and, importantly, QoL levels had a mean score of 0.87±0.06. In relation to family income, 73.2% of participants received up to 4 MW. 70 participants (21.4%) reported not using any type of continuous-use medication, although the vast majority took at least three medications continuously as prescribed. Commenting in our primary outcomes (dependent variables), mean walk capacity achieved was 498.4±78 and the mean handgrip strength by the dominant hand was of 27.1 Kg.F^{-1}±8.2 Kg.F^{-1} (min to max from 302m up to 690m and 8 Kg.F^{-1} to 60 Kg.F^{-1}, respectively for both outcomes). **Table 2** shows the descriptive analysis of dependent variables and predictors.

We regressed the 6MWT in a multivariable linear regression of 312 participants (**Table 3**). In the model 1, the following predictors were included accordingly to our conceptual framework: age, sex, BMI, number of medications, and quality of life (SF-6D). This model explained 30% (adjusted R^2) of the variability of the dependent variable. For each unit of age (P<0.001), BMI (P<0.001), to be men (P<0.001) and QoL (P=0.001), which remained independent correlates, modified the covered distance in 6 minutes about a decrease of -4.04m (-5.2m to -2.7m), -4.30m (-6.0m to -2.6m) and 72.84m (52.9m to 92.8m), in average, respectively; and, the QoL increases, the 6MWT increases, in average, 20.58m (8.9m to 32.2m). In a second model, we maintained the significant variables and added into the model 1 potential predictors/correlates as diagnosis of diabetes, family income and potential depression. The addition of such variables roughly modified the variance (adjusted R^2 = 30.8% vs 30%). All previous independent variables remained correlated to 6WMT and the new inserted variables did not reach correlation to 6MWT, and barely suffered any impact after adjustment by additional variables, neither their precision estimators: -4.04 (-5.2m to -2.7m) vs -4.05m (-5.3m to -2.8m), -4.3m (-6.0m to -2.6m) vs. -3.88m (-5.6m to -2.1m), 72.84m (52.9m to 92.8m) vs 71.40m (50.5m to 92.3m) and 20.58m (8.9m to 38.2m) vs 18.48m (6.3m to 30.6m), respectively age, BMI, sex (men) and QoL.

To the handgrip strength, the results of the analysis of multivariable regression on generalized linear models with 325 participants are presented in **Table 4**. In the first model, the following predictors of age, sex, BMI and number of medications were included according to our conceptual framework. For each unit of age (*P*=0.009), male sex (*P*<0.001) and use of seven or more medications (*P*=0.02), which remained independent correlates, modified handgrip performance in an average decrease of -0.5Kg.F^{-1}% (0.89 Kg.F^{-1} to 0.09 Kg.F^{-1}), and -13.1 Kg.F^{-1}% (22.74 Kg.F^{-1} to 2.17 Kg.F^{-1}), for age and seven or more medications, respectively; and a 65.9 Kg.F^{-1} (55.89 Kg.F^{-1} to 76.47 Kg.F^{-1}) increase for males, in average. In model 2, we maintained the significant variables from model 1 and added diagnosis of diabetes, composing model 2. Only the independent variables age (*P*=0.005) and male sex (*P*<0.001) remained correlated with the handgrip test, the number of medications (seven or more) lost correlation (*P*=0.07) and the newly inserted variable did not reach a correlation with the test. However, age and sex (men) was practically not impacted either after adjustment for the additional variables, neither their precision estimators -0.5 Kg.F^{-1} (0.89 Kg.F^{-1} to 0.09 Kg.F^{-1}) vs -0.6 Kg.F^{-1} (0.89 Kg.F^{-1} to 0.2 Kg.F^{-1}); 65.9 Kg.F^{-1} (55.89 Kg.F^{-1} to 76.47 Kg.F^{-1}) vs 65.2 Kg.F^{-1} (55.3 Kg.F^{-1} to 75.8 Kg.F^{-1}). Compared to model 1, model 2 provides minimally better results (Pseudo R^2: 0.29 vs 0.28).

DISCUSSION

In the present exploratory study, we assessed whether predictors would independently explain the 6MWT and handgrip test based on a conceptual framework construct. The main findings of our study are that social determinants of health and clinical parameters can act positively or negatively on functional outcomes, regardless of the presence of additional well-known explanatory variables such as depression. Importantly, the addition of such variables (model 2) barely modified the magnitude of effect, precision and mean explanatory capacity of the variance of the outcome. Therefore, we infer these variables did not present themselves as confounders nor modifiers of effect. While for 6MWT, age, sex (women), BMI and QoL had a relevant mean clinical impact as predictors, only sex (men) impacted importantly handgrip strength, regardless of any statistical significance.

Several variables can impact the 6WMT performance, among them, height, age, sex, body weight are variables that can be highlighted because they are part of the reference equations for the distance covered in the test (ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories, 2002; Britto et al., 2013). Age, sex, and BMI are well stablished in the literature as predictors of 6WMT performance (ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories, 2002;

Casanova et al., 2011; V. Z. Dourado, 2011; Salbach et al., 2015; Tveter et al., 2014) and the same was found in our study. Importantly, walking capacity is a proxy of QoL in a causal relationship (Lord & Menz, 2002; Serra et al., 2015). In our study, for each additional score in the SF-6D questionnaire, around 21m was added to the walking capacity on average. Although clinically important, the cross-sectional nature and causal principles (such as Hill's criteria for causality) (Hill, 1965) may impair a solid claim and put this independent relationship at risk of reverse causality - i.e., those with higher walking capacity may have better QoL and not the opposite. Lastly, medicines, diabetes diagnosis, depression and family income did not explain any variability in the mean 6MWT values of the sample. While expected, this may have been an approximation of the QoL scores of our sample, which were roughly impaired at baseline, and consequently did not change the model.

About handgrip, sex and age were the preditors linked to the test performance, consistent with previous studies (Corrêa et al., 2020; Lu et al., 2020; Tveter et al., 2014). Interestingly, diabetes did not demonstrate to be a predictor of handgrip strength in our analyses, despite the fact of leading to peripheral neuropathy and overall inflammation (Matsuda et al., 2004; Tsalamandris et al., 2019). To note, only 13% of the sample self-reported a diagnosis of diabetes and, additionally, we did not collect data regarding comorbidity related to diabetes (e.g., peripheral neuropathy). But in addition, for both performances on the walk test and handgrip strength, diabetes may not have been a significant predictor of why the population was physically active. Some classes of medications may also impair strength production, such as antihypertensives and lipid-lowering drugs (Ashfield et al., 2010; Love et al., 2020; Onder et al., 2002), which were prevalent in our sample (F. M. Dourado et al., 2021). Nonetheless, BMI may be collinear to diabetes and reflect an inherent effect of disease, mirroring the effect of the disease in the model. After all, even for the variables which appeared to be correlates, the contribution to force magnitude was clinically marginal, except for sex, since being male explained to perform an average of 66.0 $Kg.F^{-1}$ more.

Our results should be interpreted in light limitations. First, the mean values for our predicted outcomes (walking and handgrip) were similar to those of healthy and physically active ones, which may be a consequence of the engagement of our sample in a lifestyle program. Also, although using the conceptual framework model to choose explanatory variables with a solid rationale, some of them may present reverse causality in this study setting (cross-sectional study), regardless of our efforts to annulate this type of bias; also, we considered only one conceptual framework model for each multivariable analysis. The addition of more models and the comparability could allow us to better explain the phenomenon, which was diagnosed, at least statistically, by the presented R^2 (around 30% of the mean variability of outcomes). For the handgrip strength variable, the original distribution was a Poisson-like distribution. As we decided to maintain betas to see contributions in real units, the variable was log transformed. However, a sensitivity analysis using a robust variance Poisson regression with exponentialized betas (prevalence ratios - PRs) is a recommended future direction from our side.

On the other hand, we emphasize the exploratory analysis of correlates of these two outcomes, by its clinical relevance, particularly in this setting - in the older and majority in women. There is a pathophysiological rationale to assume a decline in the functional capacity during the aging process, here assumed as a combination of 6WMT performance and handgrip test performance in the older adults, due to impairments in various physiological systems of the body. To quantify the contribution of such parameters, as attenuators of contributors to the decline, is of importance, and we did this in a population-based study. Cautious should be taken into account for extrapolation in terms of sex, as a matter of importance. Then, our results should be considered for older people who are not healthy, but under treatment (pharmacological and non-pharmacological). Further exploration of the diagnosis of diabetes, number of medications, depression, and family income are also welcome.

CONCLUSION

We conclude that in an older population engaged in a municipal program of a physical activity program, the performance of the 6MWT and handgrip test was positively and negatively affected by social determinants of health and clinical parameters (sex, age, BMI and QoL). The results indicate attention for future studies and analyses. Specifically, adjustments should be considered for the 6MWT and handgrip tests for sex and age, in addition, the 6MWT may be influenced by body indicators (BMI) and QoL, suggesting that the functionality can be composed of complementary variables.

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Tables

Table 1. Baseline characteristics of all participants.

Variables	Count (%) / Mean (SD)
Sex (n=351)	
Men	63 (18)
Women	288 (82)
Age (n=351)	
60 – 69 years	209 (59.5)
70 – 79 years	118 (33.5)
≥ 80 years	24 (7)
Body mass index (kg/m²) (n=334)	
Underweight ≤ 22	47 (14)
Normal weight > 22 and > 27	129 (39)
Overweight ≥ 27	158 (47)
Waist Circumference (cm)	
Women (n=281)	90 ± 10.7
Men (n=54)	99 ± 10.2
Education level (n=351)	
Incomplete elementary	62 (18)
Complete elementar	31 (9)
Incomplete high school	22 (6)
Complete high school	114 (32)
Incomplete undergraduate	20 (6)
Complete undergraduate	59 (17)
Graduate	43 (12)
Marital status (n=348)	
Never married	53 (15)
Married	141 (40.5)
Widower	81 (23.5)
Divorced	73 (21)
Ethnicity/Color (n=349)	
White	279 (80)
Black	36 (10.5)
Brown	26 (7.5)
Indigenous	8 (2)
Family income (n=347)	
Up to 2 MW	121 (35)
From 2 to 4 MW	135 (39)
From 4 to 10 MW	71 (20.5)
From 10 to 20 MW	20 (5.5)
Self-reported hypertension (n=347)	
No	161 (47)
Yes	171 (49)
Only in pregnancy	15 (4)

Office blood pressure (n=337)	
No self-reported hypertension (n=161)	
Systolic BP (mmHg)	120±18
Diastolic BP (mmHg)	72±10
With self-reported hypertension (n=165)	
Systolic BP (mmHg)	124±16
Diastolic BP (mmHg)	72± 9
Self-reported cardiovascular disease (n=349)	
No	299 (86)
Yes	50 (14)
Stable Angina	13 (26)
Acute myocardial infarction	10 (20)
Heart failure	9 (18)
Other	1 (2)
Self-reported diabetes (any type) (n=348)	
No	296 (85)
Yes	46 (13)
Only in pregnancy	6 (2)
Glycated Hemoglobin (%) (n=336)	
No self-reported diabetes (n=285)	5.5% ± 0.4
With self-reported diabetes (n=42)	6.9% ± 1.4
Self-reported hypercholesterolemia (n=349)	
No	160 (46)
Yes	189 (54)
Self-reported Arthritis/Rheumatism (n=341)	
No	240 (70)
Yes	101 (30)
Self-reported respiratory disease (n=350)	
No	313 (89.5)
Yes	37 (10.5)
Self-reported depression (n=349)	
No	284 (81)
Yes	65 (19)
Depression measured by the GDS-15 (n=352)	
No	283 (80.5)
Yes	69 (19.5)
General health status self-assessment (n=349)	
Very good	95 (27)
Good	181 (52)
Regular	63 (18)
Bad	7 (2)
Too bad	3 (1)
QoL measured by SF-6D (n=339)	0.87 ± 0.06

Note: SD: Standard Deviation; Kg/m²: Kilogram Per Square Meter; cm: centimeter; MW: Minimum Wage; BP: Blood Pressure; QoL: Quality of Life; SF-6D: Short Form 6 Dimension; GDS-15: Geriatric Depression Scale.

Table 2. Dependent variable with the respective categorical variables used as predictors in each analysis.

Outcomes	Prevalence (%)	Mean 6WMT	CI 95% 6WMT
6MWT(m) (n=312)		500.0	(491.1 - 508.4)
Sex			
Female (n=262)	84.0	488.4	(479.7 - 497.1)
Male (n=50)	16.0	559.1	(536.1 - 582.1)
Number of medications			
None (n=69)	22.0	515.6	(497.0 - 534.1)
Up to 3 (n=149)	48.0	501.5	(489.7 - 513.4)
From 4 to 6 (n=79)	25.2	483.1	(466.5 - 499.8)
7+ (n=15)	4.8	463.9	(430.3 - 497.6)
Diabetes diagnosis			
No (n=266)	85.3	503.4	(494.0 - 512.9)
Yes (n=40)	12.8	476.0	(452.4 - 499.6)
Gestational (n=6)	1.9	495.3	(460.3 - 530.4)
Family income			
Up to 2 MW (n=109)	35.0	479.6	(466.6 - 492.6)
2 to 4 MW (n=118)	37.8	499.1	(484.2 - 513.9)
4 to 10 MW (n=65)	20.8	525.4	(508.3 - 542.5)
10 to 20 MW (n=20)	6.4	530.7	(489.5 - 571.8)
Depression - GDS-15			
No (n=257)	82.4	504.9	(495.6 - 514.2)
Yes (n=55)	17.6	475.8	(453.7 - 497.9)
		Mean Handgrip	**95%CI Handgrip**
Handgrip ($Kg.F^{-1}$) (n=325)		27.0	(26.2 - 28)
Sex			
Women (n=271)	83.4	24.5	(24.0 - 25.1)
Men (n=54)	16.6	40.0	(37.8 - 42.3)
Diabetes diagnosis			
No (n=279)	85.9	27.2	(26.2 - 28.2)
Yes (n=40)	12.2	26.5	(24.0 - 29.0)
Gestational (n=6)	1.9	25.2	(22.4 - 28.0)
Number of medications			
None (n=69)	21.3	27.8	(25.8- 29.8)
Up to 3 (n=156)	48.0	26.6	(25.4 - 27.9)
From 4 to 6 (n=83)	25.5	27.8	(25.9 - 29.7)
7+ (n=17)	5.2	24.9	(21.3 - 28.5)

Note: 6MWT: 6-minute walk test; $Kg.F^{-1}$: kilograms/force SE: Standard Error; CI: Confidence Interval; MW: Minimum Wage; GDS-15: Geriatric Depression Scale.

Table 3. Multivariable linear regression between 6MWT test, social determinants of health and clinical parameters.

Model 1: adjusted analysis for all predictors below			
Predictors (N=312)	**β**	**CI 95%**	***P*-value**
Age	-4.04	-5.2 to -2.7	<0.001
Male sex	72.84	52.9 to 92.8	<0.001
BMI	-4.30	-6.0 to -2.6	<0.001
Number of medications (up to 3)	-0.56	-19.2 to 18.1	0.95
Number of medications (from 4 to 6)	-3.34	-24.7 to 18.0	0.76
Number of medications (7+)	-17.51	-55.0 to 20.0	0.36
QoL (SF-6D)	20.58	8.9 to 32.2	0.001
R^2 = 0.32; Adjusted R^2 = 0.30			
Model 2: adjusted analysis for significant variables in model 1 plus diabetes diagnosis, family income and depression			
Age	-4.05	-5.3 to -2.8	<0.001
Male sex	71.40	50.5 to 92.3	<0.001
BMI	-3.88	-5.6 to -2.1	<0.001
QoL (SF-6D)	18.48	6.3 to 30.6	0.003
Diabetes diagnosis (yes)	-14.05	-70.6 to 42.5	0.63
Diabetes diagnosis (no)	4.40	-48.6 to 57.4	0.87
Family income (up to 2 MW)	-13.53	-45.8 to 18.7	0.41
Family income (2 to 4 MW)	-17.19	-48.6 to 14.2	0.28
Family income (4 to 10 MW)	-4.22	-37.5 to 29.0	0.80
Depression - GDS-15 (no)	16.56	-4.0 to 37.1	0.11
R^2 = 0.33; Adjusted R^2 = 0.308			

Note: CI: Confidence Interval; BMI: Body Mass Index; QoL: Quality of Life; SF-6D: Short Form 6 Dimension; MW: Minimum Wage; GDS-15: Geriatric Depression Scale. The reference category for sex: female; number of medications: no medications; diabetes diagnosis: gestational diabetes; family income: 10 to 20 minimum wages and for depression: yes.

Table 4. Multivariable regression on generalized linear models, between handgrip test, social determinants of health and clinical parameters.

Model 1: adjusted analysis for all predictors below			
Predictors (n=325)	**Variance**	**CI 95%**	***P*-value**
Age	-0.50	0.89 to 0.09	0.009
Male sex	65.86	55.89 to 76.5	<0.001
BMI	0.40	-0.09 to 1.0	0.13
Number of medications (up to 3)	-2.57	8.51 to -3.7	0.41
Number of medications (from 4 to 6)	-0.20	7.04 to -7.1	0.96
Number of medications (7+)	-13.06	22.74 to 2.2	0.02
Pseudo R^2: 0.28			
Model 2: adjusted analysis for significant variables in model 1 plus diabetes diagnosis			
Age	-0.60	0.89 to 0.2	0.005
Male sex	65.2	55.3 to 75.8	<0.001
Number of medications (up to 3)	-1.88	7.8 to -4.6	0.56
Number of medications (from 4 to 6)	-1.51	-5.7 to 9.3	0.69
Number of medications (7+)	-10.77	21.3 to -1.2	0.07
Diabetes diagnosis (yes)	-2.76	10.1 to -5.0	0.47
Diabetes diagnosis (no)	2.94	-14.3 to 23.7	0.75
Pseudo R^2: 0.29			

Note: 95%CI: Confidence Interval; BMI: Body Mass Index; R^2: R Square. Estimation method: generalized least squares method. The reference category for sex: is female; number of medications: no medications and diabetes diagnosis: gestational diabetes.

5. ARTIGO II

Association between physical exercise interventions and functional capacity in individuals with type 2 diabetes: a systematic review and meta-analysis of controlled trials

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Association between physical exercise interventions and functional capacity in individuals with type 2 diabetes: a systematic review and meta-analysis of controlled trials

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ABSTRACT

Background: The prevalence of type 2 diabetes mellitus increases with age and people with type 2 diabetes are more affected by reductions in functional performance. Although exercise interventions are recommended for people with diabetes, it is relevant to assess the effects of different training modes on the available functional outcomes.

Objective: To summarize the effects of distinct modes of exercise training in comparison to non-exercise on the functional capacity of adults with type 2 diabetes.

Methods: A systematic review and meta-analysis of randomized (RCT) and non-randomized (NRS) controlled trials was conducted. Seven databases were searched from inception to January 2021. Eligible studies should last 8 weeks or longer, comparing structured exercise training and non-exercise control for one out of six pre-specified functional capacity outcomes (Timed Up and Go test, chair stands, walking performance, upper limb muscle strength, lower limb muscle strength, physical fitness parameter), in patients with type 2 diabetes, aged ≥45 years or older. The risk of biases was assessed with the Checklist Downs & Black. Pooled mean differences were calculated using a random-effects model, followed by sensitivity and meta-regression analyses.

Results: Of 17165 references retrieved, 29 trials (1557 patients) were included. Among these, 13 studies used aerobic training, 6 studies used combined training, 4 studies used resistance training, 3 studies had multiple intervention arms and 3 studies used other types of training. Exercise training was associated with an increase in functional capacity outcomes, as reflected by changes in 6-minute-walk test (51.6 meters; 95% CI 7.6% to 95.6%; I^2 92%), one-repetition maximum leg-press (18.0 kg; 95% CI 4.0% to 31.9%; I^2 0%), and peak oxygen consumption (2.41 mL/kg·min; 95% CI 1.89% to 2.92%; I^2 100%) compared with control groups. In sensitivity and subgroup analyses using VO_{2max} as outcome and stratified by for the type of study (RCT or NRS), duration of diabetes diagnosis, and sex, we observed overlapping confidence intervals. Meta-regression showed no association between HbA1C levels and VO_{2max} ($p = 0.34$; I^2 99.6%; R^2 = 2.6%).

Conclusion: Structured exercise training based on aerobic training, resistance training, combination of both, or composed by other types of training (i.e. Pilates, Tai Chi and Whole-body vibration) is associated with an improvement in functional capacity in patients with type 2 diabetes, except for the upper limb muscle strength. However, we could not identify potential effect predictors associated with directional summary estimates.

Registration: This systematic review was registered in the PROSPERO international prospective register of systematic reviews (CRD42020162467); date of registration: 12/15/2019. The review protocol is hosted at the Open Science Framework (OSF) (Preprint DOI: 10.31219/osf.io/kpg2m).

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Key points:

Structured physical exercise lasting 8 weeks or more is associated with increases in functional capacity in people at an average age of 45 years or older with type 2 diabetes.

The additional analyses related to sex, duration of disease diagnosis, and type of study were inconclusive in this synthesis.

Future research is warranted investigating the effect of structured exercise on younger populations as well and in people with diabetes who are often excluded from trials. Furthermore, studies with primary outcomes of functional capacity are needed.

INTRODUCTION

Diabetes mellitus is an increasingly prevalent chronic-degenerative disease, generating a burden on public health. In 2019, the International Diabetes Federation estimated that 1 out of 11 adults in the world population aged 20 to 79 lived with diabetes, equivalent to 463 million people [1]. Notably, type 2 diabetes mellitus is a common disease in older adults [1], who also experience reductions in neuromuscular function, muscle mass, muscle strength, and motor performance [2]. Compared with non-diabetic individuals, older adults with diabetes have accelerated loss of morphological and neural function [3–5], worsening the performance in functional tests [3,6], contributing to a marked increase in physical disability and frailty risks in this population [7,8]. The risk of physical disability for adult people with diabetes increases by about 50 to 80% compared with age-matched individuals without diabetes [8].

Functional capacity has multidimensional features and is considered the individual's ability to perform instrumental activities in their daily lives, sustaining their autonomy. Functional performance measures reflect a particular aspect of physical functioning by using mostly objective and predetermined criteria [9]. Observational studies in adults with diabetes have identified a worsening of time to perform the timed up and go and five times sit-to-stand tests [4], walking speed [10] and greater strength deficit at high movement speeds [11]. Among the several factors involved in the relationship between diabetes and functional capacity, older adults with diabetes may have impairments of aging (i.e., neuromuscular, body composition and metabolism changes) coexisting with complications of the disease and comorbidities. Less is known about this relationship in middle-aged individuals, in which the impact of diabetic complications associated with the disease are also less known. However, exploratory evidence indicates that diabetes was associated, to a small extent, with physical disability in midlife [12]. Likewise, diabetes contributes to explaining the variance in the age trajectory of physical disability [13].

Individuals with diabetes are less likely to engage in regular physical exercise, even if this is one of the cornerstones of management [14]. Clinical trials such as Look AHEAD Study [15] and Italian Diabetes and Exercise Study (IDES) [16] demonstrated that physical activity interventions composing lifestyle programs increased physical performance in patients with type 2 diabetes [15–18]. However, such findings are still inconsistent in other exercise trials [19,20]. Such divergent results could be partly affected by several outcomes used in functional capacity and training specificity leading to variable degree of preparation for actual functional testing.

Our systematic review addresses several outcomes used to measure functional capacity, aiming to synthesize exercise training effects in patients with type 2 diabetes. Therefore, we conducted a preregistered protocol to summarize randomized controlled trials (RCTs) or non-randomized controlled studies (NRS) that assessed the changes (if any) of different modes of exercise training in outcomes related to the functional capacity of individuals with type 2 diabetes undertaking structured physical exercise compared with their non-training counterparts.

METHODS

This systematic review and meta-analysis was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [21] and our methodological approach followed the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions, Version 6.1, 2020 [22].

The study was registered in the PROSPERO International prospective register of systematic reviews (registration number CRD42020162467) and followed the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) [23]. The methodological protocol was uploaded to the Open Science Framework (OSF) (Preprint DOI: 10.31219/osf.io/kpg2m).

Search Strategy

Potential studies were identified by using a systematic search process was being conducted in the following databases: PubMed (via website), PEDro Physiotherapy Evidence Database (via website), Cochrane Library (via website), SportDiscus (via Periódicos CAPES), and Lilacs (via BVS). To minimize the prospect of publication bias, searches in Open Grey and Google Scholar were undertaken. The searches were carried out from inception until January 4, 2021.

The search strategies were developed using medical subject headings (MeSH) and EXPLODE TREES for terms: Aged, Exercise Therapy, Exercise Movement Techniques, Exercise, associated with synonyms for identification in title and summary (TIAB). Terms with study design different from clinical trials were used for identification in the title (TI) and exclusion. Search strategies can be found in the Electronic Supplementary Material (Appendix 1).

Study Selection

The review process was conducted by pairs of independent reviewers (eligibility process of titles and abstracts, full-text reading, and data extraction). Any disagreement in the study selection or extraction data processes, was solved by consensus, referring back to the original articles or, if needed, by a third external reviewer (DU).

Six reviewers independently (LOP and LXNS, ATD and DMN, CEB and JLT) conducted a pilot of 400 articles, at the level of titles and abstracts, to standardize the eligibility criteria among the reviewers. These reviewers subsequently assessed titles and abstracts according to eligibility criteria using the EndNote bibliographic reference management software), and finally read the remaining full-text articles potentially eligible for inclusion.

Eligibility criteria were established based on the concept of population, intervention, comparator/control, outcome and study design (PICOS).

Type of studies

We included randomized controlled trials (RCTs) or non-randomized controlled studies (NRS) published between January 1987 and January 2021. Although we did not restrict searches for specific languages, only articles in English, Spanish, or Portuguese were included.

Participants

Studies that included individuals (average age of 45 years or older, both sexes) with a diagnosis of type 2 diabetes, with or without comorbidities associated with the disease, were eligible for inclusion.

We excluded studies with patients who were diagnosed with neurodegenerative diseases (ataxias, Alzheimer's, Parkinson's), neuromuscular diseases (congenital/progressive, for example, dystrophies, myopathies), severe cognitive impairment, severe cardiovascular disease (congestive heart failure) or recent cardiovascular events (within the last 6 months, such as acute myocardial infarction or stroke), and cancer in the treatment period.

Type of interventions

We included all trials which reported the interventions with structured physical exercise (e.g. resistance training, power training, aerobic training or combined training; pilates, functional training, etc.,) lasting at least eight weeks. We considered purely structured exercise interventions. Studies were discarded if they presented another co-intervention with physical exercise, for example, diet, food supplements, health education or behavior change/lifestyle interventions.

The comparator could not practice any type of physical activity/exercise component, nor could they participate routinely during the period of study of groups with exercise guidance or lifestyle changes.

Outcome measures

To account for measures of functional capacity more comprehensively, any of the following outcomes was considered for inclusion:

i) Timed Up and Go test (TUG);

ii) Chair stands (5-chair stand test; 30-second chair stand test);

iii) Walking performance (6-minute-walk, 400-meter walk);

iv) Upper limb muscle strength evaluated by strength isometric (handgrip);

v) Lower limb muscle strength assessed by the test of one repetition maximum (1RM), (knee extension or leg-press);

vi) Physical fitness parameter evaluated by maximal oxygen consumption (VO_{2max}) or peak oxygen consumption (VO_{2peak}).

Data Extraction

The six reviewers (mentioned above) performed data extraction in a sheet that was designed and tested before use. The information from the eligible studies was coded and grouped into four categories: (1) general studies descriptors (authors, year of publication, journal, study design); (2) description of the study population (e.g.: gender, age, total sample size, health-related data); (3) details of interventions (e.g., type, duration, frequency, intensity); (4) and outcomes (e.g.: functional parameters, walking performance, muscle strength parameters, physical fitness parameters). For continuous outcomes, we extracted the results with raw data of means and standard deviations (SDs) and delta values when available.

When data were not available, we contacted the corresponding author(s) to request the missing data. It was not necessary to input any data. We only calculated, in some cases, the delta to observe the difference between the pre- and post-intervention moments of the outcomes of interest.

Quality assessment and of the risk of bias in individual studies

Paired reviewers independently evaluated the risk of biases from each selected study using the Checklist Downs & Black [24], which allows assessment of both randomized and non-randomized trials, in regard to the following items: reporting, external validity, internal validity (bias), internal validity (confounding - selection bias) and power. To determine the methodological quality and risk of bias of a study, for each criterion, we evaluated the presence of sufficient information. Disparities were resolved by involving a third author. The last item on the checklist (power of analysis) was used in a binary approach with a score of “0” (no sample size calculation) or “1” (reported sample size calculation) [25]. The checklist is composed of 27 questions, with a total possible score of 28 for randomized and 25 for non-randomized studies. With the following scoring ranges: excellent (26–28); good (20–25); fair (15–19); and poor (≤14).

Data Synthesis

Meta-analyses and the forest plots were performed in R version 4.0.1 (R Project for Statistical Computing, RRID:SCR_001905), using the metafor package, for the outcomes of interest that presented at least two studies and/or groups combinations.

We used the inverse-variance method (DL - tau^2), under a random-effects model, to generate effect estimates. Because our results are derived from continuous outcomes with the same scale available, we used the mean difference with 95% confidence intervals (95% CI) [22]. We also calculated the prediction interval when at least three studies were available in a given meta-analysis [26]. The evaluation of heterogeneity across trials was assessed by generating the I^2 statistics, which represents the proportion of heterogeneity that is not due to chance (rather, due to possible differences across studies, populations and interventions).

Additional analyses

As planned in our study protocol [27], when sufficient data (at least 10 studies) were available, we performed sex-stratified subgroup analysis and meta-regression with glycated hemoglobin (HbA1c) values. We also conducted a sensitivity analysis stratifying for randomized or non-randomized studies. Regarding the duration of diabetes diagnosis, we split study samples by short and long term duration of the disease (>8 years). In addition, we used the “leave-one-out” approach to check whether removing a single study at each time has had a major influence (e.g., change in the direction of results) on meta-analytic estimates. The publication bias was assessed by visual inspection through the generation of funnel plot.

It was not possible to carry out a sensitivity analysis, as we had planned, with patients with neuropathy, as none of the studies reported a population with this comorbidity.

RESULTS

Description of included studies

From 17165 articles retrieved from the electronic database, 14099 were excluded by titles and abstracts. Out of 111 reviewed full-texts, 25 RCTs [28–52] and 4 NRS [53–56] met the inclusion criteria (Figure 1), representing a total sample of 1557 participants. Of these, 489 patients were included in studies of aerobic exercise training, 193 in studies of resistance exercise training, 386 in combined aerobic/resistance exercise training studies, 375 in studies with two or more intervention arms (aerobic/combined or aerobic/resistance/combined) and 114 in others (i.e. Pilates, Tai Chi, Whole-body vibration). The articles were mostly published in English, except for 1 article in Portuguese.

In addition, we cite some studies that might appear to meet the inclusion criteria but were excluded due to the control group [57,58] (received thematic sessions with topics on nutrition and physical activity, for example; participated in a 12-session health promotion educational training), an apparently duplicated sample with included study [59], and because of the intervention (diet plus supervised exercise) [60].

Overall, the median age from participants' samples was 60 (minimum and maximum: 52 - 73) years old. No studies included participants with peripheral neuropathy. Regarding the sexes of participants enrolled in the included studies, 20 study samples consisted of both women and men, six studies included only men, whereas three studies included only women (Table 1).

Intervention characteristics

Among the 29 studies included, 13 studies used aerobic training [30,31,39–41,44–46,48,50,52,55,56], six used combined training (aerobic and resistance) [32,35,38,43,47,53], four studies used resistance training [28,29,49,54], three studies used more intervention arms [36,42,51] (two studies with aerobic training groups and combined training, and one with aerobic, resistance and combined training groups) and three studies with another type of training (Pilates, Tai Chi, Whole-body vibration) [33,34,37] (Table 2).

The mean training duration was 27.9 weeks (range: 8 to 104 weeks). Training frequency ranged from one to seven days per week, being three days a week the most employed training frequency (n = 14). The exercise sessions duration ranged from 8 to 90 min/exercise/session.

In aerobic training, the most used measures were maximal oxygen uptake (VO_{2max}), peak oxygen uptake (VO_{2peak}), maximum heart rate (HR_{max}) and heart rate reserve (HRR), and for those of resistance training were one repetition maximum (1RM) and repetitions maximum (RM). In studies that used HRmax or peak heart rate (HR_{peak}) to quantify aerobic exercise intensity, programs ranged from 50 to 90% intensity, whereas it ranged from 40 to 80% for when HRR was used as an intensity variable. VO_{2peak} ranged 50 to 90% VO_{2peak}; VO_{2max} ranged from 65 to 80% VO_{2max}. 1RM ranged from 50 to 80% 1RM and RM ranged from 8 to 15 RM.

The intensity measures less commonly used in the studies were: heart rate (HR%); peak energy-expenditure rate (55 to 70%); maximum pulse (60 to 75%); rating of perceived exertion (RPE) (12 to 15/11(1) to 12(1) RPE Borg Scale); maximum voluntary contraction

(MVC) (60 to 80 MVC); 1.3 to 3.3 Kg; 12 to 16 Hz. Only two studies did not report intensity of interventions.

Fig. 1 PRISMA Flow Diagram

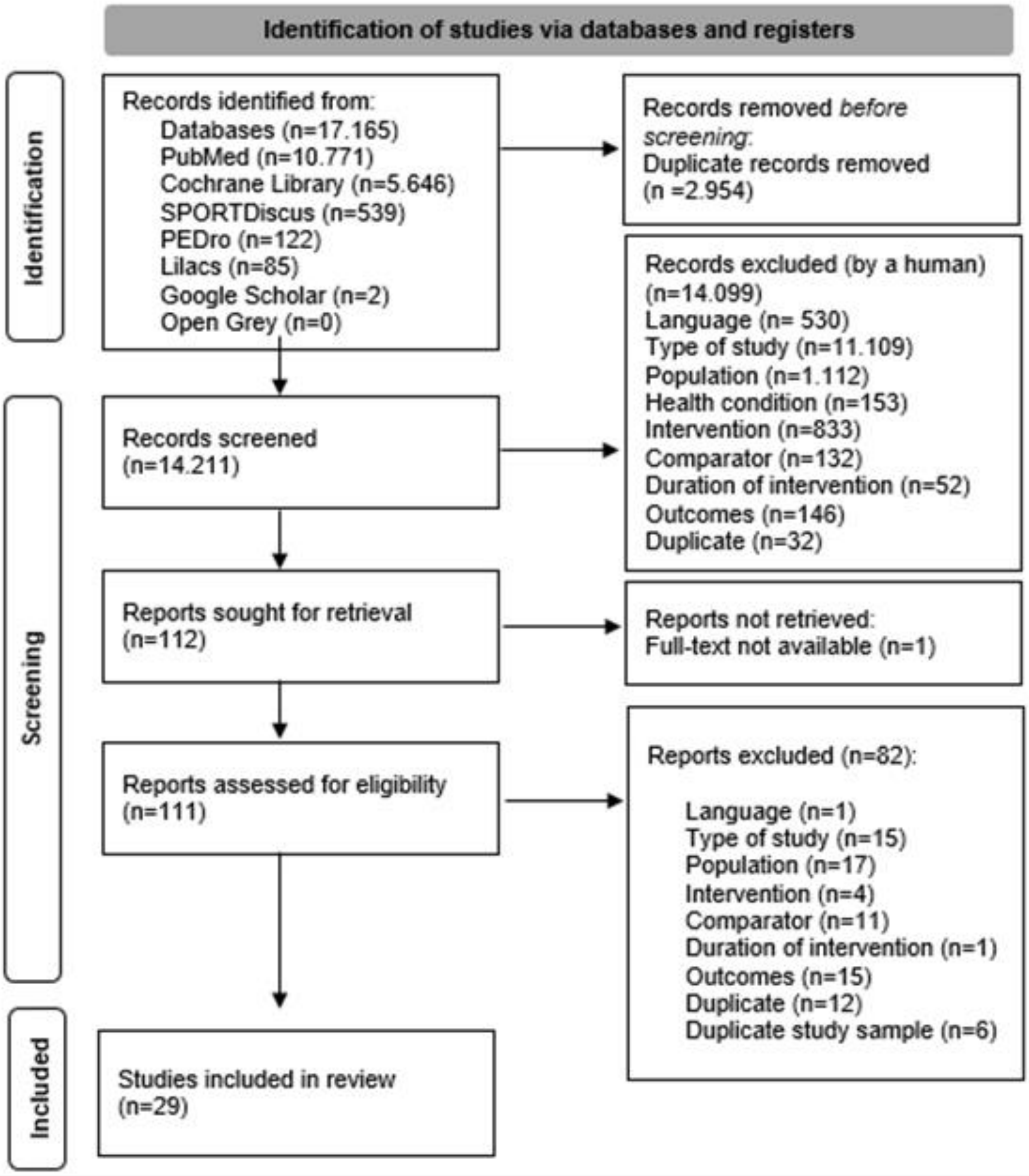


Table 1. Characteristics of the studies included

Authors	Control Group Intervention	Design	Outcomes	Sample size	Other clinical conditions	Baseline HbA1c (%), Mean (SD)	Duration of the disease (y), Range or Mean (SD)	Medications	Sex, Female (%)	Age (y), Mean (SD)
Jiang et al, 2020 [39]	Required to maintain their usual physical activity	RCT	Body composition FATmax VO_{2max} Blood chemistry Physical capacity.	49	Postmenopausal	6.72(0.7)	6 to 11 (range)	Metformin Sulfonylureas ACE inhibitors Diuretics Statins Fibrates	49	63(5)
Yamamoto et al, 2020 [29]	Instructed to maintain their daily activities	RCT	Muscle strength Gait speed Body composition	53	NR	7.24(0.77)	17.0 (10.3)	NR	47	73(2)
Shabkhiz et al, 2020 [28]	Instructed to maintain their normal activities and not to modify their lifestyles	RCT	Blood chemistry Muscle strength Body composition	44	NR	NA	10.2(3)	Insulin-secretagogue Insulin-sensitizer Lipid lowering Anti-hypertensive	0	72(6)
Hwang et al, 2019 [31]	Instructed not to change their habitual physical activity, diet, or medications	RCT	VO_{2peak} Body composition Blood chemistry Habitual physical activity Dietary analysis	50	NR	7.23(0.33)	8(1)	Metformin SGLT2 inhibitors Sulfonylureas DPP-4 inhibitors GLP-1 agonists Thiazolidinediones Insulin Statins Anti-hypertensives Aspirin	46	63(1)

Wilson et al, 2019 [52]	Instructed to maintain their usual lifestyle	RCT	VO_{2peak} Left ventricular function Body composition Blood volume	16	NR	7.77(3.61)	7.2(4.2)	Metformin Gliclazide Insulin	37.5	52(8)
Scheer et al, 2019 [53]	Instructed to maintain their usual activities	NRS	VO_{2peak} Anthropometric variables Blood chemistry Muscular strength Vascular function	27	Obese Overweight	7.1(0.84)	NR	Biguanides Sulfonylureas GLP-1 agonists DPP-4 inhibitors Statins Beta blockers Calcium channel blockers ACE inhibitors Angiotensin II receptor antagonist Anti-inflammatories Diuretic Fibrate Thyroid hormones Estrogen Testosterone, Paracetamol Other pain relief	44	62(10)
Conners et al, 2018 [30]	Instructed to maintain their current dietary and physical activity habits	RCT	Glycemic control Blood lipids Health-related fitness	26	NR	7.58	7.1(4.6)	Metformin Sitagliptin	61	58(5)
Szilágyi et al, 2018 [32]	Did not participate in any exercise	RCT	Plasma glucose Body composition Physical fitness level	208	NR	NA	20.4(7)	NR	64	61(7)
Melo et al, 2018 [33]	Received guidance for	RCT	Plasma glucose HbA1c	22	NR	7.6(0.75)	8.3(6)	Metformin Glibenclamide	100	67(7)

	maintenance of medication and the nutritional intake of foods consumed in the diet		Functional capacity					Sitagliptin Glimepiride		
Banitalebi et al, 2018 [51]	Usual medical care and received diabetes recommendations for self-management. Were not given exercise counselling and were asked to maintain physical activity levels	RCT	Myokines levels Metabolic outcomes Body composition VO_{2peak}	42	Overweight	9.41(0.82)	NR	NR	100	55(6)
Santos et al, 2014 [54]	Received no intervention and were instructed not to change their lifestyle	NRS	Maximal strength	48	NR	NA	NR	Hypoglycemic agents	63	67(5)
Pozo-Cruz et al, 2014 [34]	Receiving only standard care	RCT	Glycemic control Dyslipidemia Functional capacity	39	NR	7.17(0.96)	9.2(7.7)	NR	49	69(10)
Yan et al, 2014 [50]	--	RCT	Blood Pressure Body composition Blood chemistry	41	Hypertension	8.7(2.8)	NR	Nifedipine Amiloride Hydrochlorothiazide Methyldopa	0	53(11)

			VO_{2max}					Enalapril Atenolol Chlorthalidone Metformin Glyburide		
Tan et al, 2012 [35]	Instructed to maintain their individual habits of physical activities and refrain from engaging in any other forms of prescribed exercise training	RCT	Body composition Glycemic control Lipid profile Functional capacity	25	NR	6.38(0.97)	16.7(6.7)	Oral hypoglycaemic	48	66(4)
Labrunée et al, 2012 [40]	Received counsels regarding physical activity practice	RCT	Anthropometric variables Blood chemistry Physical capacities Maximal isometric strength QOL	23	Obesity (stage 2–3)	8.67(1.81)	> 1 year	Insulin Metformin Sulfonylureas	56.5	53(9)
Karstoft et al, 2012 [44]	Were instructed to continue their habitual lifestyle	RCT	VO_{2max} Body composition Blood pressure Blood chemistry	32	NR	6.66(0.2)	4.7(1.2)	Metformin Sulfonylureas DPP-4 inhibitors GLP-1 analogues	31.57	59(2)
Kadoglou et al, 2010 [46]	Maintenance of usual activities	RCT	VO_{2peak} Body composition Blood chemistry	89	Overweight or Obese	8.02(1.04)	6.3(3.3)	Metformin Gliclazide	63	59(8)

Plotnikoff et al, 2010 [49]	Non-training and maintenance of physical activity levels	RCT	Muscle strength Blood chemistry Body composition Social cognitions	48	Obese	6.86(1.21)	NR	Insulin Metformin Sulfonylureas Thiazolidinediones α-glucosidase inhibitors ACE inhibitors Angiotensin receptor blockers Diuretics β-blockers Calcium channel blockers Statins Fibrates Cholesterol absorption inhibitors Aspirin	67	55(12)
Balducci et al, 2010 [36]	Remained sedentary	RCT	Biochemical parameters VO_{2max} Body composition Volume of physical activity	82	Metabolic syndrome	7.41(1.41)	8.9(6)	Sulfonylurea Glinide Metformin Thiazolidinedione Insulin ACE inhibitors Angiotensin-receptor blocker Diuretic Calcium-channel blocker β-blocker α1-adrenergic blocker Statins Fibrates Antiplatelet agents	40.32	62(8)

Larose et al, 2010 [42]	Instructed to revert to their level of activity at baseline and to maintain this level	RCT	VO_{2peak} Submaximal exercise response Muscular strength	251	Obesity	7.68(0.88)	5.3(4.4)	NR	36.2	54(7)
Loimaala et al, 2009 [47]	Standard treatment for type 2 diabetes	RCT	Cardiovascular risk factors Arterial pulse wave velocity Blood chemistry Muscle strength VO_{2max}	48	Hypertension	8.1(1.2)	NR	Metformin Sulfonylureas	0	54(6)
Lam et al, 2008 [37]	Wait list control	RCT	Blood chemistry Blood pressure Body composition Health status Functional capacity	53	NR	8.54(1.25)	NR	Insulin	54.71	62(10)
Brun et al, 2008 [41]	Usual routine treatment	RCT	Lifestyle and fitness outcomes Body composition Metabolic outcomes QOL Healthcare costs	25	Overweight Obesity	8.86(1.35)	10(7)	NR	26	60(10)
Kadoglou et al, 2007 [45]	Maintenance of usual activities	RCT	Body composition VO_{2peak} Blood chemistry Blood pressure	60	Overweight	7.88(0.96)	6.8(4.1)	Sulfonylurea Metformin Antihypertensives	57	62(5)

Bjørgaas et al, 2005 [38]	Not given any specific recommendations concerning physical activity	RCT	VO_{2max} Fitness, clinical and laboratory variables	29	Overweight	7.4(1.2)	NR	Metformin Sulfonylurea Antihypertensives Lipids-lowering Aspirin	0	57(8)
Fritz et al, 2006 [55]	Received no exercise instructions	NRS	Blood chemistry Blood pressure Body composition VO_{2max}	52	NR	6.15(0.8)	5.5(4.3)	Glucose lowering agents Antihypertensives Lipids-lowering	50	60(7)
Loimaala et al, 2003 [43]	Received conventional treatment of type 2 diabetes only	RCT	Body composition Blood chemistry VO_{2max} Muscle endurance Isometric strength Baroreflex sensitivity Heart rate variability Whole-body impedance cardiography	49	Hypertension	8.1(1.69)	> 3 years	Hypoglycemic agents	0	53(5)
Verity et al, 1989 [48]	Instructed to to maintain their normal daily activities	RCT	Body composition Blood chemistry VO_{2max}	10	Postmenopausal Overweight	8.85(1.79)	4.5	None	100	59(12)

Skarfors et al, 1987 [56]	Not physical training	NRS	VO_{2max} Blood chemistry	16	Musculoskeletal problems Asthma on exertion Hypertension only control group	NA	2.6(3)	Digoxin Antihypertensives Sulfonylurea Bronchodilators	0	59(2)

Abbreviations: SD: Standard Deviation; RCT: Randomized Controlled Trial; NRS: Non-Randomised Controlled Study; NR: Not Reported; NA: Not Applicable; VO_{2max}: Maximum Oxygen Volume; VO_{2peak}: Peak Oxygen Consumption; QOL: Quality of Life; ACE: Angiotensin-converting enzyme inhibitor; DPP-4: Dipeptidyl Peptidase-4 inhibitors; SGLT2: Sodium-glucose Cotransporter-2 Inhibitors .

Table 2. Characteristics of studies' interventions

Authors	Intervention setup	Frequency, Times per week	Intensity, Range or Mean (SD)	Time for intervention, minutes per session, Range	Average length, Weeks
Jiang et al, 2020 [39]	Aerobic	3	41.3(3.2) to 46.1(10.3)% VO_{2max}	20 to 60	16
Yamamoto et al, 2020 [29]	Resistance	7	1.3 to 3.3 kg	NR	48
Shabkhiz et al, 2020 [28]	Resistance	3	70% 1RM	NR	12
Hwang et al, 2019 [31]	Aerobic	4	70 to 90% HR_{peak}	40 to 47	8
Wilson et al, 2019 [52]	Aerobic	3	90% HR_{peak}	20	13
Scheer et al, 2019 [53]	Combined	3	60 to 80% HR_{max}; 12 to 15 RPE Borg Scale	60	8
Conners et al, 2018 [30]	Aerobic	3	40 to 70% HRR	10 to 20	12
Szilágyi et al, 2018 [32]	Combined	4	60 to 75% Max. pulse	60	24
Melo et al, 2018 [33]	Pilates	3	11(1) to 12(1) RPE Borg Scale	60	12
Banitalebi et al, 2018 [51]	Aerobic, Combined	3	10 to 15 RM; 50 to 70% HR_{max}	50	10
Santos et al, 2014 [54]	Resistance	3	50 to 70% 1RM	50	16
Pozo-Cruz et al, 2014 [34]	Whole-body vibration	3	12 to 16 Hz	8 to 16	12
Yan et al, 2014 [50]	Aerobic	3 to 5	50 to 75% VO_{2peak}	45	12
Tan et al, 2012 [35]	Combined	3	55 to 70% HR_{max} 50 to 70% 1RM	60	26
Labrunée et al, 2012 [40]	Aerobic	7	HR% (the first ventilatory threshold measured the test of effort)	30	13
Karstoft et al, 2012 [44]	Aerobic	5	55 to 70% peak energy-expenditure rate	60	17

Kadoglou et al, 2010 [46]	Aerobic	4	50 to 80% VO_{2peak}	45 to 60	52
Plotnikoff et al, 2010 [49]	Resistance	3	50 to 85% 1RM	NR	16
Balducci et al, 2010 [36]	Aerobic, Combined	2	70 to 80% VO_{2max}; 80% 1RM	60	52
Larose et al, 2010 [42]	Aerobic, Resistance, Combined	2 to 3	60 to 75% HR_{max}; 8 to 15 RM	20 to 45	22
Loimaala et al, 2009 [47]	Combined	4	65 to 75% VO_{2max}; 60 to 80 MVC	30	104
Lam et al, 2008 [37]	Tai Chi	1 to 2	NR	60	26
Brun et al, 2008 [41]	Aerobic	2	HR% (level of the ventilatory threshold)	45	52
Kadoglou et al, 2007 [45]	Aerobic	4	50 to 75% VO_{2peak}	45 to 60	26
Bjørgaas et al, 2005 [38]	Combined	2	50 to 85% HR_{max}	90	12
Fritz et al, 2006 [55]	Aerobic	3	NR	45	17
Loimaala et al, 2003 [43]	Combined	2	65 to 75% VO_{2max}; 70 to 80% 1RM	≥30	52
Verity et al, 1989 [48]	Aerobic	3	65 to 80% HRR	60 to 90	16
Skarfors et al, 1987 [56]	Aerobic	3	Up to 75% VO_{2max}	45	104

Abbreviations: NR: Not Reported; VO_{2max}: Maximum Oxygen Volume; VO_{2peak}: Peak Oxygen Consumption; HR_{max}: Maximum Heart Rate; HRR: Heart Rate Reserve; HR: Heart Rate; HR_{peak}: Peak Heart Rate; Max. pulse: Maximum Pulse; 1RM: one Maximum Repetition; RM: Maximum Repetition; MVC: Maximal Voluntary Contraction; kg: kilogram; Hz: hertz; RPE: Rating of Perceived Exertion.

Functional capacity

Among the outcomes prespecified in the study protocol, the 400-meter walk test was not assessed in the included studies. The results of the remaining outcomes of interest are presented below.

Walking performance

Out of the 29 included studies, eight articles [30,32,34,35,37,39–41] with 441 patients, demonstrated that structured physical exercise interventions were associated with an increase of 51.59 meters in walking performance evaluated by the 6-minute-walk test (6MWT) (95% CI 7.55% to 95.63%; I^2 92%; p for heterogeneity < 0.01) as compared with control (Figure 2, panel 1 (A)).

Chair stands

Three articles (296 patients) [32,34,39] demonstrated that structured physical exercise interventions were associated with an increase of 4.66 times in 30-second chair stand test (95% CI 1.79% to 7.52%; I^2 68%; p for heterogeneity = 0.05) as compared with control (Figure 2, panel 1 (B)).

One study reported the 5-chair support test [33] and there were significant improvements for the Pilates intervention group compared with the control (Δ mean: intervention group -4 seconds; control group 1.3 seconds).

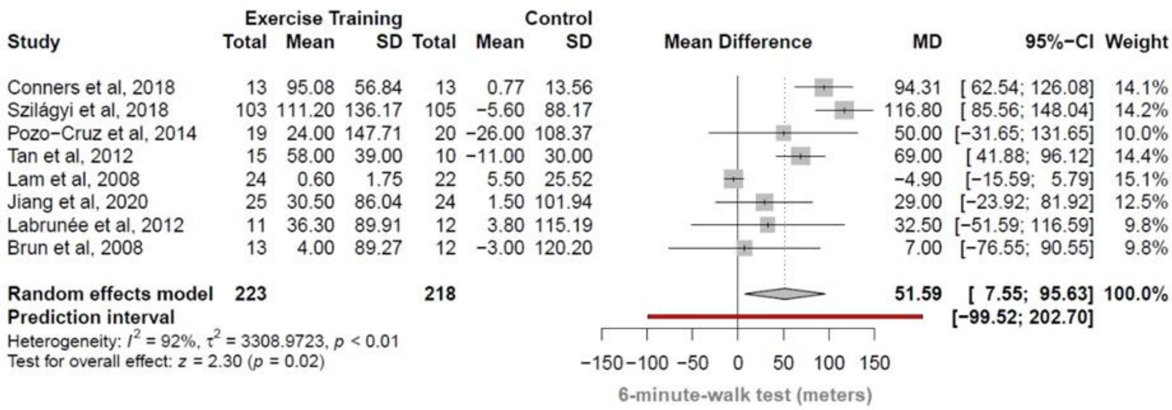
Timed Up and Go test

Two articles (88 patients) [34,39] demonstrated that structured physical exercise interventions were associated with a decrease of 0.16 seconds in the performance of the timed up and go test (95% CI -1.07% to 0.74%; I^2 0%; p for heterogeneity = 0.67) as compared with controls (Figure 2, panel 1 (C)).

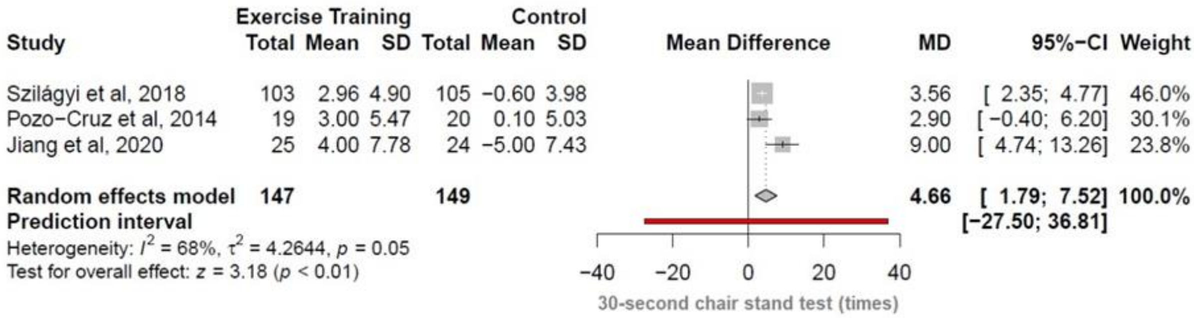
Fig. 2 Functional capacity outcomes

Panel 1. Meta-analysis of included studies comparing changes in walking performance (panel A), chair stands (panel B), and timed up and go test (panel C) by structured physical exercise *vs* control.

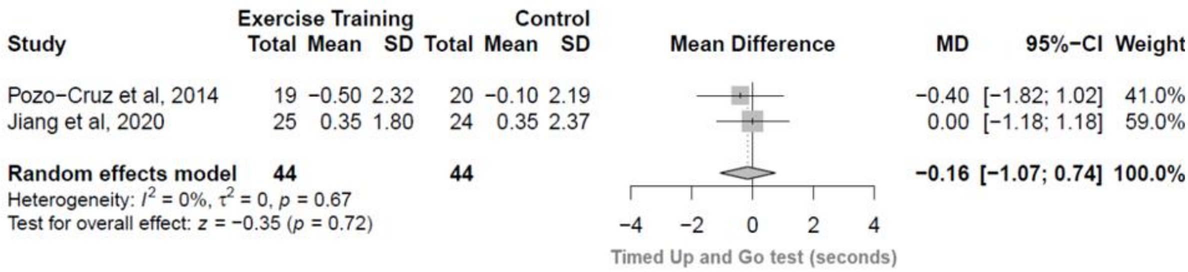
A - Walking Performance (6-minute-walk test)



B - Chair Stands (30-second chair stand test)



C - Timed Up and Go test (TUG)



CI indicates confidence interval. Changes in 6-minute-walk test, 30-second chair stand test and Timed Up and Go test of individual studies included in the meta-analysis of structured physical exercise *vs* no intervention in patients with type 2 diabetes.

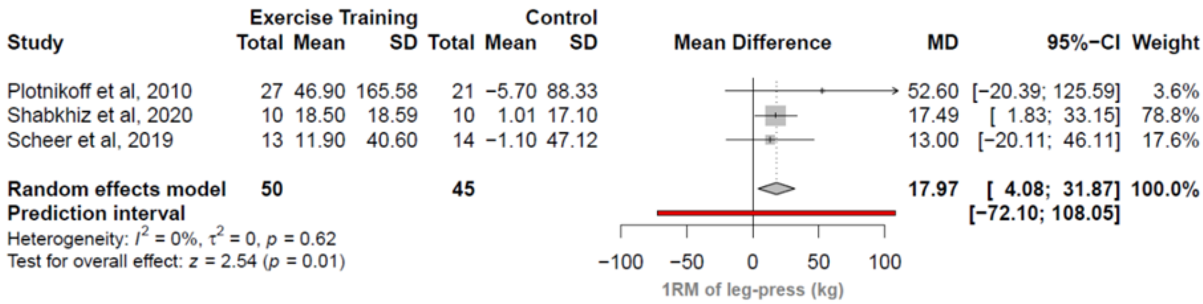
Lower limb muscle strength

Out of the 29 included studies, three articles (95 patients) [28,49,53] demonstrated that structured physical exercise interventions were associated with an increase of 17.97 kg in the strength measures of lower limb muscle evaluated by 1RM of leg-press (95% CI 4.08% to 31.87%; I^2 0%; p for heterogeneity = 0.62) as compared with control (Figure 3). Another study [54] showed an increase in muscle strength evaluated by the 1RM of knee extension test for the intervention group in relation to control [54] (Δ mean: intervention group 5.03; control group 0.8).

Upper limb muscle strength

One study [29] reported isometric strength assessed by handgrip and showed no differences (Δ mean: intervention group 0.3; control group -0.03).

Fig. 3 Meta-analysis of included studies comparing changes in one repetition maximum by structured physical exercise *vs* control



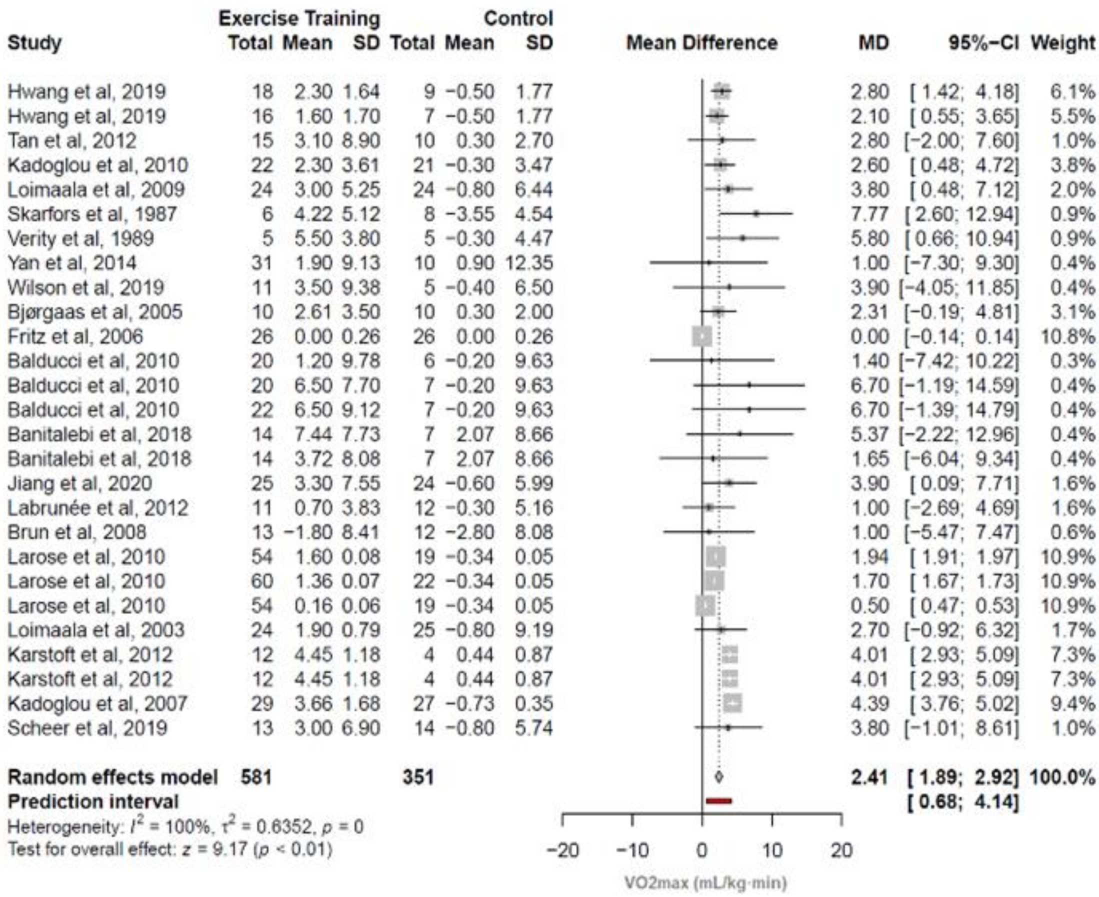
CI indicates confidence interval. Changes in the strength of lower limb muscle evaluated by 1RM of leg-press test of individual studies included in the meta-analysis of structured physical exercise *vs* no intervention in patients with type 2 diabetes.

Physical fitness

Out of the 29 included studies, 20 articles [31,35,36,38–48,50–53,55,56] with 27 groups of comparison (932 patients) demonstrated that structured physical exercise interventions were associated with an increase of 2.41 mL/kg·min in the VO_{2max} (95% CI 1.89% to 2.92%; I^2 100%; p for heterogeneity = 0) as compared with control (Figure 4).

Of these, 12 studies [35,36,38,39,41,43,44,47,48,50,55,56] presented the results of oxygen consumption in VO_{2max}, being 10 studies [35,36,38,39,41,43,44,47,48,50] with the unit of measure in mL/kg·min, one study [56] in mL/min and another study in L/min [55]. The last two studies were transformed to mL/kg·min using the body weight presented by each of the studies. The other eight studies [31,40,42,45,46,51–53] had the measure of oxygen consumption in VO_{2peak} and all of them with the unit of measure in mL/kg·min. The results of VO_{2max} and VO_{2peak} were combined in the same meta-analysis.

Fig. 4 Meta-analysis of included studies comparing changes in maximal oxygen consumption by structured physical exercise *vs* control



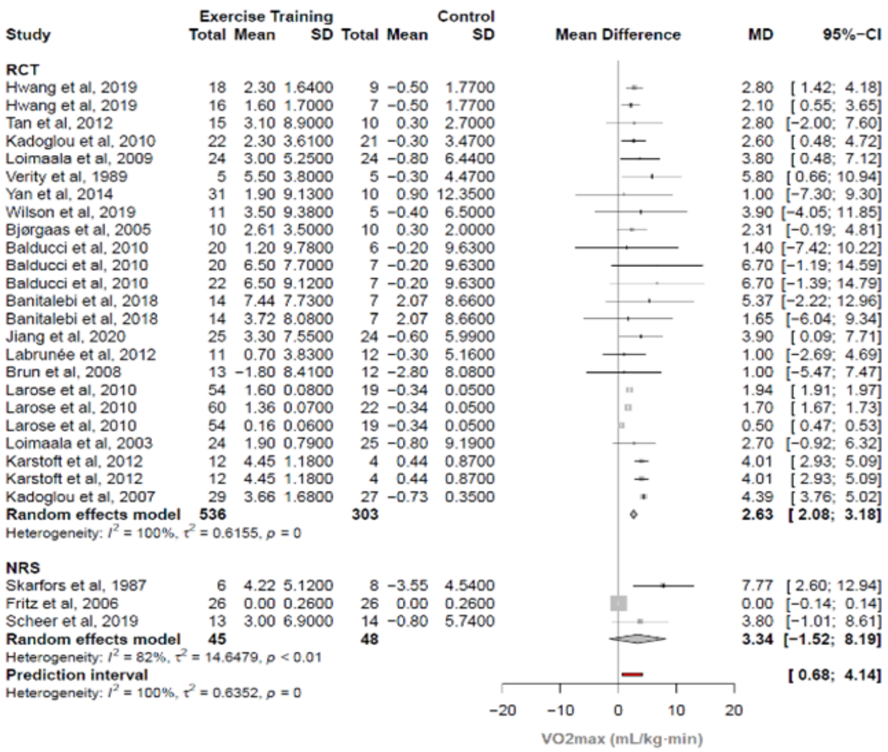
CI indicates confidence interval. Changes in physical fitness evaluated by VO_{2max} of individual studies included in the meta-analysis of structured physical exercise *vs* no intervention in patients with type 2 diabetes. Studies that included more than 1 modality or different training protocols within the same type of structured physical exercise were evaluated as separate observations.

Additional analyses

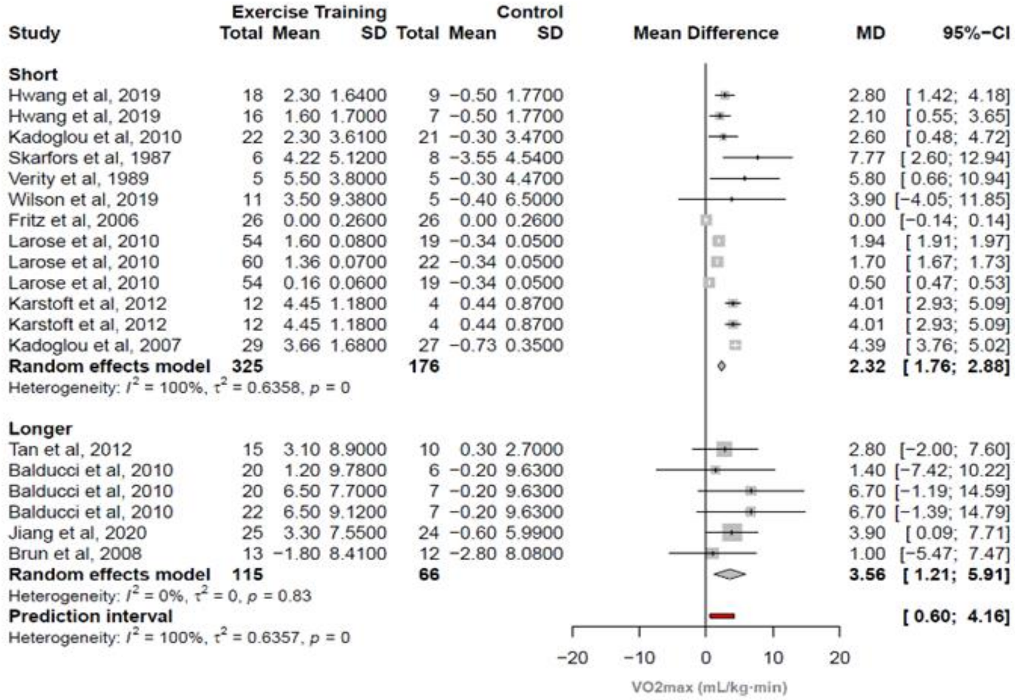
In sensitivity analysis, RCT studies [31,35,36,38–48,50–52] (17 studies, 24 comparisons, 839 patients) were associated with an increment of 2.63 mL/kg·min in the VO_{2max} (95% CI 2.08 to 3.18; I^2 100%, p for heterogeneity = 0) as compared with control. The NRS studies [53,55,56] (3 studies, 93 patients) were associated with an increment of 3.34 mL/kg·min in the VO_{2max} (95% CI −1.52 to 8.19; I^2 82%, p for heterogeneity < 0.01) as compared with control (Figure 5, panel 2 (A)). Regarding the duration of diabetes, we split study samples by short and long term duration of the disease (>8 years). The studies that included diabetes of short duration [31,42,44–46,48,52,55,56] (9 studies, 13 comparisons, 501 patients) were associated an increment of 2.32 mL/kg·min in the VO_{2max} (95% CI 1.76 to 2.88; I^2 100%, p for heterogeneity = 0) as compared to control. Studies that included diabetes with longer duration [35,36,39,41] (4 studies, 6 comparisons, 181 patients) were associated with an increment of 3.56 mL/kg·min in the VO_{2max} (95% CI 1.21 to 5.91; I^2 0%, p for heterogeneity = 0.83) as compared to control (Figure 5, panel 1 (B)).

Fig. 5 Panel 1, Sensitivity analysis for type of study and duration of diabetes diagnosis.

A - Sensitivity analysis for type of study



B - Sensitivity analysis stratified by the duration of diabetes diagnosis



CI indicates confidence interval. Changes in physical fitness evaluated by VO2max of individual studies included in the meta-analysis of structured physical exercise *vs* no intervention in patients with type 2 diabetes. Studies that included more than 1 modality or different training protocols within the same type of structured physical exercise were evaluated as separate observations.

Structured physical exercise and control group in the randomized clinical trials (RCT) and non-randomized controlled studies (NRS).

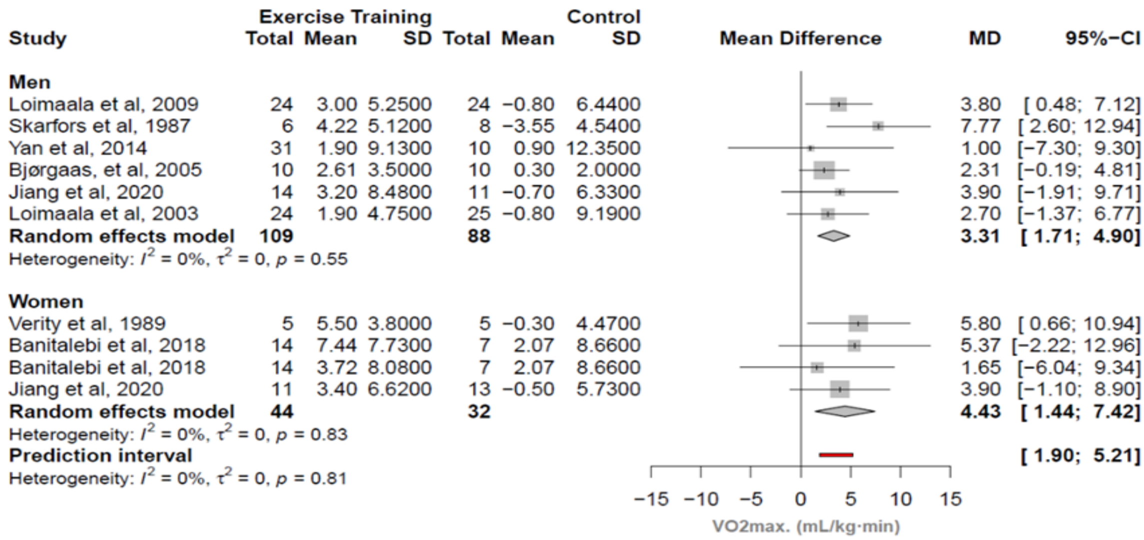
Structured physical exercise and control group with studies showing short and longer (>8 years of diabetes) duration of type 2 diabetes.

When studies were individually omitted from the meta-analysis, heterogeneity was unchanged. A table with the values of the heterogeneity from each study can be found in the Electronic Supplementary Material (Appendix 2).

In the subgroup analysis, studies with women [39,48,51] (3 studies, 4 comparisons, 76 patients) showed that interventions were associated with an increase of 4.43 mL/kg·min in VO_{2max} (95% CI 1.44 to 7.42; I^2 0%, p for heterogeneity = 0.83) and studies with men [38,39,43,47,50,56] (6 studies, 197 patients) showed that interventions were associated with an increase of 3.31 mL/kg·min in VO_{2max} (95% CI 1.71 to 4.90; I^2 0%, p for heterogeneity = 0.55), compared to control.

Meta-regression showed no association between HbA1c levels and VO_{2max} ($p = 0.34$; I^2 99.6%; $R^2 = 2.6\%$; p for heterogeneity <0.0001). Publication bias was assessed using a contour-enhanced funnel plot of each trial's effect size against the standard error. We did not find any publication bias ($p = 0.76$) and the funnel plot is presented in Electronic Supplementary Material (Appendix 3).

Fig. 6 Subgroup analysis stratified by sex



CI indicates confidence interval. Changes in physical fitness evaluated by VO_{2max} of individual studies included in the meta-analysis of structured physical exercise *vs* no intervention in patients with type 2 diabetes. Studies that included more than 1 modality or different training protocols within the same type of structured physical exercise were evaluated as separate observations.

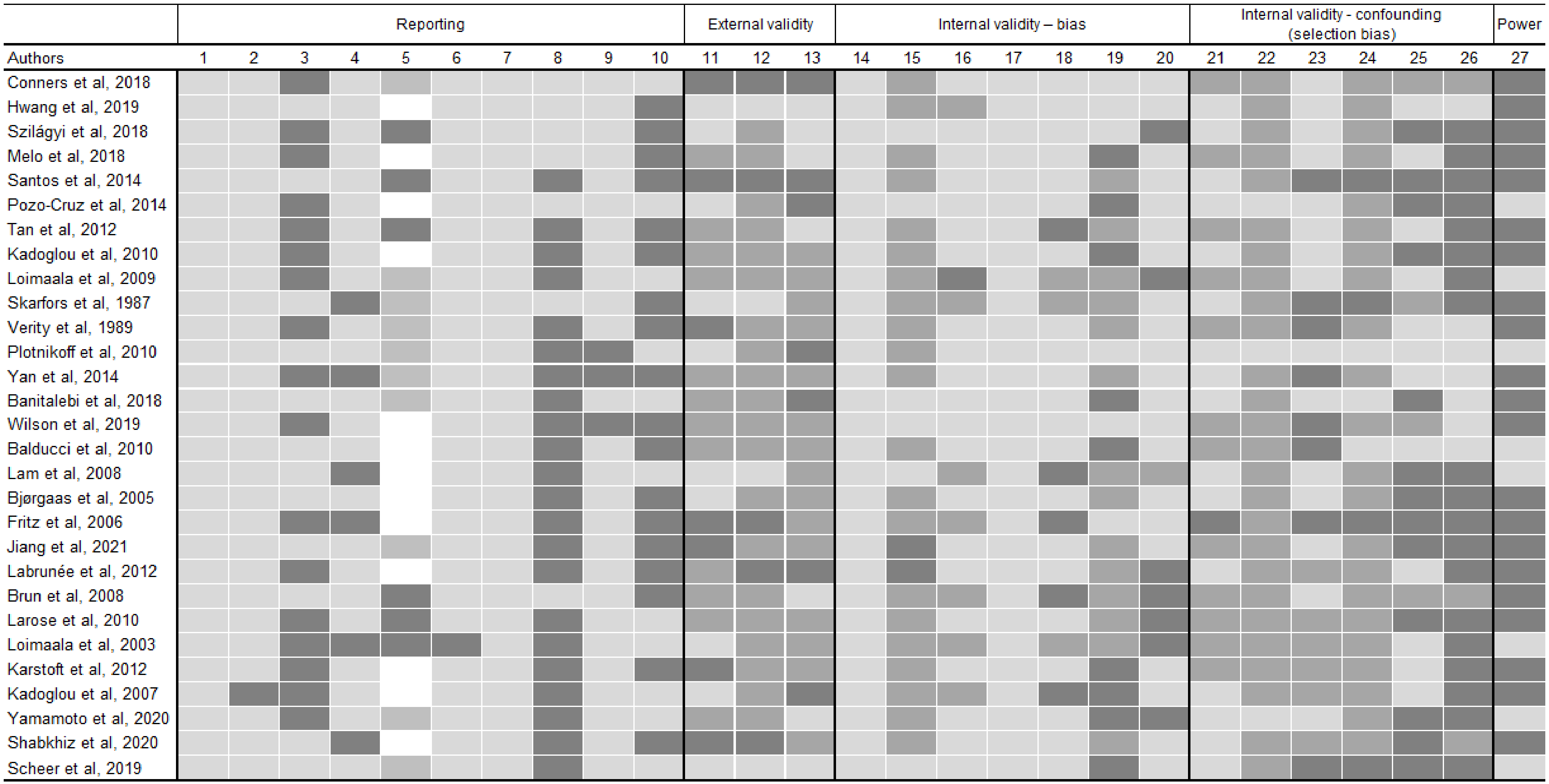
Quality assessment and risk of bias in individual studies

The following items were evaluated with respect to: reporting, external validity, internal validity (bias), internal validity (confusion - selection bias) and power. For item 14, we answered yes to all of the studies, because these are studies with exercise interventions, so, the blinding of the participants generally does not occur. Remembering that the checklist consists of 27 questions, RCTs score up to 28 and NRS at most 25. Four studies [31,34,49,53] scored good (20-25), 10 studies [29,30,32,33,36–38,46,51,52] fair (15-19) and 15 studies [28,35,39–45,47,48,50,54–56] poor (≤14), with available data in Electronic Supplementary Material (Appendix 4). In figure 7 we represent the evaluation of the studies for each of the items present in the Checklist Downs & Black [24].

DISCUSSION

This systematic review with meta-analysis summarizes the effects of exercise training on functional outcomes of people with type 2 diabetes. Although several syntheses have addressed exercise for patients with type 2 diabetes, the present study used a comprehensive assessment by including different functional outcomes. We observed that in individuals with type 2 diabetes, structured aerobic, resistance, combined, or other type (i.e., Pilates, Tai Chi, Whole-body vibration) of exercise training was associated with increases in functional capacity as indicated by walking performance, chair stands, time up and go tests, 1RM of leg-press, and VO_{2max}. In additional sensitivity and meta-regression analyses, we could not identify isolated factors or studies that may have had differential influence in summary estimates. Most studies' scores indicate a high risk of biases, which underscores the importance of careful interpretation regarding the summarized evidence. Most of the studies included participants with an average age close to 60 years or more, therefore, our results are more widely generalizable to patients with type 2 diabetes over 45 years old.

Fig. 7 Risk of biases rating based on the Downs & Black checklist.



Description: score for each item with their respective colors Yes 2 | Yes 1 | Partially 1 | Unable to determine 0 | No 0

The present meta-analysis demonstrated that cardiorespiratory fitness, measured by VO_{2max} can be improved with structured physical exercise interventions in people with type 2 diabetes, supporting previous observations in this population [61,62]. We emphasize that the number of studies included in the present meta-analysis was greater. Considering that low cardiorespiratory fitness has been explored as a predictor of cardiovascular mortality in people with diabetes [63], the present findings may reflect major clinical benefits. A cohort study, including nondiabetic and diabetic individuals, showed that increments equivalent to 1.44 ml/kg/min in VO_{2max} were associated with a 7.9% reduction in overall mortality [64]. Moreover, subjects with type 1 and 2 diabetes mellitus present lower walking capacity compared with non-diabetic controls [65]. Of note, we observed that in the present synthesis supervised interventions from included studies show an increase of 11% (51.59 meters) in the 6MWT, which is considered a reliable, validated and clinically meaningful test for patients with diabetes [66].

Low muscle strength has been shown to be associated with an increased risk of all-cause mortality [67,68]. Furthermore, in patients with type 2 diabetes, there is a pronounced decline in muscle mass and strength, in agreement with a worsening in functional performance [4]. Therefore, we can highlight the importance of increases in muscle strength. It is also important to highlight the clinical importance of observing increases in functional variables in the elderly after interventions, such as gait and lower limb strength, for example, due to their negative predictive capacity in relation to the use of health care and adverse events (i.e., institutionalization, falls, disability, mortality) [69–71]. However, it is important to emphasize that the results from our meta-analysis and its estimates related to muscle strength should be interpreted with caution due to the low number of included studies.

To explore the expected methodological and statistical heterogeneity, we used a prespecified strategy based on sensitivity and meta-regression analyses and did not detect associated factors. In addition, the quality of the studies was mostly low, which may have contributed to heterogeneity in the present meta-analyses [22]. Due to the low number of studies available, exploratory analyses were not performed for five of the six intended outcomes, which would require at least 10 studies [22], and for peripheral neuropathy which was not present in any sample. As for analyses with VO_{2max}, it was not possible to demonstrate conclusive results due to the occurrence of overlapping confidence intervals, and we did not identify any association between HbA1c and VO_{2max}.

Regarding the quality and risk of bias of individual studies, in general, the reporting and internal validity items, the studies obtained good scores on questions such as: description of hypothesis/aim, clear description of outcomes and main results, description of variability estimates, number of lost participants, follow-up period for groups. Items of external validity, internal validity - confounding (selection bias) and power were identified as more prone to bias. We emphasize that characteristics contemplating the generalization to the population from which the study participants were derived, adjustment of confounding factors in the analyses, loss of patients in the course of the study and sample size calculation should be considered for the interpretation of results and future studies.

Limitations

This study has some limitations. Although the search was not limited by language, the studies included were only in Portuguese, English and Spanish. The clinical conditions that we used as exclusion criteria for the studies were chosen because they strongly influence the functional results, which would end up being a confounding factor and difficult to methodological control. We tried to broadly address the functional outcomes in this population, however, within the criteria used to select the studies, some ended up being identified in a low number, thus not being explored as planned. Finally, we analyzed only structured physical exercise interventions, which may not be feasible for all patients with type 2 diabetes. Therefore, the results presented cannot be generalized to all exercise programs in this population.

Moreover, high heterogeneity was identified in the meta-analyses, especially in the walking performance (6MWT) and physical fitness (VO_{2max}) meta-analysis, and although we did try to explore it, no additional information was retrieved with this strategy. In addition, the overall quality of the studies was low, increasing the risk of bias in the studies, which may limit the interpretation of results.

Future Directions

Because many comorbidities are associated with type 2 diabetes, future trials should consider minimizing eligibility criteria to allow more representative samples for this clinical population. In addition, establishing common outcomes, such as implementing the use of Core Outcome Set (COS), would be beneficial to increase the number of comparable studies in future reviews [72].

This systematic review demonstrates that structured physical exercise is associated with improvements in functional outcomes with clinical relevance for people with diabetes. This highlights the need and importance of a recommendation for physical exercise in order to preserve and/or improve physical function in this population.

CONCLUSIONS

In conclusion, the current meta-analysis suggests that in people with type 2 diabetes, structured physical exercise consistent with aerobic training, resistance training, both combined or other types of training (Pilates, Tai Chi and Whole-body vibration) is associated with an improvement in functional capacity (i.e., cardiorespiratory fitness, walking performance, lower limb muscle strength, sit and stand up and walk tests). These increments are better perceived in the VO_{2max} and 6MWT outcomes. However, subgroup and sensitivity analyses were inconclusive due to the small number of studies in some comparison groups and the high variability observed in confidence interval values.

It is expected that these results may demonstrate a reduction in the propensity for physical disability and that they may considerably reduce the risk of cardiovascular disease for this population.

Availability of data, code and other materials

The data and analytic codes used in the meta-analyses and the scripts used to generate the meta-analysis are available with the other materials in the OSF (https://osf.io/h47r8/).

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Supplementary Material

Appendix 1. Search strategy

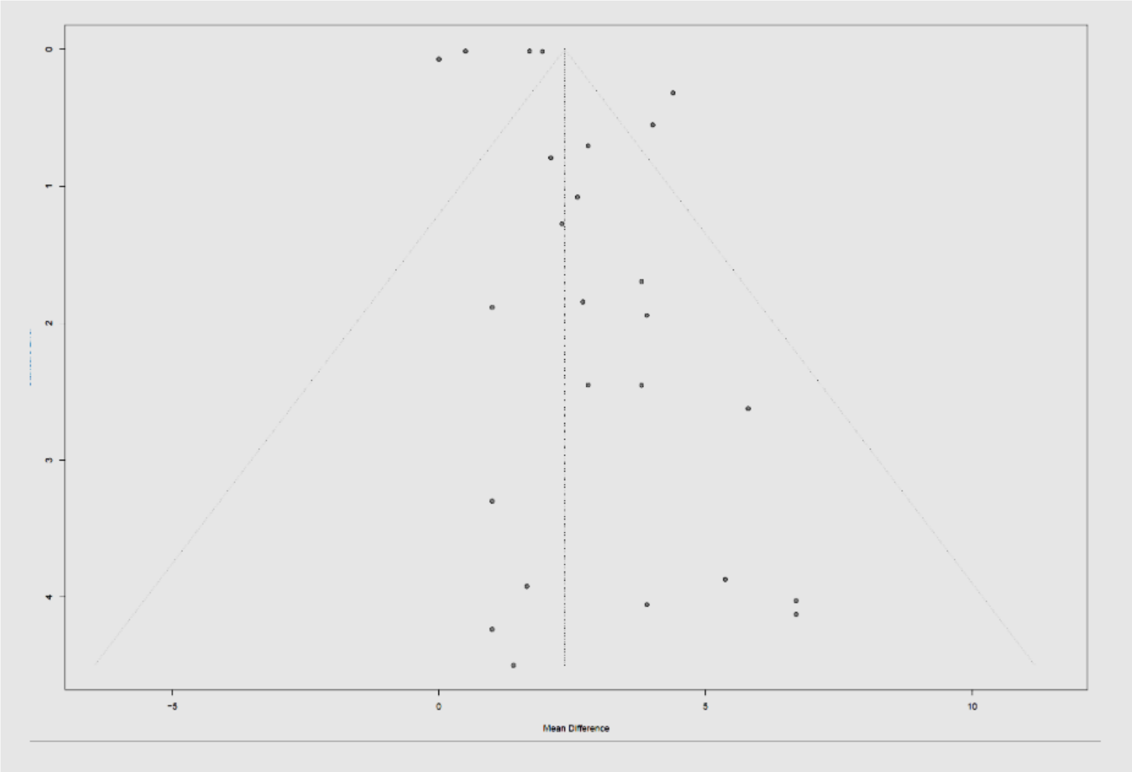
Search Strategy	Terms
PubMed	#1 (Aged[Mesh] OR Aged[tiab] OR Elderly[tiab] OR Older[tiab] OR "Older Adults"[tiab] OR "Frail Older"[tiab] OR Aging[tiab] OR "Frail Elderly"[tiab] OR "Seniors"[tiab]) #2 ("Diabetes"[tiab] OR "Mellitus"[tiab] OR "Non Insulin Dependent"[tiab] OR "T2DM"[tiab] OR "Diabetic*"[tiab] OR "Diabetes Mellitus Noninsulin Dependent"[tiab]) #3 ("Exercise Therapy"[Mesh] OR "Exercise Therapy"[tiab] OR "Exercise Movement Techniques"[Mesh] OR Pilates[tiab] OR "Combined Training"[tiab] OR "Concurrent Training"[tiab] OR "Power Training"[tiab] OR "High-intensity Power Training"[tiab] OR "High-Velocity Resistance Exercise"[tiab] OR "Resistance Training"[Mesh] OR "Resistance Training"[tiab] OR "Exercise"[Mesh] OR "Exercise"[tiab] OR Exercises[tiab] OR "Isometric Exercise"[tiab] OR "Aerobic Exercise"[tiab] OR "Aerobic Exercises"[tiab] OR "Aerobic Exercise"[tiab] OR "Training Resistance" [tiab] OR "Strength Training"[tiab] OR "Weight Lifting"[tiab] OR "Strengthening Program" [tiab] OR "Strengthening Programs"[tiab] OR "Physical Exercise"[tiab] OR "Physical Exercises"[tiab] OR “Physical Activity”[tiab] OR “Physical Activities”[tiab]) #4 (Review[ti] OR Cohort[ti] OR Cross-sectional[ti] OR "Observational"[ti] OR Case-control[ti] OR "Case report"[ti] OR Meta-analysis[ti] OR Synthesis[ti] OR Consensus[ti]) #1 AND #2 AND #3 NOT #4
PEDro Physiotherapy Evidence Database	#1 Aged AND Exercis* AND Diabetes #2 Clinical Trial #1 AND #2
Cochrane Library	#1 Aged OR Elderly OR Older OR Older Adults OR Frail Older OR Aging OR Frail Elderly OR Seniors #2 Diabetes OR Mellitus OR Non Insulin Dependent OR T2DM OR Diabetic* OR Diabetes Mellitus Noninsulin Dependent #3 Exercise Therapy OR Exercise Movement Techniques OR Pilates OR Combined Training OR Concurrent Training OR Power Training OR High-Intensity Power Training OR High-Velocity Resistance Exercise OR Resistance Training OR Exercise OR Exercises OR Isometric Exercise OR Aerobic Exercise OR Aerobic Exercises OR Training Resistance OR Strength Training OR Weight Lifting OR Strengthening Program OR Strengthening Programs OR Physical Exercise OR Physical Exercises OR Physical Activity OR Physical Activities #1 AND #2 AND #3

SPORTDiscus	#1 Older People #2 Diabetes OR NON-insulin-dependent Diabetes #3 Exercise OR Exercise Therapy OR Physical Activity #4 Cohort Analysis OR Meta-analysis OR Systematic Review #1 AND #2 AND #3 NOT #4
Lilacs	#1 (tw:(Aged OR “Frail Elderly” OR Aging OR "Frail Older" OR Seniors)) #2 (tw:(“Diabetes Mellitus” OR “Diabetes Mellitus, Type 2” OR Diabetes)) #3 (tw:(“Exercise Therapy” OR Exercise OR "Physical Activity" OR "Physical Exercise")) #4 (tw:(“Systematic Review” OR “Cohort Studies” OR “Observational Study“)) #1 AND #2 AND #3 AND NOT #4
Grey Literature	
Google Scholar	#1 With all the words: Aged Elderly Older Diabetes Diabetes Mellitus Exercise Physical Activity Physical Exercise #2 At least one of the words: Aging Diabetes Mellitus Exercise Therapy #3 NOT: Review Cohort Cross-Sectional Observational Meta-Analysis
OpenGrey	Exercise AND type 2 diabetes (associated terms)

Appendix 2. Leave one out with VO_{2max}

Omiting	**I^2**
Hwang et al, 2019	99.6%
Hwang et al, 2019	99.6%
Tan et al, 2012	99.6%
Kadoglou et al, 2010	99.6%
Loimaala et al, 2009	99.6%
Skarfors et al, 1987	99.6%
Verity et al, 1989	99.6%
Yan et al, 2014	99.6%
Wilson et al, 2019	99.6%
Bjørgaas, et al, 2005	99.6%
Fritz et al, 2006	99.6%
Balducci et al, 2010	99.6%
Balducci et al, 2010	99.6%
Balducci et al, 2010	99.6%
Banitalebi et al, 2018	99.6%
Banitalebi et al, 2018	99.6%
Jiang et al, 2020	99.6%
Labrunée et al, 2012	99.6%
Brun et al, 2008	99.6%
Larose et al, 2010	99.4%
Larose et al, 2010	99.5%
Larose et al, 2010	97.1%
Loimaala et al, 2003	99.6%
Karstoft et al, 2012	99.6%
Kadoglou et al, 2007	99.6%
Scheer et al, 2019	99.6%
Pooled estimate	99.6%

Appendix 3. Funnel Plot VO_{2max}



Appendix 4. Quality assessment and of the risk of bias in individual studies assessed by using the Checklist DOWNS & BLACK

Authors	Score	Classification	Design
Jiang et al, 2020	14	Poor	RCT
Yamamoto et al, 2020	17	Fair	RCT
Shabkhiz et al, 2020	14	Poor	RCT
Scheer et al, 2019	20	Good	NRS
Hwang et al, 2019	22	Good	RCT
Wilson et al, 2019	15	Fair	RCT
Conners et al, 2018	16	Fair	RCT
Szilágyi et al, 2018	17	Fair	RCT
Melo et al, 2018	16	Fair	RCT
Banitalebi et al, 2018	19	Fair	RCT
Pozo-Cruz et al, 2014	21	Good	RCT
Santos et al, 2014	13	Poor	NRS
Yan et al, 2014	13	Poor	RCT
Tan et al, 2012	13	Poor	RCT
Labrunée et al, 2012	14	Poor	RCT
Karstoft et al, 2012	14	Poor	RCT
Kadoglou et al, 2010	15	Fair	RCT
Plotnikoff et al, 2010	22	Good	RCT
Balducci et al, 2010	18	Fair	RCT
Larose et al, 2010	11	Poor	RCT
Loimaala et al, 2009	13	Poor	RCT
Lam et al, 2008	17	Fair	RCT
Brun et al, 2008	12	Poor	RCT
Kadoglou et al, 2007	14	Poor	RCT
Fritz et al, 2006	11	Poor	NRS
Bjørgaas et al, 2005	17	Fair	RCT
Loimaala et al, 2003	10	Poor	RCT
Verity et al, 1989	14	Poor	RCT
Skarfors et al, 1987	14	Poor	NRS

6. CONCLUSÕES E CONSIDERAÇÕES FINAIS

A partir dos objetivos de identificar a contribuição de determinantes sociais de saúde e determinantes clínicos na capacidade funcional em uma amostra de base populacional de idosos e sintetizar os efeitos do treinamento físico sob resultados utilizados para medir a capacidade funcional em indivíduos com diabetes tipo 2; foi possível concluir, que o desempenho de pessoas ativas com mais de 60 anos em testes funcionais, pode ser explicado parcialmente pela idade, sexo, IMC e qualidade de vida para desempenho no TC6 e, na força de preensão manual, por idade e sexo. Além disso, a partir da meta-análise atual, observou-se que em pessoas com diabetes tipo 2, o exercício físico (i.e. aeróbico, força, ambos combinados ou outros tipos de treinamento - Pilates, Tai Chi e vibração de corpo inteiro) promove melhora da capacidade funcional (aptidão cardiorrespiratória, performance de caminhada, força muscular de membros inferiores, sentar e levantar e testes de caminhada). Esses incrementos são melhor percebidos nos resultados do $VO_{2máx.}$ e TC6, possivelmente pela maioria dos estudos incluídos na síntese serem com treinamento aeróbico. Além disso, as análises de subgrupo e sensibilidade foram inconclusivas devido ao pequeno número de estudos em alguns grupos de comparação e à alta variabilidade observada nos valores do intervalo de confiança.

Estudos e análises futuras devem considerar ajustes para os testes TC6 e de preensão manual para sexo e idade, e considerar que o TC6 pode ser influenciado por indicadores corporais e pela qualidade de vida, sugerindo que a funcionalidade pode ser composta por outras variáveis complementares. Além disso, destacamos a importância do exercício físico para pessoas com diabetes tipo 2, a fim de preservar e/ou melhorar a capacidade funcional, além dos benefícios já conhecidos para essa população.