Metformin and physical performance in older people with probable sarcopenia and physical prefrailty or frailty in England (MET-PREVENT): a double-blind, randomised, placebo-controlled trial

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Summary

Background Metformin has effects on multiple biological systems relevant to ageing and has been posited as a candidate therapy for sarcopenia and physical frailty. We aimed to test the efficacy and safety of metformin, a candidate geroprotector, to improve physical performance in older people with probable sarcopenia and physical prefrailty or frailty.

Methods In this double-blind, randomised, parallel-group, placebo-controlled trial (MET-PREVENT), participants aged 65 years and older with a 4-m walk speed of less than 0·8 m/s and probable sarcopenia, characterised by low handgrip strength (<16 kg for women and <27 kg for men) or five times sit-to-stand time of longer than 15 s (or inability to complete five sit-to-stands) were recruited from primary care and hospital clinics in Gateshead and Newcastle, UK. Participants were randomly assigned (1:1), via a web-based system with minimisation to ensure balance by sex and baseline 4-m walk speed, to receive either 500 mg oral metformin or matching placebo three times a day for 4 months. The primary outcome was the adjusted between-group difference in 4-m walk speed at 4 months. The primary outcome was analysed in the intention-to-treat population (ie, all participants randomly assigned to treatment) who had complete data, and safety was assessed in all participants who received at least one dose of study treatment. This study is registered with the ISRCTN registry, ISRCTN29932357, and is now complete.

Findings Between Aug 1, 2021, and Sept 30, 2022, 268 individuals were screened for inclusion in the trial, and 72 participants were randomly assigned to either metformin (n=36) or placebo (n=36; intention-to-treat population). Mean age was 80·4 years (SD 5·7), 42 (58%) of 72 participants were female, 30 (42%) were male, and 70 (97%) were White British. 70 (97%) of 72 participants had complete follow-up data (n=34 in the metformin group and n=36 in the placebo group). Mean 4-m walk speed at 4 months was 0·57 m/s (SD 0·19) in the metformin group and 0·58 m/s (0·24) in the placebo group (adjusted treatment effect 0·001 m/s [95% CI −0·06 to 0·06]; p=0·96). 108 adverse events occurred in 35 (100%) of 35 participants who received metformin and 77 adverse events occurred in 33 (92%) of 36 participants who received placebo, and 12 (34%) of 35 participants had hospital admissions in the metformin group versus three (8%) of 36 participants in the placebo group. One death occurred, in the metformin group (one [3%] of 35), and was judged to be unrelated to study treatment.

Interpretation Metformin did not improve 4-m walk speed and was poorly tolerated in this population.

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Introduction

Sarcopenia is a major cause of ill-health for older people, often leading to increased likelihood of falls, impaired activities of daily living, an increased need for care, extended stays in hospital, and earlier death.[1,2] Sarcopenia is also an important component of physical frailty syndrome, conceptualised as a downward spiral of impaired energy use, exhaustion, low activity, weakness, and weight loss.[3] Resistance exercise has been shown to be effective in improving strength and physical function in people with sarcopenia and is also effective for those with frailty.[4,5] However, not all patients are able or willing to undertake resistance exercise; therefore, alternative therapies to prevent and treat sarcopenia and frailty are required.

Metformin has been a mainstay of treatment for type 2 diabetes for decades. Metformin has also been shown to have a broad range of actions relevant to hallmarks of ageing—the fundamental biological processes that are thought to underpin multiple age-related conditions. As such, metformin might have a role as a generic so-called

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Research in context

Evidence before this study

We searched PubMed for articles using the terms "randomi*" AND "metformin" AND ("frailty" OR "sarcopenia" OR "muscle") from database inception to Sept 30, 2024. We found four relevant trials: two in healthy older people, one in men with prefrailty, and one in men with sarcopenia. In healthy older people, metformin blunted the effect of exercise training on both strength and endurance outcomes; in older men with prefrailty or sarcopenia, metformin had mixed effects on measures of physical performance.

Added value of this study

Despite the low physical performance of our participants, our trial design delivered high retention in this group who have historically been underserved by clinical trials, with high dropout rates. We found that metformin did not improve measures of physical performance, activities of daily living or quality of life in older people with sarcopenia and frailty or prefrailty and it caused a high number of adverse events.

Implications of all the available evidence

Our results suggest that metformin is unlikely to be a suitable geroprotective agent for long-term use by older people with sarcopenia and frailty or prefrailty. Existing evidence suggests that the best balance of efficacy and tolerability in improving physical performance might lie between healthy older people and older people with frailty and future trials should target this group.

geroprotector agent, with activity across conditions including sarcopenia and frailty. A range of actions of metformin might have potentially beneficial effects on skeletal muscle metabolism and, hence, sarcopenia.[6] These include, but are not limited to, modulation of mammalian target of rapamycin (mTOR) activity, modulation of mitochondrial complex 1 activity, senostatic activity, reduction of proinflammatory cytokine production, and modulation of the gut microbiome. However, some actions of metformin might have potentially deleterious consequences. AMP kinase activation might lead to short-term catabolic effects that could reduce muscle mass, and metformin has been shown to blunt physiological responses to exercise training in healthy older people.[7,8]

Observational studies suggest that metformin use is associated with reduced rates of loss of muscle mass in men[9] and women[10] with type 2 diabetes compared with use of other therapeutic agents. Both incident and prevalent frailty (measured using a cumulative deficits index)[11] and frailty-related events including falls[12] are less common in people with diabetes using metformin than in non-users. Trial evidence for effects of metformin on skeletal muscle function and physical performance in patients without type 2 diabetes is scant and conflicting. One trial of older people (mean age 69 years) with prefrailty—an early and potentially reversible risk state before frailty—found a significant and clinically important improvement in 4-m walk speed of 0·13 m/s with 500 mg three times a day of metformin for 16 weeks compared with matched placebo.[13] Another trial performed in older men (mean age 73 years) with sarcopenia found a small improvement in handgrip strength and sarcopenia-related quality of life at 4 months compared with placebo, but no difference in walk speed.[14] However, the MASTERS trial[7] found that adding 850 mg of metformin twice daily to a 14-week resistance training programme did not improve response to strength training in healthy older people (age range 64–91 years, median 69 years). Instead, the hypertrophic response to training was blunted in the metformin group compared with the placebo group.[7] Similar attenuation in the response to exercise training was seen in a small trial of metformin versus placebo when added to aerobic training in healthy older people (mean age 62 years).[8]

Patients with sarcopenia and prefrailty or frailty are a priority for treatment in clinical practice but are also a group who are at risk of adverse effects and many have multiple long-term conditions with attendant polypharmacy. Therefore, defining the balance of benefit and risk in this key target population is important. We aimed to test whether metformin could improve walk speed and physical performance in older people living with probable sarcopenia and physical frailty or prefrailty.

Methods

Study design and participants

MET-PREVENT was a double-blind, randomised, parallel-group, placebo-controlled trial. Participants were recruited at two NHS Trusts in the northeast of England (Gateshead and Newcastle) through primary care practices and hospital clinics. Potentially eligible participants underwent a pre-screening assessment in which initial eligibility details were confirmed and the SARC-F questionnaire was administered; a score of 1 or more (from a maximum score of 10) was required to progress to a screening visit. Participants were eligible for inclusion if they were aged 65 years and older and had probable sarcopenia, according to the European Working Group on Sarcopenia in Older People (EWGSOP) 2019 definition of sarcopenia,[15] operationalised as low maximum handgrip strength (<16 kg for women and <27 kg for men) or a five times sit-to-stand time of longer than 15 s (or inability to complete five sit-to-stands). Participants also had to have a 4 m walk speed of less than 0·8 m/s—a measure that denotes severe sarcopenia in the 2019 EWGSOP guidelines. Through inclusion of low walk speed as a criterion, we ensured that all included participants met at least one of the five criteria for the phenotype model for frailty, the Fried frailty score,[3] ensuring that all participants had at least prefrailty at screening. Low muscle mass was not required for inclusion in the trial; we chose to base trial inclusion on the EWGSOP definition of probable

sarcopenia, which does not require low muscle mass and better reflects current clinical practice.[16] Exclusion criteria included diabetes (type 1 or type 2), previous intolerance to metformin or current receipt of metformin for another condition, estimated glomerular filtration rate of less than 45 mL/min per 1·73 m^2, and life expectancy of less than 3 months. Participants with skeletal myopathy clearly due to an alternative cause rather than sarcopenia were excluded because the mechanisms underlying such conditions might have differed from those underlying sarcopenia and might thus have been less likely to respond to metformin therapy. Full eligibility criteria are listed in the appendix (p 2) and are available in the protocol.[17]

The trial was approved by the UK Health Research Authority North-West—Liverpool Central Research Ethics Committee (approval number 20/NW/0470). The trial was also approved by the UK Medicines and Healthcare products Regulatory Agency (trial reference number 2020-004023-16). The trial has been included in the National Institute for Health and Care Research (NIHR) Clinical Research Network portfolio (study ID 47772) and is registered on the ISRCTN trial database (ISRCTN29932357). The trial sponsor was the Newcastle Upon Tyne Hospitals NHS Foundation Trust. The trial was conducted according to the principles of the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all participants, and trial safety was overseen by an Independent Data Monitoring Committee. A public representative (SC) sat on the trial management group and contributed to oversight and management of the trial.

Randomisation and masking

Participants were randomly assigned (1:1) to either metformin or matched placebo. Randomisation was done with an interactive web-based system (designed by Sealed Envelope, London, UK). Minimisation (with a 30% random element) was used to ensure balance across the two groups on the basis of sex (male or female) and baseline walk speed (≤0·6 m/s or >0·6 m/s) as stratification variables. Study medication was prepared in identical bottles by ModePharma (Beckenham, UK) and dispensed by site trial pharmacies with no indication of randomisation group on the bottle. Participants, investigators, and outcome assessors were all masked to treatment assignment.

Procedures

Participants received 4 months of oral metformin 500 mg (Aurobindo Pharma, Hyderabad, India) or matched placebo (lactose and microcrystalline cellulose) tablets three times a day.

Participants who wished to discontinue study medication (due to side-effects, adverse events, treatment burden, or personal choice) could do so but were encouraged to remain in the trial for follow-up visits, including the final outcome visit at 4 months, to maximise contribution to the intention-to-treat analysis. Adherence was evaluated by comparing the final tablet count with the initial tablet allocation; adherence was calculated as (the number of tablets taken / the number of tablets expected to be taken by the final study visit) × 100. If a participant had missing information on the returned tablet count, we assumed that adherence was the median of the percentage adherence of those with adherence data. For those who discontinued early, we adjusted this according to their time on treatment.

The following measures were done at baseline and at 4 months at the hospital clinic or participants' home. Walk speed measures were conducted by research staff who were masked to treatment allocation either in the research unit or in the participant's own home using a measured 4-m course. Timing commenced from a static start and ended when the first part of the body crossed the 4-m point. The walk was timed to the nearest 0·1 s by a research staff member using a stopwatch; the fastest of two attempts was recorded. Physical performance was assessed using the Short Physical Performance Battery (SPPB).[18] Handgrip strength was measured using a Jamar dynamometer (Sammons Preston, Bolingbrook, IL, USA) according to a standard protocol.[19] Three measurements were taken from each side and the maximum value was used in analyses. For participants attending the research centre, or with sufficient outdoor space at home, the 6-min walk test was performed over a 10 m course. Standardised encouragement was given and the distance walked in 6 min was recorded to the nearest metre.[20] Skeletal muscle mass was estimated by bioimpedance analysis using the Akern 101 bioimpedance system (Akern, Pontassieve, Italy); raw values of resistance and reactance were used to estimate appendicular skeletal muscle mass via the Sergi equation.[21] The Fried frailty score was calculated using parameters derived from the English Longitudinal Study of Ageing;[22] individual components of the Fried frailty score were measured, with exhaustion operationalised as a positive response to the question "During the last month I could not get going" or to the question "During the last month, everything I did was an effort". Health-related quality of life was measured using the EQ-5D-5L, EQ-5D thermometer (0–100 scale), and the Short Form 36 questionnaire (SF-36 v2). Instrumental activities of daily living were measured using the Nottingham Extended Activities of Daily Living score.[23]

Blood samples for analysis of serum creatinine, bilirubin, alanine aminotransferase, alkaline phosphatase, non-fasting glucose, and lactate were obtained at baseline and at 1, 2, 3, and 4 months and analysed by local hospital systems as samples for clinical care. Baseline insulin concentrations were analysed from spun serum samples stored at –80°C before batch analysis using a Mercodia Iso-Insulin ELISA kit (10-1128-01; Mercodia, Uppsala, Sweden), performed on the Grifols Triturus automated ELISA platform (Grifols, Barcelona, Spain). Adverse events were collected at each study contact and participants' clinical records were followed up until 28 days after the last participant visit. Events were coded by the chief investigator (MDW) and data manager (LS) using the Medical Dictionary for Regulatory Activities coding system (version 24). Adverse reactions

See Online for appendix

were defined as adverse events which were possibly, probably, or definitely causally related to metformin.

Outcomes

The primary outcome was between-group difference in 4-m walk speed at 4 months, adjusted for baseline values.

Secondary outcomes were grip strength; five-time sit-to-stand time; appendicular skeletal muscle mass (measured using bioimpedance); Fried frailty score; other individual components of the Fried frailty score (ie, activity level, self-reported exhaustion, and weight); transition from prefrail to frail, death, inability to continue in trial, or to non-frail measured, using the Fried frailty score; SPPB score; 6-min walk distance; instrumental activities of daily living (Nottingham Extended Activities of Daily Living score); and health-related quality of life (measured by the EQ-5D-5L and SF-36 v2 [1 week recall] physical and mental component score).

Additionally, we had secondary outcomes related to trial processes, recruitment, and retention, which were conversion rate from screening to randomisation and retention rate of recruited participants at the end of the trial; and related to potential mechanisms of action of metformin, which were advanced glycosylation end-products measured via skin auto fluorescence. These outcomes will be reported elsewhere.

Statistical analysis

We used the minimum clinically important difference for 4-m walk speed of 0·1 m/s[24] to derive the sample size. On the basis of previous trials,[25,26] we assumed an SD of 0·24 m/s for the primary outcome, and a correlation between baseline and follow-up measures of 0·8. Therefore, for an analysis adjusting for baseline values, a sample size of 33 participants per group (66 in total) was required to detect a 0·1 m/s difference between groups at an α level of 0·05 with 80% power. We anticipated a dropout rate of 17·5%, thus the recruitment target for the trial was set at 80 participants being randomly assigned to treatment groups.

The primary outcome and secondary outcomes were assessed in the intention-to-treat population, which included all participants who were randomly assigned to treatment, regardless of whether they received the treatment they were allocated to, discontinued, or withdrew. For the primary and secondary outcome analyses, we did a complete-case analysis, such that we excluded all participants with missing data (ie, did not attend the 4-month study visit). In prespecified analyses, the primary outcome was also assessed in the per-protocol population, which included all participants assigned to treatment who had adherence to the study medication of 80% or higher. Safety was assessed in all participants who received at least one dose of study medication.

The primary outcome of 4-m walk speed is reported descriptively by treatment group at baseline and at 4 months as mean (SD). We used linear regression to compare 4-m walk speed between the metformin and placebo groups at 4 months, adjusted for baseline 4-m walk speed and sex. We present results as adjusted mean difference (95% CI), and p value.

For continuous secondary outcomes, we used a linear regression model for analysis, and for ordinal secondary outcomes we used an ordinal logistic regression model for analysis, provided the assumption of proportional odds was met. We analysed the five times sit-to-stand test as an ordinal outcome because we mapped the time taken into points on the basis of the SPPB scoring criteria.[18] We did this because a high number of participants were unable to complete five chair rises at baseline. Although we had planned use of ordinal regression for the Fried frailty score, we used linear regression analysis because of evidence against the assumption of proportional odds. All models were adjusted for baseline measure and sex. Details on how missing data were handled for questionnaires are given in the appendix (pp 3–4). Safety was assessed using descriptive statistics.

We did pre-planned exploratory subgroup analyses of the primary outcome by age (>75 years *vs* ≤ 75 years), sex (male *vs* female), and baseline 4-m walk speed (>0·6 m/s *vs* ≤0·6 m/s). An additional post-hoc subgroup analysis was done to examine the effect of baseline insulin resistance (measured using the Homeostatic Model Assessment for Insulin Resistance [HOMA-IR],[27] calculated as [glucose in mmol/L × insulin in mU/L] / 22·5; >median *vs* ≤median) on the primary outcome, because this has recently been proposed as a possible mechanism to explain the heterogeneous effects of metformin in previous studies.[28] For each subgroup variable, we fitted a linear regression model regressing 4-month 4-m walk speed on treatment group, baseline 4-m walk speed, sex, the subgroup variable, and a treatment-by-subgroup interaction term with accompanying p value for the interaction. For example, in a subgroup analysis of sex, the walk speed at 4 months was regressed on baseline 4-m walk speed, treatment group, sex, and a treatment-by-sex interaction term. Results are presented as a forest plot. We also did a post-hoc exploratory analysis including study site as a fixed effect in the regression model.

A two-sided p value of less than 0·05 was taken to denote statistical significance for all analyses. No adjustments were performed for multiple testing. Statistical analyses were done using Stata (version 17) and R (version 4.2.1).

Role of the funding source

The funder (NIHR Newcastle Biomedical Research Centre) and sponsor (Newcastle upon Tyne Hospitals NHS Foundation Trust) provided oversight of the design and conduct of the trial and data collection, but had no role in the data analysis, data interpretation, writing of the report, or the decision to submit the results for publication.

Results

Between Aug 1, 2021, and Sept 30, 2022, 268 individuals expressed interest in taking part in the trial, of whom 112 were potentially eligible and willing to take part after the pre-screening process. 72 individuals passed the screening

process and were randomly assigned to metformin (n=36) or placebo (n=36; intention-to-treat population; figure 1; appendix p 9). Mean age was 80·4 years (SD 5·7), 42 (58%) of 72 participants were female, 30 (42%) were male, and 70 (97%) were White British (table 1). All participants fulfilled the EWGSOP 2019 criteria for probable sarcopenia at screening, but only 25 (35%) had muscle mass low enough to fulfil the criteria for a diagnosis of confirmed sarcopenia. 42 (58%) of 72 participants fulfilled Fried frailty criteria frailty score of three out of five or higher); one participant in the placebo group did not fulfil the criteria for either prefrailty or frailty on baseline testing due to marginal improvements in strength and walk speed at baseline compared with at screening.

71 (99%) of 72 participants received at least one dose of the allocated study medication (n=35 in the metformin group and n=36 in the placebo group; safety population). Adherence was lower in the metformin group (median 82% [IQR 14–92]) than in the placebo group (92% [85–98]). The number of participants with suboptimal adherence (<80%) was higher in the metformin group (17 [47%] *vs* eight [22%]) and the number of participants who started but then discontinued the trial medication before the end of the trial was higher in the metformin group than the placebo group (13 [38%] of 34 participants with available data *vs* five [14%] of 36).

70 (97%) of 72 participants attended the baseline visit and completed the 4-month visit and so were included in the complete case analysis (n=34 in the metformin group and n=36 in the placebo group). At 4 months, the mean 4-m walk speed was 0·57 m/s (SD 0·19 m/s) in the metformin group and 0·58 m/s (0·24 m/s) in the placebo group (adjusted mean difference: 0·001 m/s [95% CI –0·06 to 0·06]; p=0·96; table 2). The minimum clinically important difference of 0·1 m/s was not included within the 95% CI. The unadjusted analysis was consistent with the primary analysis (table 2), the per-protocol analysis population showed similar results (table 2), and preplanned and post-hoc exploratory subgroup analyses also showed no significant differences between subgroups (figure 2). Additionally, a post-hoc exploratory analysis including study site as a fixed effect in the regression model showed no change to the primary outcome treatment effect estimate (data not shown).

Apart from exhaustion as an individual component of the Fried frailty score, no secondary outcomes showed a significant difference between the metformin and placebo groups on adjusted analysis (table 3, appendix pp 4–5). We found no difference in the odds of having a higher (ie, better) chair stand category using SPPB cutoffs between the metformin and placebo groups at 4 months (adjusted odds ratio 1·25 [95% CI 0·47–3·29]; p=0·66). The distribution of transitions between prefrail and frail states was similar in both groups, with most participants remaining in the same frailty category as they were in at baseline.

108 adverse events occurred in 35 (100%) of 35 participants who received metformin and 77 adverse events occurred in 33 (92%) of 36 participants who received placebo, and 12 (34%) of 35 participants had hospital admissions in the metformin group versus three (8%) of 36 participants in the placebo group (table 4). One death occurred; this was in the metformin group (one [3%] of 35) but was judged to be unrelated to the study medication. Adverse events that were more common in the metformin group than in the placebo group were diarrhoea (26 events in 19 [54%] of 35 participants *vs* ten events in nine [25%] participants), nausea (six events in six [17%] participants *vs* no events), vomiting (three events in one [3%] participant *vs* no events), and elevated plasma lactate (13 events in 13 [37%] participants *vs* eight events in seven [19%] participants; appendix pp 6–8).

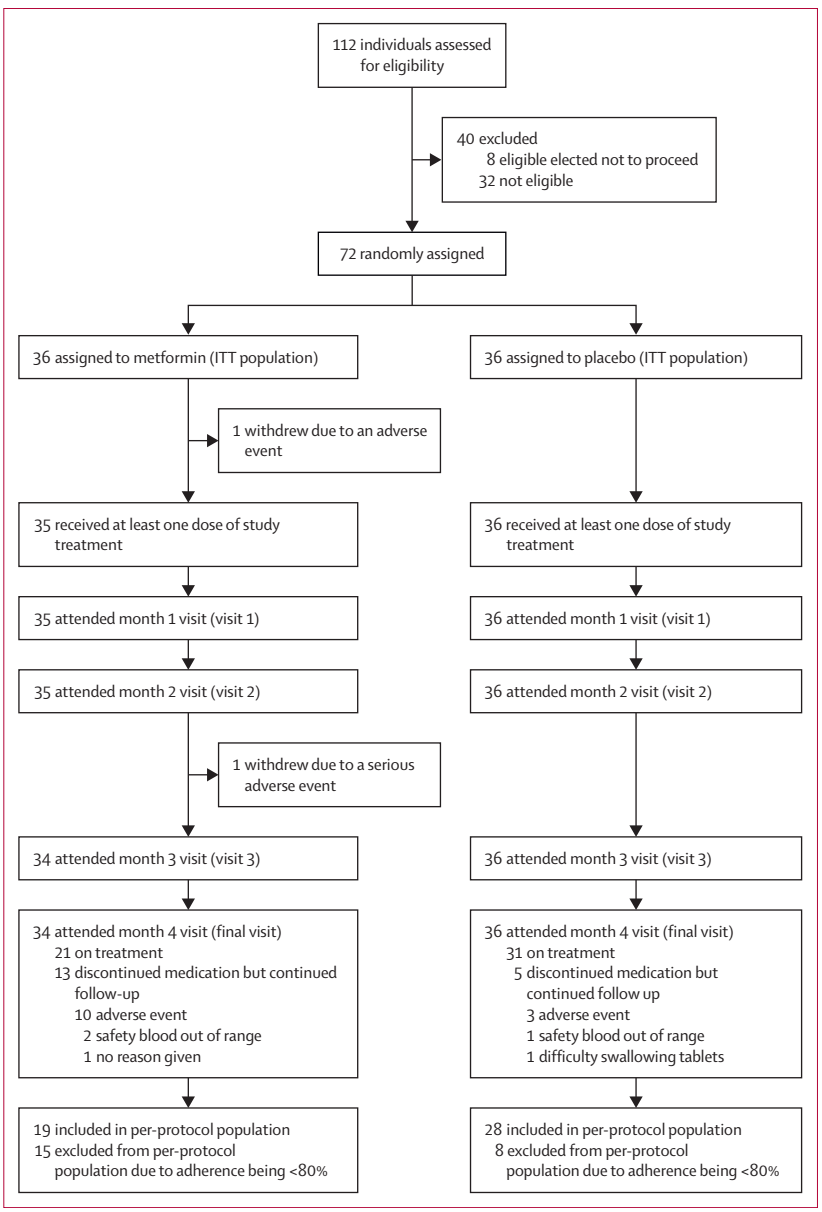

Figure 1: **Trial profile**
ITT=intention-to-treat.

	Metformin group (n=36)	Placebo group (n=36)
Site		
Gateshead	11 (31%)	9 (25%)
Newcastle	25 (69%)	27 (75%)
Age, years	80·8 (6·0)	79·9 (5·5)
Sex		
Female	21 (58%)	21 (58%)
Male	15 (42%)	15 (42%)
Ethnicity		
White British	35 (97%)	35 (97%)
Any other White background	1 (3%)	1 (3%)
Not White	0	0
Lives in own home	28 (78%)	34 (94%)
Walking aid	19 (53%)	20 (56%)
Comorbidities		
Ischaemic heart disease	4 (11%)	5 (14%)
Stroke	9 (25%)	6 (17%)
Hypertension	17 (47%)	21 (58%)
Anxiety	5 (14%)	5 (14%)
Depression	10 (28%)	9 (25%)
Parkinsonism	1 (3%)	2 (6%)
Asthma	4 (11%)	6 (17%)
Other lung disease	4 (11%)	5 (14%)
Osteoarthritis	23 (64%)	25 (69%)
Physical performance measures		
Maximal handgrip strength, kg		
Men	21·5 (7·2)	21·3 (8·1)
Women	12·0 (5·0)	13·9 (4·8)
Five times sit-to-stand test completed (%)	27 (75%)	26 (72%)
Five times sit-to-stand time for those that completed the test	19·5 (15·5–26·9)	16·6 (15·2–20·8)
4-m walk speed, m/s	0·59 (0·17)	0·60 (0·26)
Short Physical Performance Battery score	5·6 (2·5)	6·1 (2·8)
6-min walk distance, m*	181 (61)	192 (104)
Fried frailty score of ≥3 points	22 (61%)	20 (56%)
BMI, kg/m^2	27·1 (5·0)	27·4 (6·2)
Appendicular skeletal muscle mass index, kg/m^2		
Men	6·8 (0·9)	7·2 (1·2)
Women	6·1 (0·9)	6·3 (1·3)
EQ-5D-5L†	0·68 (0·22)	0·67 (0·30)
EQ-5D thermometer†	66 (16)	60 (23)
SF-36 v2		
Physical component score	36·6 (9·1)	35·5 (9·8)
Mental component score	49·4 (12·0)	48·3 (13·2)
Nottingham Extended ADL score	15 (5)	16 (5)
Non-fasting glucose, mmol/L‡	5·3 (1·0)	5·2 (0·9)
HbA_{1c}, mmol/mol§	39 (4)	39 (3)
AGE reader score¶	2·9 (0·6)	3·1 (1·3)
HOMA-IR‡	3·3 (1·4–4·5)	1·5 (1·1–3·5)

Data are n (%), mean (SD), and median (IQR). ADL=Activities of Daily Living. AGE=advanced glycated end-products. HbA_{1c}=glycated haemoglobin. HOMA-IR=Homeostatic Model Assessment for Insulin Resistance. SF-36=Short Form 36 questionnaire. *Available for 44 participants (19 in the metformin group and 25 in the placebo group). †Available for 71 participants (36 in the metformin group and 35 in the placebo group). ‡Available for 70 participants (35 in the metformin group and 35 in the placebo group). §Available for 69 participants (35 in the metformin group and 34 in the placebo group). ¶Available for 50 participants (24 in the metformin group and 26 in the placebo group).

Table 1: **Baseline participant characteristics, intention-to-treat population**

Discussion

We found no evidence that metformin 500 mg taken three times a day for 4 months improved 4-m walk speed, grip strength, physical performance, muscle mass, quality of life, or activities of daily living in people aged 65 years and older with probable sarcopenia and physical prefrailty or frailty versus placebo. At the dose used in this trial, metformin was poorly tolerated, with more adverse events recorded in the metformin group than in the placebo and higher discontinuation rates. Recruitment of older people with sarcopenia to clinical trials is challenging[29] and previous drug trials have been characterised by high dropout rates[26]—a reflection of the high burden of multimorbidity and frailty in some people with sarcopenia. In this trial, we successfully recruited participants with high rates of retention in the trial, enabling the trial to have adequate power for the detection of the minimum clinically important difference in the primary outcome.

There are several possible reasons why metformin did not improve measures of physical performance in this trial. One possibility is that the high discontinuation rate of metformin diluted any treatment effect. However, this hypothesis is not supported by the results of the per-protocol analysis, which, notwithstanding the biases inherent in such analyses, did not show evidence of a treatment effect when the analysis was restricted to those with 80% or higher adherence to their study treatment. A second possibility is that the dose of metformin was too low or that treatment was for too brief a duration to produce sufficient biological effect on target mechanisms. This dose of metformin (at the lower end of doses commonly used in clinical practice in older people) was used to minimise the risk of side-effects. We did not select an extended-release preparation (despite the lower risk of gastrointestinal side-effects) because of concerns that use of continuous, sustained-release metformin might have deleterious effects on protein synthesis and muscle maintenance that intermittent dosing could avoid.[30] The dose used in the current trial is the same as that used in a trial of older people with prefrailty that did show a positive effect of metformin on walk speed,[13] and the cumulative daily dose is similar to that used in another trial of metformin in older men with sarcopenia that showed improvement in handgrip strength.[14] A third possibility is that the dose of metformin was too high (at least in this target population), leading to excessive suppression of mechanisms (eg, mTOR activity[30]) that are necessary for the maintenance of muscle health. Notably, two trials in healthy older people (mean ages of 69 years[7] and 62 years[8]) have shown that metformin blunts the effect of exercise training (both resistance training and aerobic training) on measures of physical performance,[7,8] including inhibition of exercise-induced gains in mitochondrial respiration. The number and complexity of metformin's actions on biological pathways relevant to muscle health challenges our ability to understand why metformin did not improve physical performance in the current trial. For instance, different groups of patients might respond

	Metformin group (n=34)		Placebo group (n=36)		Unadjusted mean difference (m/s)	p value	Adjusted mean difference* (m/s)	p value
	n	Mean estimate (m/s)	n	Mean estimate (m/s)				
ITT population								
Baseline	34	0·58 (0·17)	36	0·60 (0·26)	..	..	..	..
4 months	34	0·57 (0·19)	36	0·58 (0·24)	–0·02 (–0·12 to 0·09)	0·76	0·001 (–0·06 to 0·06)	0·96
Per-protocol population								
Baseline	19	0·61 (0·16)	28	0·64 (0·25)	..	..	..	..
4 months	19	0·61 (0·20)	28	0·61 (0·24)	–0·004 (–0·14 to 0·13)	0·96	0·02 (–0·05 to 0·10)	0·54

Data are mean (SD) or mean difference with 95% CI in parentheses, unless otherwise stated. ITT=intention-to-treat. *Adjusted for baseline 4-m walk speed and sex.

Table 2: **4-m walk speed outcome results (primary outcome)**

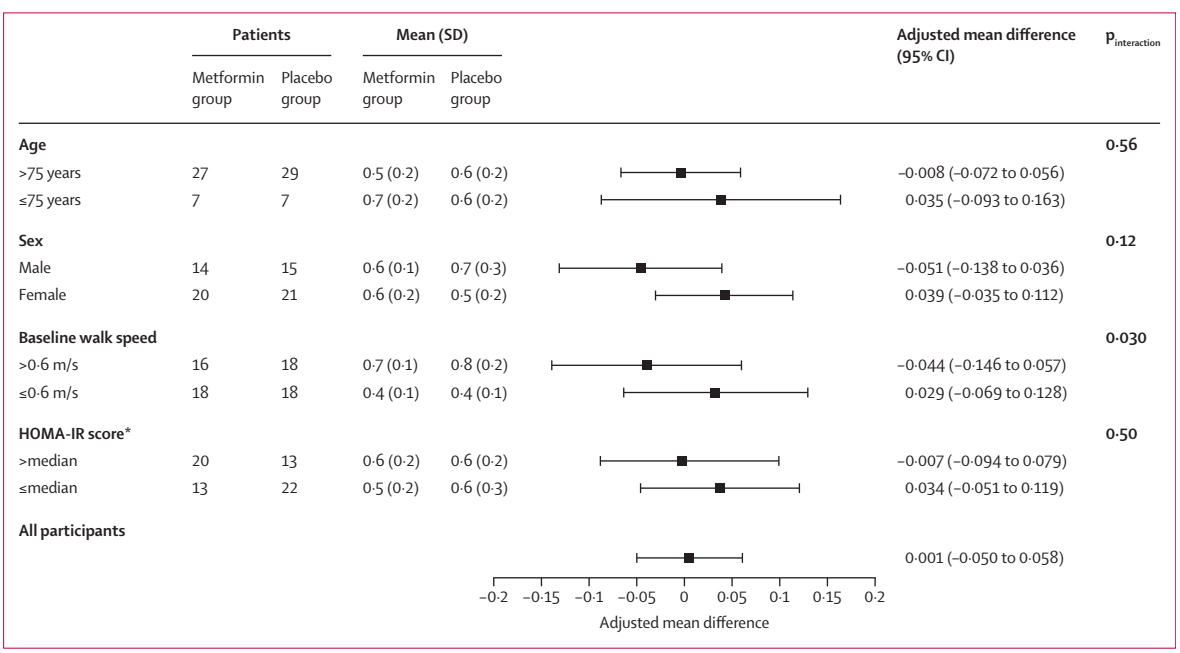

Figure 2: **Forest plot of subgroup analyses for 4-month 4-m walk speed, intention-to-treat population complete-case analysis**
For the subgroup analyses of age and HOMA-IR, models are adjusted for baseline walk speed and sex. For subgroup analysis of sex, models are adjusted for baseline walk speed. For subgroup analysis of baseline walk speed, models are adjusted for sex. HOMA-IR=Homeostatic Model Assessment for Insulin Resistance. *Post-hoc analysis.

differently to metformin, not only because of differences in pharmacokinetics and tolerability, but also because of differences in the relative importance of each of metformin's mechanisms.[28] Additionally, it is possible that the one trial[13] that has shown improvement in walk speed with metformin was a chance finding. Notably, in that trial,[13] walk speed improved but not grip strength or health status, and, conversely, in another recent trial,[14] handgrip strength improved with metformin but not walk speed. Although this more recent trial[14] was restricted to men, and differential mechanistic underpinnings for sarcopenia have been posited in men and women,[31] we did not find any evidence of a difference in response to metformin by sex in our results.

A final possibility is that a subgroup of patients with sarcopenia or frailty might have had sufficiently compromised muscle physiology to derive benefit from the effects of metformin, but they were still sufficiently robust for the side-effects of metformin to be well tolerated. Notably, both trials[13,14] that have shown positive effects of metformin on muscle function enrolled patients with prefrailty or sarcopenia and, in contrast with MET-PREVENT, who had relatively mild functional impairment (mean 4-m walk speeds of 1·16 m/s[13] and 0·77 m/s[14]). By contrast, the population recruited to MET-PREVENT had much more severe frailty and functional impairment (mean 4-m walk speed of 0·59 m/s). Further trials and synthesis of findings via meta-analysis will be required to resolve this issue, and the existing evidence would most strongly support the need for additional trials to test the effect of metformin on physical performance in older people with prefrailty. Our post-hoc exploratory subgroup analysis did not find evidence to support the hypothesis that patients with insulin resistance might show a greater response to metformin. However, the number of participants included in all subgroup analyses was small and a definitive test of this

	Metformin group (n=34)		Placebo group (n=36)		Adjusted mean difference* (95% CI)	p value
	n	Estimate	n	Estimate		
Grip strength, kg						
Baseline	34	15·9 (7·7)	36	17·0 (7·3)	..	..
4 months	34	16·5 (7·9)	36	17·4 (6·8)	–0·1 (–2·1 to 1·9)	0·91
SPPB score						
Baseline	34	5·5 (2·5)	36	6·1 (2·8)	..	..
4 months	34	5·6 (2·6)	36	5·8 (2·9)	0·3 (–0·5 to 1·1)	0·47
6-min walk distance, m						
Baseline	12	192 (62)	21	216 (93)	..	..
4 months	12	219 (86)	21	232 (89)	11 (–19 to 40)	0·46
Appendicular skeletal muscle mass, kg						
Baseline	33	17·8 (4·1)	33	18·2 (4·4)	..	..
4 months	33	17·3 (4·1)	33	17·7 (3·9)	–0·0 (–0·8 to 0·8)	0·95
Nottingham Extended ADL score						
Baseline	34	15·0 (4·6)	36	16·0 (5·3)	..	..
4 months	34	15·3 (4·8)	36	15·7 (5·2)	0·4 (–1·1 to 1·9)	0·64
EQ-5D-5L score						
Baseline	32	0·67 (0·23)	34	0·66 (0·30)	..	..
4 months	32	0·56 (0·32)	34	0·65 (0·28)	–0·08 (–0·17 to 0·01)	0·10
EQ-5D thermometer						
Baseline	32	66 (16)	34	60 (23)	..	..
4 months	32	63 (20)	34	59 (23)	1 (–7 to 8)	0·89
SF-36 v2 physical component score						
Baseline	34	36·1 (9·1)	36	35·5 (9·8)	..	..
4 months	34	37·2 (8·2)	36	37·9 (9·5)	–1·0 (–3·9 to 1·9)	0·50
SF-36 v2 mental component score						
Baseline	34	48·9 (12·1)	36	48·3 (13·2)	..	..
4 months	34	47·8 (13·0)	36	46·8 (13·1)	0·7 (–2·9 to 4·3)	0·69
Five times sit-to-stand score (%)†						
Baseline	34	..	36	..	..	..
0	..	9 (26%)	..	10 (28%)	..	..
1	..	18 (53%)	..	12 (33%)	..	..
2	..	3 (9%)	..	11 (31%)	..	..
3	..	2 (6%)	..	3 (8%)	..	..
4	..	2 (6%)	..	0	..	..
4 months	34	..	36	..		
0	..	10 (29%)	..	13 (36%)	1·25 (0·47–3·29)‡	0·66
1	..	17 (50%)	..	11 (31%)	..	..
2	..	3 (9%)	..	7 (19%)	..	..
3	..	1 (3%)	..	3 (8%)	..	..
4	..	3 (9%)	..	2 (6%)	..	..

Estimate data are mean (SD) or n (%). ADL=activities of daily living. SF-36=Short Form 36 questionnaire. SPPB=short physical performance battery. *Adjusted for baseline value of the outcome of interest, baseline 4-m walk speed, and sex. †Higher score indicated better performance. ‡Adjusted odds ratio (95% CI) for category improvement.

Table 3: **Select secondary outcomes**

	Metformin group (n=35)	Placebo group (n=36)
Participants with at least one adverse event	35 (100%)	33 (92%)
Participants with at least one adverse reaction	28 (80%)	17 (47%)
Participants with at least one serious adverse event	9 (26%)	3 (8%)
Participants with at least one serious adverse reaction	0	0
Participants with at least one suspected unexpected serious adverse reaction	0	0
Total number of adverse events	108	77
Number of adverse events per participant	3 (2–4)	2 (1–3)
Most common adverse events		
Diarrhoea	26	10
Nausea	6	0
Vomiting	3	0
Elevated plasma lactate	13	8
Number of hospital admissions	12	3
Number of deaths	1	0

Data are n (%), n or median (IQR).

Table 4: **Summary of adverse events, safety population**

hypothesis should be possible with the publication of results from an ongoing trial, comparing the effect of metformin on muscle function in predefined strata of patients with and without insulin resistance.[28]

Key strengths of our trial were the randomised design, placebo control, adequate statistical power, and successful recruitment and excellent retention of a group of older people with sarcopenia whose baseline physical performance and comorbidities closely reflected those of patients seen in secondary care geriatric medicine outpatient services—a key target group for sarcopenia treatments and a group underserved by current clinical trials. The ability to deliver study visits in participants' own homes and the low burden of trial procedures are likely to have contributed to the high retention rate. The selection of walk speed as the primary outcome ensured that our results are relevant to clinical practice as well as being robust—walk speed is a powerful predictor of prognosis and adverse outcomes in older people, including death, falls, and loss of independence.[32,33] The minimum clinically important difference for this measure has been estimated to be 0·1 m/s[24] and walk speed has been used as an outcome measure in previous trials, including those of metformin.[13]

Our study also has several limitations. Discontinuation rates in the metformin group were higher than anticipated and might have diluted any treatment effect, making it more difficult to demonstrate a difference between the groups despite exceeding the pre-planned evaluable sample size. There was a high rate of adverse events in both the metformin and placebo groups, which is in keeping with the burden of comorbid disease and frailty of the trial population, and the discontinuation rates reflect those likely to be seen in clinical practice in this group of patients. Additionally, metformin might require a longer duration of treatment than 4 months to deliver a meaningful treatment effect, although improvements in walk speed were seen with a similar duration of therapy in a previous trial in older people with prefrailty.[13] We did not titrate the dose of

metformin from a lower starting dose, and if we had done so we might have improved the safety profile of the intervention. Although a broad range of participants were included, some key groups (eg, those with diabetes, chronic kidney disease, and those unable to consent due to cognitive impairment) were not included, limiting the generalisability of the results. Participants were recruited from two NHS Trusts in northeast England, an area with low ethnic diversity, and our results might not be generalisable to non-White ethnic groups. Although most outcome measures were successfully collected in participants' homes, we were not able to conduct the 6-min walk test for all participants on a home visit due to limitations on appropriate interior living space and inclement weather when attempting the test outdoors. Finally, our ability to assess subgroups that might respond to metformin is limited by the size of the trial. However, we have collected a range of blood and stool samples to enable future mechanistic studies that might provide some insights into which mechanisms are most important in mediating benefits and harms of metformin to muscle health.

In conclusion, despite successfully recruiting and retaining a group of older people with probable sarcopenia and frailty or prefrailty, metformin was poorly tolerated at the selected dose in this population and we did not find any beneficial effect of metformin on walk speed, grip strength, physical performance, quality of life, or activities of daily living.

Contributors

MDW, APC, HH, CM, AAS, CJS, TvZ, and JW designed the trial. MDW, CM, MB, PB, SC, KN, KJR, LR, AJS, BS, and LS conducted the trial. NW and SH accessed and verified the underlying study data and conducted the statistical analyses, with oversight from JW. MDW drafted the manuscript. All authors had access to the data, interpreted the results, critically revised the manuscript, and all authors approved the final version for publication.

Declaration of interests

MDW reports receiving consultancy fees from Rejuvenate Biomed for work on sarcopenia trials. APC reports funding from the National Institute for Health and Care Research (NIHR), UK Research and Innovation, and Dunhill Medical Trust; being a Data Monitoring and Ethics Committee and Trial Steering Committee member for NIHR; participating on grant funding panels for NIHR, Dunhill Medical Trust, and Medical Research Council; being Chair of the global Ageing Research Trialists collaborative; and being a member of the National Institute for Health and Care Excellence Falls Prevention Guideline Development Group. APC has received travel grants and honoraria from the Australia and New Zealand Society of Geriatric Medicine, the Geras Centre for Aging Research, and Alberta Health Services; and had led the development and UK implementation of the electronic frailty index, which is licensed to suppliers of electronic health record systems at no cost, on the basis a premium charge is not applied to the end National Health Service user. All other authors declare no competing interests.

Data sharing

De-identified individual participant-level data from this trial are stored at the NIHR Newcastle Biomedical Research Centre and will be made available to other researchers subject to completion of appropriate collaboration agreements and data sharing agreements with the trial team. For access to trial documents (information sheet, consent form, protocol, statistical analysis plan), contact the chief investigator (Miles.Witham@newcastle.ac.uk).

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