

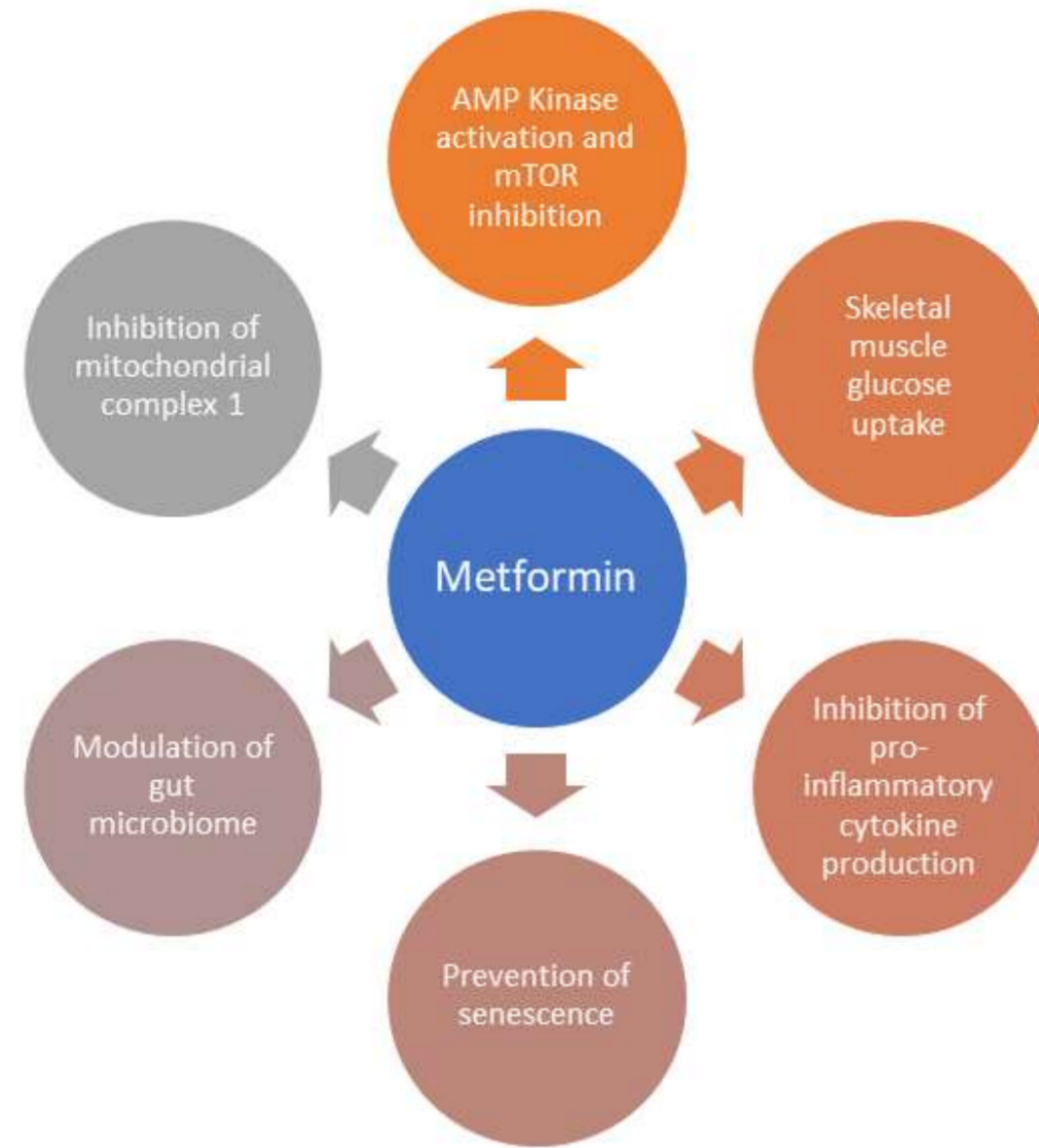
# Effects of metformin on metabolic and inflammatory markers in older people with sarcopenia and frailty: analysis from the MET-PREVENT randomised controlled trial

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## Background

- Chronic inflammation and metabolic dysfunction may contribute to sarcopenia and physical frailty. Both may be targets for metformin therapy, which has multiple mechanisms of action



- We investigated the association between physical performance measures and inflammatory and metabolic biomarkers in a group of older people with sarcopenia and frailty/prefrailty
- We also investigated the effect of metformin treatment on this biomarker panel.

## Methods

- MET-PREVENT recruited 72 people aged 65 and over with probable sarcopenia (European Working Group 2019 definition) and low walk speed.
- Participants were randomised to receive 4 months of metformin 500mg three times a day or matching placebo
- Blood sampling and physical performance measures (handgrip strength, 4m walk speed, six-minute walk distance, 5x sit to stand) were conducted at baseline and 4 months.
- Main results have been reported previously: metformin did not improve physical function measures and increased the number of adverse events

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 proposed as a candidate therapy for sarcopenia and physical frailty. We aimed to test the efficacy and safety of metformin, a

- We measured blood biomarkers on baseline and follow-up samples using ELISA and Luminex platforms for insulin, CRP, adiponectin, leptin, MCP-1, IL-1b, IL-6, IL-8, and TNF-alpha
- Baseline correlations and correlations of changes between baseline and follow-up were analysed using Spearman's test; median change between baseline and follow-up in the metformin and placebo groups was compared using Mann-Whitney tests

## Results

- Participant mean age was 80 years
- 42/72 (58%) were women.
- The mean 4m walk speed was 0.59 m/s
- The mean Short Physical Performance Battery score was 5.8 (max 12)
- 70/72 (97%) of participants completed the trial



Table 1. Baseline cytokine analyses vs baseline physical performance

	Grip strength		Walk speed		6MWD		5x STS	
	r	p	r	p	r	p	r	p
Insulin	0.24	0.26	-0.02	0.87	-0.19	0.23	0.18	0.21
CRP	-0.01	0.92	-0.07	0.55	-0.23	0.14	0.07	0.60
Adiponectin	-0.14	0.23	0.10	0.40	0.24	0.12	-0.22	0.11
Leptin	-0.15	0.22	-0.01	0.91	-0.18	0.24	0.11	0.42
IL-1B	0.03	0.81	-0.18	0.14	-0.22	0.15	0.02	0.90
IL-6	0.17	0.15	-0.09	0.48	-0.40	0.008	0.14	0.92
IL-8	0.14	0.24	-0.12	0.32	-0.18	0.24	0.03	0.86
MCP-1	0.04	0.75	0.05	0.65	0.07	0.68	0.02	0.89
TNFa	-0.01	0.92	-0.07	0.58	0.03	0.87	-0.08	0.59

Spearman's rho. Colours: blue = better performance correlates with higher biomarker concentration. 6MWD: six minute walk distance. 5x STS: five times sit to stand time

Table 2. Change in cytokines vs change in physical performance from baseline to 4 mths

	Grip strength		Walk speed		6MWD		5x STS	
	r	p	r	p	r	p	r	p
Insulin	-0.24	0.09	0.04	0.78	-0.13	0.54	0.07	0.71
CRP	-0.13	0.29	0.00	0.99	-0.25	0.18	0.17	0.29
Adiponectin	0.29	0.016	-0.12	0.32	-0.12	0.51	0.02	0.92
Leptin	-0.21	0.09	0.11	0.36	-0.07	0.69	0.02	0.91
IL-1B	-0.25	0.04	0.00	1.00	-0.06	0.77	0.09	0.59
IL-6	-0.22	0.08	-0.14	0.27	-0.21	0.26	0.09	0.60
IL-8	-0.16	0.21	-0.22	0.07	0.02	0.93	-0.06	0.73
MCP-1	0.03	0.80	-0.09	0.46	0.00	0.99	0.38	0.02
TNFa	-0.12	0.33	-0.13	0.31	0.18	0.32	-0.32	0.04

Spearman's rho. Colours: blue = improved performance correlates with reducing biomarker concentration. 6MWD: six minute walk distance. 5x STS: five times sit to stand time

Table 3. Treatment effect of metformin (vs placebo) on change in cytokines from baseline to 4 mths

	Metformin (median, IQR)	Placebo (median, IQR)	P*
Insulin (pg/ml)	-178 (-462 to 180)	147 (-89 to 353)	0.04
CRP (ng/ml)	-17 (-579 to 457)	39 (-287 to 357)	0.98
Adiponectin (ng/ml)	473 (-694 to 1211)	52 (-782 to 1548)	0.80
Leptin (pg/ml)	-362 (-1652 to 642)	-195 (-1167 to 796)	0.88
IL-1B (pg/ml)	-0.09 (-0.23 to 0.07)	-0.02 (-0.17 to 0.08)	0.47
IL-6 (pg/ml)	-0.08 (-3.10 to 0.90)	-0.16 (-1.53 to 0.60)	0.94
IL-8 (pg/ml)	-1.27 (-5.75 to 1.44)	-1.50 (-3.08 to 0.75)	0.88
MCP-1 (pg/ml)	-0.1 (-16.6 to 16.7)	-3.7 (-19.2 to 14.0)	0.59
TNFa (pg/ml)	0.06 (-0.60 to 0.51)	-0.21 (-0.76 to 0.13)	0.12

Mann-Whitney U test. IQR: Interquartile range

## Conclusions

- Only **weak and inconsistent associations** were seen between physical performance and inflammatory/metabolic biomarkers
- Metformin **did not beneficially affect most biomarkers** measured
- This **accords with the main results of the MET-PREVENT trial** which found no beneficial effect of metformin on physical function in older people with sarcopenia and frailty
- All participants had sarcopenia and frailty – it is possible that **different results could be obtained when studying a population of older people with a broader range of physical function**

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