

Table S1. Medications co-prescribed with folic acid on >5% of occasions

Medication/Supplement	Number of prescriptions*	Percentage of folic acid prescriptions
Folic acid	177,918	100.00
Methotrexate	45,697	25.68
Atorvastatin	41,296	23.21
Lansoprazole	35,611	20.02
Omeprazole	32,909	18.50
Bisoprolol	26,445	14.86
Levothyroxine	25,482	14.32
Ramipril	21,990	12.36
Aspirin	21,696	12.19
Paracetamol	20,830	11.71
Amlodipine	18,354	10.32
Simvastatin	16,878	9.49
Amitriptyline	13,573	7.63
Furosemide	12,983	7.30
Metformin	11,460	6.44
Hydroxychloroquine	11,038	6.20
Clopidogrel	10,918	6.14
Prednisolone	10,475	5.89
Alendronic acid	10,198	5.73

*General practice prescription data from 1st of January 2019 through to 27th September 2021

Table S2. COVID-19 diagnosis in people prescribed methotrexate and / or folic acid in the UKBB, compared to people not prescribed methotrexate or folic acid

	<i>Unadjusted</i>		<i>Model 1</i>		<i>Model 2</i>	
	OR [95% CI]	<i>P</i>	OR [95% CI]	<i>P</i>	OR [95% CI]	<i>P</i>
Prescribed folic acid only ¹	1.58 [1.49 ; 1.68]	<0.001	1.60 [1.5 ; 1.7]	<0.001	1.51 [1.42 ; 1.61]	<0.001
Prescribed methotrexate only ¹	0.94 [0.51 ; 1.72]	0.83	0.89 [0.48 ; 1.65]	0.72	0.86 [0.47 ; 1.6]	0.64
Prescribed methotrexate and folic acid ¹	1.09 [0.96 ; 1.23]	0.18	1.15 [1.02 ; 1.3]	0.021	1.09 [0.96 ; 1.23]	0.18
60-70 years of age ²			0.60 [0.58 ; 0.62]	<0.001	0.59 [0.57 ; 0.61]	<0.001
70-75 years of age ²			0.41 [0.4 ; 0.43]	<0.001	0.40 [0.38 ; 0.41]	<0.001
>75 years of age ²			0.40 [0.38 ; 0.41]	<0.001	0.38 [0.37 ; 0.4]	<0.001
Male sex			1.09 [1.07 ; 1.12]	<0.001	1.09 [1.06 ; 1.12]	<0.001
Former smoker ³			0.87 [0.84 ; 0.92]	<0.001	0.87 [0.83 ; 0.91]	<0.001
Never smoked ³			0.88 [0.86 ; 0.91]	<0.001	0.89 [0.86 ; 0.91]	<0.001
BMI			1.03 [1.03 ; 1.03]	<0.001	1.03 [1.03 ; 1.03]	<0.001
Asian British ⁴			1.38 [1.29 ; 1.48]	<0.001	1.33 [1.25 ; 1.43]	<0.001
Black British ⁴			1.08 [1 ; 1.17]	0.057	1.08 [1 ; 1.18]	0.058
Other ethnicity ⁴			1.05 [0.95 ; 1.15]	0.35	1.04 [0.95 ; 1.15]	0.40
Townsend deprivation index			1.03 [1.02 ; 1.03]	<0.001	1.03 [1.02 ; 1.03]	<0.001
Rheumatoid arthritis					1.4 [1.12 ; 1.74]	0.003
Sickle cell disease					1.00 [0.74 ; 1.35]	1.00
Prescribed anticonvulsant medication					1.07 [0.89 ; 1.29]	0.48
Prescribed statins					1.08 [1.05 ; 1.12]	<0.001
Prescribed iron supplements					1.29 [1.22 ; 1.36]	<0.001

1 Compared to Prescribed neither methotrexate nor folic acid; 2 Compared to <60 years of age; Compared to Current smoker; 4 Compared to White British; Model 1 and Model 2 contain all variables with odds ratios present (and comparative groups) as respectively listed below the titles.

Table S3. Sex-specific associations between prescription of methotrexate, folic acid, and the combination of both with the risk of COVID-19

	COVID-19 diagnosis - Male						COVID-19 diagnosis -Female					
	<i>Unadjusted</i>		<i>Model 1</i>		<i>Model 2</i>		<i>Unadjusted</i>		<i>Model 1</i>		<i>Model 2</i>	
	OR, [95% CI]	<i>P</i>	OR, [95% CI]	<i>P</i>	OR, [95% CI]	OR, [95% CI]	OR, [95% CI]	<i>P</i>	OR, [95% CI]	<i>P</i>	OR, [95% CI]	<i>P</i>
Neither folic acid nor methotrexate	1.0	-	1.0	-	1.0	-	1.0	-	1.0	-	1.0	-
Folic acid only	1.52 [1.39 ; 1.66]	<0.001	1.57 [1.44 ; 1.72]	<0.001	1.50 [1.37 ; 1.64]	<0.001	1.64 [1.51 ; 1.77]	<0.001	1.61 [1.48 ; 1.75]	<0.001	1.52 [1.39 ; 1.65]	<0.001
Methotrexate only	0.96 [0.39 ; 2.38]	0.93	0.93 [0.37 ; 2.32]	0.88	0.92 [0.37 ; 2.30]	0.86	0.92 [0.4 ; 2.11]	0.85	0.87 [0.38 ; 1.99]	0.74	0.83 [0.36 ; 1.90]	0.65
Methotrexate and folic acid	1.08 [0.89 ; 1.31]	0.45	1.15 [0.94 ; 1.40]	0.17	1.11 [0.91 ; 1.36]	0.29	1.11 [0.95 ; 1.29]	0.19	1.16 [0.99 ; 1.36]	0.060	1.07 [0.91 ; 1.26]	0.38

diagnosis

Model 1 adjusted for age group, sex, ethnicity, Townsend deprivation index, BMI, smoking status

Model 2 is model 1 plus adjustment by the presence of rheumatoid arthritis, sickle cell disease, use of statins, anticonvulsants and iron supplementation.

Table S4. The association of prescription of methotrexate and folic acid with COVID-19-related death in the UK Biobank.

	<i>Unadjusted</i>		<i>Model 1</i>		<i>Model 2</i>	
	OR [95% CI]	<i>P</i>	OR [95% CI]	<i>P</i>	OR [95% CI]	<i>P</i>
Prescribed folic acid only ¹	1.47 [0.81 ; 0.67]	0.21	2.91 [2.38 ; 3.55]	<0.001	2.64 [2.15 ; 3.24]	<0.001
Prescribed methotrexate only ¹	N/A	N/A	N/A	N/A	N/A	N/A
Prescribed methotrexate and folic acid ¹	5.14 [4.23 ; 6.24]	<0.001	1.26 [0.7 ; 2.3]	0.44	1.07 [0.57 ; 1.98]	0.84
60-70 years of age ²			3.05 [2 ; 4.65]	<0.001	2.98 [1.95 ; 4.56]	<0.001
70-75 years of age ²			5.70 [3.76 ; 8.64]	<0.001	5.46 [3.59 ; 8.31]	<0.001
>75 years of age ²			14.7 [9.86 ; 21.91]	<0.001	13.87 [9.26 ; 20.78]	<0.001
Male sex			2.13 [1.84 ; 2.46]	<0.001	2.13 [1.84 ; 2.47]	<0.001
Former smoker ³			1.37 [1.11 ; 1.7]	0.004	1.37 [1.11 ; 1.7]	0.004
Never smoked ³			0.76 [0.65 ; 0.89]	<0.001	0.77 [0.66 ; 0.89]	0.001
BMI			1.09 [1.08 ; 1.11]	<0.001	1.09 [1.08 ; 1.11]	<0.001
Asian British ⁴			2.48 [1.76 ; 3.49]	<0.001	2.33 [1.65 ; 3.29]	<0.001
Black British ⁴			1.74 [1.15 ; 2.63]	<0.001	1.72 [1.13 ; 2.63]	0.012
Other ethnicity ⁴			1.44 [0.86 ; 2.42]	0.16	1.44 [0.86 ; 2.41]	0.17
Townsend deprivation index			1.09 [1.07 ; 1.11]	<0.001	1.08 [1.06 ; 1.11]	<0.001
Rheumatoid arthritis					2.48 [1.19 ; 5.17]	0.015
Sickle cell disease					1.22 [0.29 ; 5.15]	0.78
Prescribed anticonvulsant medication					2.22 [1.18 ; 4.17]	0.014
Prescribed statins					1.08 [0.93 ; 1.25]	0.33
Prescribed iron supplements					1.44 [1.16 ; 1.79]	0.001

1 Compared to Prescribed neither methotrexate nor folic acid; 2 Compared to <60 years of age; Compared to Current smoker; 4 Compared to White British; N/A = not applicable due to no deaths in the methotrexate only group. Model 1 and Model 2 contain all variables with odds ratios present (and comparative groups) as respectively listed below the titles.

Table S5. Sex-specific associations between prescription of methotrexate, folic acid, and the combination of both with the risk of COVID-19 related mortality.

	COVID-19 related death – Male						COVID-19 related death - Female					
	<i>Unadjusted</i>		<i>Model 1</i>		<i>Model 2</i>		<i>Unadjusted</i>		<i>Model 1</i>		<i>Model 2</i>	
	OR, [95% CI]	<i>P</i>	OR, [95% CI]	<i>P</i>	OR, [95% CI]	OR, [95% CI]	<i>P</i>	OR, [95% CI]	<i>P</i>	OR, [95% CI]	<i>P</i>	
Neither folic acid nor methotrexate	1.0	-	1.0	-	1.0	-	1.0	-	1.0	-	1.0	-
Folic acid only	4.73 [3.71;6.04]	<0.001	2.83 [2.20;3.64]	<0.001	2.59 [2.00;3.36]	<0.001	5.67 [4.10;7.82]	<0.001	3.07 [2.20;4.28]	<0.001	2.72 [1.93;3.84]	<0.001
Methotrexate and folic acid	2.00 [0.99;4.03]	0.053	1.62 [0.80;3.26]	0.18	1.54 [0.75;3.15]	0.24	1.01 [0.32;3.16]	0.99	0.80 [0.25;2.50]	0.70	0.56 [0.17;1.84]	0.34

Model 1 adjusted for age group, sex, ethnicity, Townsend deprivation index, BMI, smoking status

Model 2 is model 1 plus adjustment by the presence of rheumatoid arthritis, sickle cell disease, use of statins, anticonvulsants and iron supplementation.

Table S6. Risk of death related to COVID-19 in the COVID-19-positive group

	<i>Unadjusted</i>		<i>Model 1</i>		<i>Model 2</i>	
	OR [95% CI]	<i>P</i>	OR [95% CI]	<i>P</i>	OR [95% CI]	<i>P</i>
Neither folic acid nor methotrexate	1.0	-	1.0	-	1.0	-
Folic acid only	3.58 [2.93 ; 4.39]	<0.001	1.82 [1.47 ; 2.26]	<0.001	1.46 [1.16 ; 1.83]	0.0011
Methotrexate and folic acid	1.37 [0.75 ; 2.52]	0.31	1.03 [0.55 ; 1.91]	0.94	0.96 [0.50 ; 1.83]	0.90

Model 2 additionally adjusted by quarterly categorical time variable.

A total of 25,816 COVID-19-positive cases were analyzed. 217 COVID-19-positive cases who were diagnosed after 13th September 2021 (28 days before the last recorded death) were removed from the cohort given the unknown outcome in these individuals