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Should Non-Diabetics Take Metformin For Longevity?

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How to Read My Evidence Tables

Level of evidence

The **Level of Evidence** looks at how likely health claims are to be true.

For each health claim, I show the highest level of evidence for that claim.

To achieve the highest level of evidence ranking in my guides, there must be high-quality randomised controlled trial evidence on the given topic. These are colour coded as **Dark Green** and the studies can be thought to be "Likely true".

Other studies that are low risk of bias, but not randomised are colour coded **Moderate Green** and can be seen as "Possibly true".

Finally, studies with high bias are coloured **Light Green** and should be thought to have "Unclear truth" (you shouldn't rely on their claims to have a high likelihood of being true).

Tables are arranged so the claims with the strongest evidence are at the top.

The table below lists the hierarchy of evidence used in my reports.

The highest level of evidence is > 1 randomised controlled trial (RCT) with low bias.

The lowest level of evidence are cell studies.

GRADE	TRUTH LEVEL	HOW TO READ THIS
>1 RCT Low-bias	Likely true	>1 randomised controlled trial that are low bias
1 RCT Low-bias	Likely true	1 randomised controlled trial that is low bias
>1 NRCT Low-bias	Possibly true	>1 non-randomised controlled trial with exceptional results
1 NRCT Low-bias	Possibly true	1 non-randomised controlled trial with exceptional results
>1 NRNCT Low-bias	Possibly true	>1 non-randomised non-controlled trial with exceptional results
1 NRNCT Low-bias	Possibly true	1 non-randomised non-controlled trial with exceptional results
>1 Obs Low-bias	Possibly true	>1 observational studies with exceptional results
1 Obs Low-bias	Possibly true	1 observational study with exceptional results
>1 RCT High-bias	Unclear if true	>1 randomised controlled trial with high bias
1 RCT High-bias	Unclear if true	1 randomised controlled trial with high bias
>1 NRCT	Unclear if true	>1 non-randomised controlled trial with high bias

High-bias		
1 NRCT High-bias	Unclear if true	1 non-randomised controlled trial with high bias
>1 NRNCT High-bias	Unclear if true	>1 non-randomised non-controlled trials with high bias
1 NRNCT High-bias	Unclear if true	1 non-randomised non-controlled trial with high bias
>1 Obs High-bias	Unclear if true	>1 observational study with high bias
1 Obs High-bias	Unclear if true	1 observational study with high bias
Anecdotal	Unclear if true	Personal experience from healthcare professionals or patients/end-users
Large-mammal	Unclear if true	Studies in large mammals such as monkeys, pigs, dogs
Small mammal	Unclear if true	Studies in small mammals such as rats or mice
Non-mammal	Unclear if true	Studies in non-mammals such as fish or flies
Cells	Unclear if true	Studies in human or animal cells
In Silico	Unclear if true	Studies in computer simulations
TBC	Unclear if true	"To Be Confirmed": Ongoing clinical trials without results yet.

Understanding other sections of my evidence tables

Effect: The effect is the health claim that this row is analysing the studies for.

Change: Down arrow symbol (↓) means the intervention decreases this health effect. Up arrow symbol (↑) means the intervention increases this effect.

Scientific studies: This contains the link to the highest quality studies relevant to the health effect. It includes the date it was published, to give you an idea of how old the study is: studies in the last 10 years are less likely to have been seen by your doctor, and less likely for the interventions used in the studies to be available in your hospitals or clinics. For studies over 10 years old, your doctor is more likely to have heard of them, and the interventions are more likely to be easily accessible in the healthcare system.

Also included is the type of study that was analysed. Randomised controlled trials are often the best type of trials to prove that an intervention works. Randomised controlled trials are a type of "interventional study" where researchers actively give people an intervention. Observational studies,

where you look at patient characteristics over time but do not actively give them an intervention, can never prove that an intervention causes a certain outcome, making them inherently flawed.

Meta-analyses refer to studies that look at more than 1 similar study and compare the results; “meta” meaning “above or after”. Meta-analyses are often misunderstood to be “better” than any other study. This is a mistake – a meta-analysis that compares dozens of worm studies, mouse studies or observational studies is worse evidence than one good randomised controlled trial. Likewise, a meta-analysis of high risk of bias randomised controlled trials in irrelevant demographics, isn’t superior to one low risk of bias randomised controlled trial in a demographic highly relevant to you.

“Systematic reviews” are studies where researchers use a reproducible method to search for all studies relevant to a topic, and to summarise the information.

Population: This is the demographic/s that was/were used in the studies. This is important to know, as the more different the demographic is from yourself, the less likely the intervention is to work in the same way for you.

Intervention: This is the exact dosage protocol used, and for how long, alongside any additional interventions that were used simultaneously.

Comparator: In trials that were comparing an intervention to another intervention (such as placebo, or another therapy) this is listed here.

Outcome: Medicine is all about probabilities, so when you undertake an intervention, it may have a different effect in different people. You can rarely predict that an intervention will cause an exact effect e.g. 55% reduction. Instead you can be 95% sure that the effect will fall within a certain range, e.g. there’s a 95% chance that this drug will reduce your blood pressure somewhere between 5 and 8 points, with 6 points being the average reduction seen.

Risk of bias analysis: Depending on the type of study, I analyse the study for bias in a different way. While the full details of how I do this are beyond the scope of this introduction, I will give some common examples of what this can include. For all studies, I look to see if the demographic in the study is relevant to the demographic the report is looking to answer questions for. For randomised controlled trials, I may use the “A, B, C” approach looking at

- "Attrition" (how many people dropped out of the study after being assigned to intervention or control groups)
- "Blinding" (whether the patients, healthcare professionals, study organisers and statisticians knew which patient was receiving which therapy after they had been assigned to a certain group, and;
- "Concealment" (when trial participants were being assigned to intervention or control groups, whether healthcare professionals or researchers knew how likely the next patient to be enrolled would end up in the next group

This "A, B, C" method for randomised controlled trials is important as there is evidence that for each one of these components a trial doesn't meet, there could be 20% to 100% change in the stated results.

For meta-analyses, I will often remove the highest risk of bias studies that the meta-analysis includes, leaving only the best studies, to see if the conclusions still remain the same. I also look at the differences in study populations or intervention doses used to see if this explains why some studies performed better than others in the meta-analysis.

Take away message: This message summarises all the information on this section into a practical insight for you.

Summary

Conclusion

Metformin has use for some non-diabetics, non-prediabetics who have colorectal adenomas or poor gum health. It is not clear If metformin will have benefit in preventing adenomas in people that have fasting insulin under 5 mIU/L and fasting glucose under 5 mmol/L already.

Topical metformin in gum and tooth regeneration is particularly interesting. Some non-diabetics may want to experiment with metformin to see if it improves advanced glycation end products. Additionally, some non-diabetics may not want to wait for clinical trial results and may want to try metformin to see if it improves the health markers which are being investigated in these ongoing trials.

What Metformin Works for in Non-diabetics

LEVEL OF EVIDENCE	EFFECT	MAGNITUDE OF EFFECT
4 RCT Low- bias	Pre-diabetes conversion to full diabetes	**Population:** Pre-diabetics, BMI 17 – 50, age 30+ **Interventions:** 500 mg to 1700 mg metformin a day (no dose relationship with outcome) **Outcome:** 7% to 35% less risk of developing full diabetes over 1.5 to 10 years **Comment:** Lifestyle changes can outperform metformin for preventing full diabetes
4 RCT Low- bias	Weight loss	**Population:** Pre-diabetics, BMI 17 – 50, age 30+ **Interventions:** 500 mg to 1700 mg metformin a day (no dose relationship with outcome) **Outcome:** 0 – 3.5 kg weight loss at 1.5 to 10 years (control groups may gain weight) **Comment:** May be more sustainable than lifestyle, but lifestyle can reach much higher total weight loss. *Weight loss may include muscle, organ or bone loss*.
1 RCT Low- bias	Colorectal adenomas (swellings that can lead to cancer)	**Population:** Non-diabetic, non-prediabetic with previous adenomas **Interventions:** 500 mg metformin vs placebo **Outcome:** 8% to 61% less after 1 year vs placebo **Comment**: More likely to benefit if fasting glucose > 5mmol/L or fasting insulin > 5 mIU/L. Unclear if better than other options for adenoma prevention (e.g. diet, supplements)
1 RCT Low- bias	Gum & tooth health	**Population:** Had periodontitis, non-diabetic, non-prediabetic **Intervention:** 1% metformin gel + scaling and root planing (SRP) vs SRP **Gum pocket depth outcome**: 8 mm to 4 mm (50% reduction), after 6 months, 2 mm more than control **Tooth bone loss outcome**: Regenerated 2 mm (33%) of bone after 6 months. Control: 0%
2 RCT High-bias	Advanced glycation end-product (AGE) formation	**Comment**: Lowers AGEs in diabetics, unclear if does so in non-diabetics, non-prediabetics
3 Obs High-bias	Chance of dying from any cause	**Population:** Diabetics taking metformin versus non-diabetics not taking metformin **Outcome:** 1% to 12% less **Comment:** Many factors that could result in the population taking metformin living longer were not considered.
Cell Studies	Scar formation after injury	**Comment:** No human data, hypothesis only.
TBC	Response to flu or bacterial pneumonia vaccines	Ongoing trial
TBC	Infections in COPD patients	Ongoing trial

LEVEL OF EVIDENCE	EFFECT	MAGNITUDE OF EFFECT
TBC	Lung cancer progression (LKB1-inactive adenocarcinoma type)	Ongoing trial
TBC	Oral pre-cancer progression	Ongoing trial
TBC	Endometrial cancer recurrence, after hysterectomy	Ongoing trial
TBC	Speed of oral cancer growth	Ongoing trial
TBC	TAME trial: biological aging surrogate and clinical markers	Ongoing trial

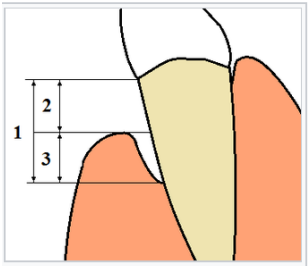
Common or Dangerous Side Effects

LEVEL OF EVIDENCE	EFFECT	LIKELIHOOD	SERIOUSNESS IF OCCURS	HOW TO SOLVE
>3 RCT Low-bias	Ongoing diarrhoea, bloating, nausea, reflux, flatulence, gut pain	>50%	★★☆ Moderate	Metformin slow release instead of instant release + dosing strategies
>3 RCT Low-bias	Low blood sugar	Only occurs if other low blood sugar risks present	★★★ Severe	Avoid binge drinking, be careful with other blood sugar lowering drugs, avoid starvation
1 RCT Low-bias	Feeling of low physical or mental strength	5%	★☆☆ Mild	Trial 12-hour gap before exercise
1 RCT Low-bias	Reduced B12 level, Folate (B9) level	100%	★☆☆ Mild	100 micrograms oral B12 daily + increase folate rich plant intake
>3 Obs High-bias	Lactic acidosis (dangerously high levels of acid in body)	Only occurs in low kidney or heart function	★★★ Severe	Annual kidney test + stop in certain situations
Anecdotal	Reduced exercise capacity	4% ? (unclear)	★☆☆ Mild	Trial 12-hour gap before exercise

What Metformin Works for in Non-diabetics

LEVEL OF EVIDENCE	EFFECT	CHANGE	MAGNITUDE OF BENEFIT	COMMENTS
4 RCT **Low-bias**	Pre-diabetes conversion to full diabetes	↓	★★☆ Moderate	**Scientific studies:** 2018 systematic review of 4 randomised controlled trials in adults at least 18 months long **Population:** Pre-diabetics, BMI 17 – 50, age 30+ **Intervention:** 500 mg to 1700 mg metformin a day (no dose relationship with outcome) **Comparator:** Pill placebo, or lifestyle program **Outcome:** 7% to 35% less risk of developing full diabetes over 1.5 to 10 years **Comment:** Lifestyle changes can outperform metformin for preventing full diabetes
4 RCT **Low-bias**	Weight loss	↓	★★☆ Moderate	**Scientific studies:** 2018 systematic review of 4 randomised controlled trials in adults at least 18 months long **Population:** Pre-diabetics, BMI 17 – 50, age 30+ **Intervention:** 500 mg to 1700 mg metformin a day (no dose relationship with outcome) **Comparator:** Pill placebo, or lifestyle program **Outcome:** 0 – 3.5 kg weight loss at 1.5 to 10 years (control groups may gain weight) **Comment:** May be more sustainable than lifestyle, but lifestyle can reach much higher total weight loss
1 RCT **Low-bias**	Colon or rectal adenomas (swellings that can lead to colon or rectal cancer)	↓	★★☆ Moderate	**Scientific studies:** 2017 Randomised controlled trial **Population:** Age 40 – 80, BMI 18 – 28, Japanese, M & F, no diabetes, no pre-diabetes, no genetic increased risk of polyps, had recently had a colonoscopy and had had at least 1 polyp removed, 70% had more than 1 polyp OR severe dysplasia OR large adenomatous polyps OR villous adenoma type polyps (this population is above average risk for people undergoing colonoscopy) **Intervention:** 250 mg metformin (low dose) instant release daily for 1 year. **Comparator:** Pill placebo **Outcome:** 8% - 61% less adenomas after 1 year **Risk of bias analysis:** ✔ Attrition: < 20% lost to follow up in out-patient study ✔ Blinding: Used ✔ Concealment: Low risk of allocation bias **Take away message:** If you have had any adenomas on colonoscopy, 250 mg metformin indefinitely may help prevent future adenomas. Slow release form metformin and 100 micrograms vitamin B12 daily will likely reduce metformin side effects; but no side effects were noted different from placebo at this low 250 mg dose. Take into account evidence for other options to

LEVEL OF EVIDENCE	EFFECT	CHANGE	MAGNITUDE OF BENEFIT	COMMENTS
				prevent adenomas such as regular screening via stool tests or colonoscopy & removal of adenomas, aspirin, increased fiber intake, anti-cancer diets, reduced alcohol intake, calcium intake, genetic testing in cases of family history of bowel cancer, sleep & exercise optimization. Those with higher fasting insulin or fasting blood glucose, even if they do not have pre-diabetes or diabetes, may have more benefit from metformin for preventing adenomas. Increasing the dose of metformin to reach HOMA-IR of 1.1 or less might enhance adenoma preventing efficacy.
1 RCT **Low-bias**	Gum & tooth health markers 1) Clinical attachment level 2) Probing depth 3) Bone loss on X-ray	↓	★★☆ Moderate	**Scientific studies:** 2013 randomised controlled trial **Population:** Healthy, systemically well, people (no diabetes, no smoking, no alcoholism, no major conditions) with periodontitis (loss of gums, tooth, or tooth ligaments). **Intervention:** Scaling and root planing (SRP) under local anaesthetic until the root service was considered smooth and clean by the operator, followed by 10 microliters of 1% metformin gel injected with a blunt needle into each affected periodontal pocket. Patients were instructed to refrain from chewing hard or sticky foods, brushing near the treated areas, or using any interdental aids for 1 week. **Comparator:** Scaling and root planing only. **Risk of bias analysis:** ✔ Attrition: < 20% lost to follow up in out-patient study ✔ Blinding: Used ✔ Concealment: Low risk of allocation bias **Outcomes:** 1) Reduced pocket depth from 8 mm to 4mm (50%), whilst SRP only reduced pocket depth from 8 mm to 6 mm (25%)), by 6 months. 2) Reduced clinical attachment level (CAL) from 6.4 to 2.6 (4mm, or 60% reduction), whist SRP alone reduced CAL by 1.2 mm or 20%, by 6 months. 3) Regenerated lost bone by 33% (reduced 5 mm bone loss to 3 mm bone loss), whilst SRP did not regenerate any bone, by 6 months. **Take away message:** If you have periodontitis and are having scaling and root planning (SRP), it could be worth asking a pharmacy or your dentist to create some 1% metformin gel to inject after the SRP. The benefit seems to be the anti-inflammatory effect of the metformin at a slowly declining concentration in the gum pocket until it reaches zero concentration after 4 weeks (it doesn't get washed out easily from the gum as it is a gel). The metformin at such concentrations and time-periods also activates osteoblasts (bone making cells) hence the regeneration of bone. In theory, you could repeat the injection more often, e.g. every 2 – 6 months to enhance its effect, until you reach target pocket depth, clinical attachment level, or bone regeneration – but the potential side effects of this are not clear. People without periodontitis may still benefit from this metformin therapy, but it is not clear. Given the low risk of side effects, it could be considered. One could check their own clinical attachment level, pocket depth or bone

LEVEL OF EVIDENCE	EFFECT	CHANGE	MAGNITUDE OF BENEFIT	COMMENTS
				loss and experiment if this metformin therapy improves the results 6 months later. **How to make metformin gel:** MF gel was prepared as described by Mohapatra et al.15 Briefly, all the required ingredients of the formulation were weighed accurately. Dry gellan gum powder was dispersed in distilled water maintained at 95C. The dispersion was stirred at 95C for 20 minutes using a magnetic stirreri to facilitate hydration of gellan gum. The required amount of mannitol was added to the gellan gum solution with continuous stirring, and the temperature was maintained above 80C. A weighed amount of MF was added with stirring. Then sucralose, citric acid, and preservatives (methylparaben, propylparaben) were added with stirring. Finally, the required amount of sodium citrate was dissolved in 10 mL distilled water and added to the mixture. The mixture was allowed to cool to room temperature to form gel. The gels were prepared to 1% concentration. **What are clinical detachment level and probing depth?**  **1**: Total loss of attachment (clinical attachment loss, CAL) is the sum of **2**: Gingival recession, and **3**: Probing depth
3 Obs **High-bias**	Chance of dying from any-cause	↓	★☆☆ Small	**Scientific studies:** 2017 Meta-analysis of observational studies **Population:** Type 2 Diabetics **Intervention:** Diabetics taking any metformin for 6+ months. **Comparator:** Non-diabetics not taking metformin. **Outcome:** 1% - 12% reduced mortality, over 7 years **Risk of bias analysis:** Data on many factors that could account for the diabetic metformin users surviving longer than the non-diabetic controls were not tracked **Take away message:** This study does not justify taking metformin.
2 RCT **High-bias**	Advanced glycation end-product (AGE) formation	↓	Unclear	**Additional search done** **Scientific studies:** 2 randomised controlled trials *in diabetics* (2006 study; 2011 study) **Population:** Type 2 Diabetics **Intervention:** Any metformin. **Comparator:** "Optimal diet therapy" +/- insulin +/-sulphonylurea anti-diabetic drug.

LEVEL OF EVIDENCE	EFFECT	CHANGE	MAGNITUDE OF BENEFIT	COMMENTS
				Risk of bias analysis: These patients were diabetic, it is not clear if metformin will lower AGE markers in non-diabetics, as diabetics have higher AGE levels than non-diabetics. **Take away message:** If you do not have diabetes, one could experiment with metformin to see if it improved your AGE markers, by measuring AGE markers before and 6 months after starting a dose of metformin and making minimal other lifestyle changes. The easiest way to measure the build up of AGEs in the skin is to purchase a ~£1,000GBP device called the Mu Mini Reader from Diagnoptics (email asking for the Mu Mini AGE reader (not the large one)). You can also measure AGEs via blood tests such as methylglyoxal, pentosidine, fructosamine and CML, but these are hard to access. All types of blood sugar markers are related to AGE accumulation, so these could be tested as surrogate markers of AGE build up in the body (but these markers do not measure AGE accumulation directly).
Cell Studies	Scar formation after injury	↓	Unclear	**Scientific studies:** 2016 systematic review of cell studies **Take away message:** Increased advanced glycation end products (AGEs) may make scars worse according to human observational studies; cell studies show metformin can reduce AGEs. It has not yet been tested in humans, but taking metformin may reduce AGE formation during scar formation in some people as AGE levels will be lower.
TBC	Flu & bacterial pneumonia Vaccine responses	↑	Ongoing trial	**Scientific studies:** Ongoing randomised controlled trial in flu and pneumococcal vaccine (bacterial pneumonia vaccine) **Population:** Non-diabetics, non-prediabetics **Intervention:** 1.5g a day metformin extended release for 12 weeks prior to vaccination **Comparator:** Pill placebo **Take away message:** Those wanting to experiment with boosting their vaccine response may want to implement this as part of their vaccine boosting response protocol (alongside other vaccine response boosting interventions such as exercise and morning vaccination timing)
TBC	Infections in COPD patients	↓	Ongoing trial	**Scientific studies:** Ongoing randomised controlled trial **Population:** Non-diabetics, non-prediabetics with COPD and at least 15 years smoking history **Intervention:** 500 mg metformin instant release twice a day **Comparator:** Pill placebo **Take away message:** For COPD patients, they may want to experiment with this metformin intervention.
TBC	Lung cancer progression (LKB1-inactive adenocarcinoma type)	↓	Ongoing trial	**Scientific studies:** Ongoing randomised controlled trial **Population:** Non-diabetics with LKB1-inactive adenocarcinoma lung cancer, BMI under 20

LEVEL OF EVIDENCE	EFFECT	CHANGE	MAGNITUDE OF BENEFIT	COMMENTS
				Intervention: Metformin up to 1500 mg a day (max tolerated) alongside chemotherapy regimens AND 5 day fasting mimicking diet **Comparator:** Pill placebo **Take away message:** Those with this type of lung cancer, or similar lung cancers may want to discuss this with their oncologist.
TBC	Oral pre-cancerous lesions	↓	Ongoing trial	**Scientific studies:** Ongoing randomised controlled trial **Population:** Non-diabetics **Intervention:** 500 mg extended release metformin per day **Comparator:** Pill placebo **Take away message:** Those with oral pre-cancer lesions may want to discuss trying this protocol with their doctors.
TBC	Endometrial cancer recurrence, after hysterectomy	↓	Ongoing trial	**Scientific studies:** Ongoing randomised controlled trial **Population:** Non-diabetics with endometrial cancer that will be removed via hysterectomy **Intervention:** Metformin 850 mg instant release per day for 4 weeks prior to total hysterectomy **Comparator:** Pill placebo **Take away message:** Those with endometrial cancer, who are or are not planned to have it treated via hysterectomy, may want to discuss this protocol with their doctors.
TBC	Speed of oral cancer growth	↓	Ongoing trial	**Scientific studies:** Ongoing non-randomised intervention trial **Population:** Non-diabetics with oral cavity squamous cell carcinoma **Intervention:** 850 mg instant release metformin twice per day for 14 days prior to surgical removal **Comparator:** Pill placebo **Hypothesised mechanism of action:** Increases oxygen content in cancer cells and tumour microenvironment, which slows tumour growth (as some tumours may grow faster in low oxygen environments) **Take away message:** Those with oral cancer may want to discuss this study with their doctors.
TBC	TAME trial Biological aging surrogate and clinical markers	↓	Ongoing trial	**Scientific studies:** Trial details not identified **Take away message:** Trial details not identified at this point.

Side Effects of Metformin

LEVEL OF EVIDENCE	EFFECT	CHANCE	SERIOUSNESS IF OCCURS	COMMENTS
>3 RCT **Low-bias**	Diarrhoea, bloating, nausea, flatulence or gut pain	Over 50%	★★☆ Moderate	**Scientific studies:** Randomized controlled trials of metformin **Take away message:** Metformin commonly causes digestive symptom side effects. We searched doctor and patient reported tips and ongoing clinical trials for ways to reduce side effects. **Instant release form:** Up to 42% chance of diarrhoea Up to 18% chance of nausea/ vomiting **Extended release form:** Up to 7% chance of diarrhoea Up to 5% chance of nausea/ vomiting **How to solve this side effect:** • Using slow release metformin can reduce chances of gastrointestinal side effects by up to 90% • Skipping straight to slow release metformin rather than trying instant release metformin • Starting at a very low dose of e.g. 250 mg straight after a meal and building up the dose very slowly, e.g. 125 mg per 2 weeks • Peppermint tea may reduce nausea and vomiting side effect severity in first few months (according to patient reports) • If have severe gastro intestinal side effects that cause you to stop it, you can stop it and restart it from the lowest dose, slowly building up and you may be more tolerant the second time round (source of ongoing clinical trial for this) • Psyllium husk powder to reduce diarrhoea with metformin in T2DM patients (source of ongoing clinical trial for this) • Probiotics to prevent and treat gastrointestinal side effects of metformin: A multi-strain probiotic is being tested for this, containing: Sanprobi Barrier (Bifidobacterium lactis W52, Lactobacillus brevis W63, Lactobacillus casei W56, Lactobacillus lactis W19, Lactobacillus lactis W58, Lactobacillus acidophilus W37, Bifidobacterium bifidum W23, Lactobacillus salivarius W24) (source of ongoing clinical trial for this) • Separate doses by at least 6 hours to reduce gastrointestinal side effects
>3 RCT **Low-bias**	Dangerously low blood sugar in certain situations	Only occurs if have other risk factors for low blood sugar	★★★ Severe	**Scientific studies:** Link to side effects info leaflet Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when: • Caloric intake is deficient • When strenuous exercise is not compensated by caloric supplementation

LEVEL OF EVIDENCE	EFFECT	CHANCE	SERIOUSNESS IF OCCURS	COMMENTS
				• During concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) **or ethanol** • In elderly, debilitated, or malnourished patients • In those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs.
1 RCT **High-bias**	B12 level, Folate (B9) level	100%	★★☆ Moderate	**Scientific studies:** 2003 Randomised controlled trial **Population:** Diabetics **Intervention:** 850 mg metformin instant release once daily for 4 months **Comparator:** Pill placebo **Outcome:** **B12:** 95% chance of 5% decrease, 50% chance of 14% decrease **Folate:** 95% chance of 1.4% decrease, 50% chance of 7% decrease **Risk of bias analysis:** ✔ GRADE Rank 1A It is not clear if non-diabetic users will have reduced B12 or B9 levels too. **Take away message:** This may affect non-diabetics taking metformin as well. Metformin may lower B12 levels by 80 pmol/L within 6 weeks (1.5 months), those within 100 pmol/L of the lower limit of normal total B12 should supplement B12 to prevent moving to the deficiency range. Taking 125 micrograms methylcobalamin a day or 1000 micrograms a week (which can be part of a b complex pill) should prevent B12 deficiency from metformin, and B12 deficiency in general. Methylcobalamin is better used by the body than cyanocobalamin for most people. Pills are just as effective as B12 injections so there is no need to undergo logistically more burdonesome and painful and riskier injections every month (unless as medically indicated such as unable to absorb by the gut or in severe B12 deficiency cases etc.). For folate, one should increase vegetable dietary sources, as this is the best and safest source of folate. If this doesn't work, one should consider a L-5-methyltetrahydrofolate supplement as opposed to straight folic acid supplement, due to this working more consistently for people with different genes involved with metabolizing folate. The maximum dose of supplemental folate should be 200 micrograms for most people, with the rest coming from diet. This is because 400 micrograms supplemental dose provides 90% of the potential benefits on reducing homocysteine (2003 randomised controlled trial), which is a marker of cardiovascular disease risk, and higher levels of supplemental folate may increase cancer or other disease risk (accumulating observational and cell mechanistic study evidence over the years – evidence Level C).
>3 Obs **High-bias**	Lactic acidosis	Only occurs when blood	★★★ Severe	**Scientific studies:** Link to various articles on google ; Link to side effects info leaflet

LEVEL OF EVIDENCE	EFFECT	CHANCE	SERIOUSNESS IF OCCURS	COMMENTS
	(dangerously high levels of acid in body)	flow to kidneys is reduced		Metformin is known to cause lactic acidosis, dangerously high levels of acid in your body, if blood concentrations of metformin get too high as a result of metformin not being able to be cleared by your kidneys. **Take away message:** • Ensure your kidney function is over 30 mL/min glomerular filtration rate, or as advised by your doctor • Considering adjusting for age-related reductions in metformin metabolism independent of kidney function, e.g. halving the dose if over age 80. • Ensuring you tell your doctors that you are taking metformin, especially if you are ordering it off the internet without a prescription, or privately and your public insurance doctors don't know about it • Stopping metformin in emergency medical situations and at least 2 days before having contrast imaging • Considering not taking metformin if you have chronic or acute lactic acidosis or diabetic ketoacidosis • Discontinuing metformin when experiencing diarrhoea or vomiting resulting in further diarrhoea, vomiting and dehydration • Not drinking alcohol in access when taking metformin e.g. over 10 units, as increases risk of lactic acidosis - especially in those with impaired kidney function already (e.g. any glomerular filtration rate under 60 ml/min) • Metformin **instant release** scored only 3.7/5 from 938 patient user reviews at iodine.com, mostly due to diarrheoa, nausea, flatulence and bloating side effects • Occasionally, the inactive ingredients of metformin hydrochloride extended-release tablets may be eliminated as a soft mass in your stool that may look like the original tablet; this is not harmful and will not affect the way metformin hydrochloride extended-release tablets work to control your diabetes Knowing the following symptoms that may be because of lactic acidosis (from a metformin overdose) • you feel dizzy or lightheaded • you have a slow or irregular heartbeat • you feel very weak or tired • you have unusual (not normal) muscle pain • you have trouble breathing • you feel sleepy or drowsy • you have stomach pains, nausea or vomiting • you feel cold in your hands or feet
Anecdotal	Exercise benefits (making new mitochondria)	Unclear	★☆☆ Small	**Scientific studies:** None – conversations with metformin users. **Take away message:** No human studies could be found on the effect of metformin on exercise benefits. There is a ~4% chance of muscle weakness with metformin which may be related to this. If one experiences muscle

LEVEL OF EVIDENCE	EFFECT	CHANCE	SERIOUSNESS IF OCCURS	COMMENTS
				weakness with metformin, they may want to not take metformin for e.g. at least 12 hours before undergoing strenuous exercise.

Instant release metformin VS extended release metformin

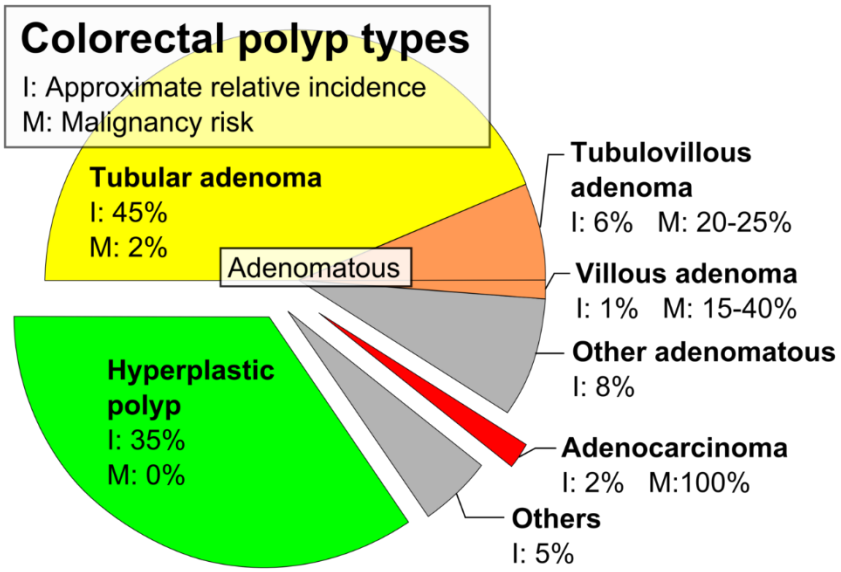
RISK	INSTANT RELEASE METFORMIN	EXTENDED RELEASE METFORMIN	PLACEBO
Diarrhoea	53%	7%	11%
Nausea / vomiting	25%	5%	8%

Instant release versus extended (modified/slow) release metformin: Top 2 side effects

Source

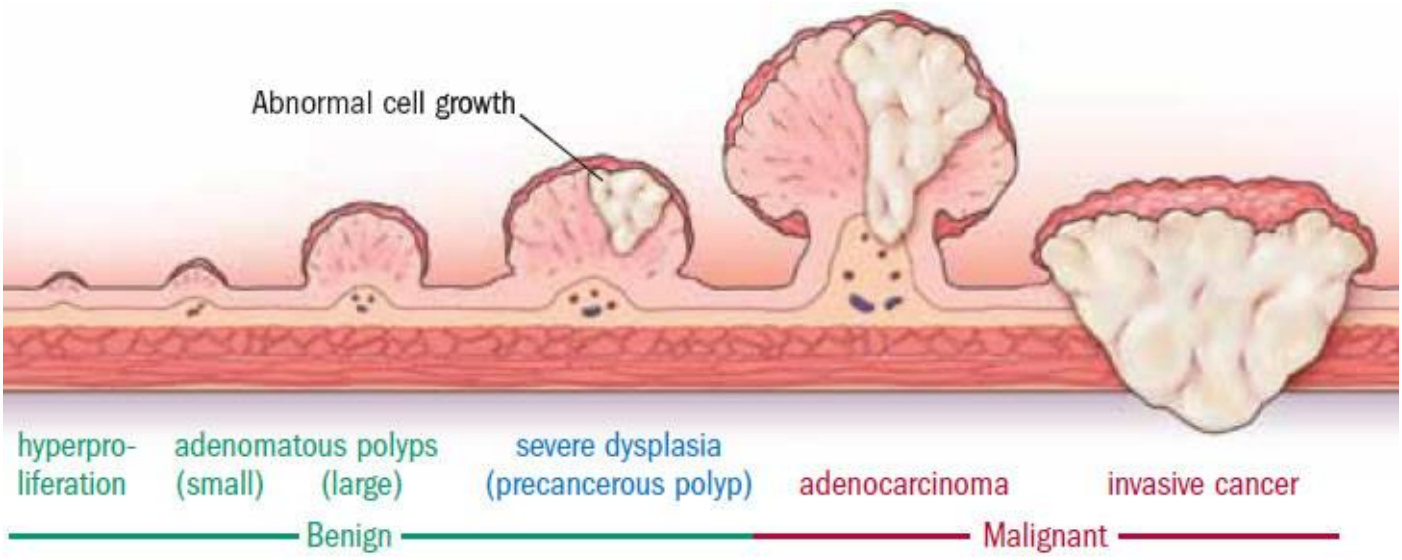
Background Information

Colon & rectal (colorectal) adenomas and polyps



Source of image

Wikipedia explainer article



Source of image

Systematic review strategy

Search strategy:

Identify all past and ongoing trials of metformin in any form in people without any form of pre-diabetes or diabetes in conditions that are age-related.

PubMed Search:

systematic[sb] AND (metformin NOT gestational NOT polycystic ovary syndrome NOT dialysis)

((((systematic review[ti] OR systematic literature review[ti] OR systematic scoping review[ti] OR systematic narrative review[ti] OR systematic qualitative review[ti] OR systematic evidence review[ti] OR systematic quantitative review[ti] OR systematic meta-review[ti] OR systematic critical review[ti] OR systematic mixed studies review[ti] OR systematic mapping review[ti] OR systematic cochrane review[ti] OR systematic search and review[ti] OR systematic integrative review[ti]) NOT comment[pt] NOT (protocol[ti] OR protocols[ti])) NOT MEDLINE [subset]) OR (Cochrane Database Syst Rev[ta] AND review[pt]) OR systematic review[pt])AND (("metformin"[MeSH Terms] OR "metformin"[All Fields]) NOT gestational[All Fields] NOT ("polycystic ovary syndrome"[MeSH Terms] OR ("polycystic"[All Fields] AND "ovary"[All Fields] AND "syndrome"[All Fields]) OR "polycystic ovary syndrome"[All Fields]) NOT ("renal dialysis"[MeSH Terms] OR ("renal"[All Fields] AND "dialysis"[All Fields]) OR "renal dialysis"[All Fields] OR "dialysis"[All Fields] OR "dialysis"[MeSH Terms]))

328 articles identified; unrecorded subset retrieved for abstract, further subset retrieved for full text

Date performed: 1st October 2019

Reviewer: Oliver Zolman MD

Clinicaltrials.gov search

Search URL:
https://clinicaltrials.gov/ct2/results?cond=metformin&term=&type=&rslt=&age_v=&age=1&gndr=&intr=&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&lupd_s=&lupd_e=&sort=nwst

Search term: metformin; Filter: adults 18-64 AND adults 65+; Sort order: most recent first

Date performed: 1st October 2019

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Side effects searches:

https://www.iodine.com/drug/metformin/reviews/4

http://sideeffects.embl.de/drugs/4091/

https://www.iodine.com/drug/metformin/fda-package-insert

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