Metformin and woman health

~ Metformin對防治婦女疾病的檢視 ~

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Metformin is made from *Galega officinalis* flower

From Plant to Pill: A Look at Metformin's 100-Year History

Written by Amber Walsh, PharmD Candidate | Reviewed by Christina Aungst, PharmD

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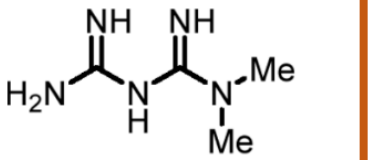
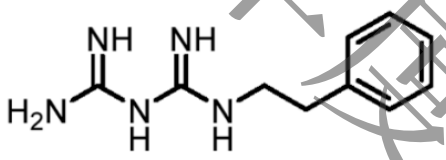
Key takeaways:

- Metformin is an oral diabetes medication that has been around for about 100 years. However, it wasn't approved for use in the U.S. until 1995. Despite its popularity today, metformin has a complicated history.
- Metformin was made using a natural substance called guanidine. This happened after guanidine from the *Galega officinalis* plant was found to lower blood glucose in animals.
- Until 2016, metformin's use was more limited. This was because it was similar to other medications that had been removed from the market for safety reasons. Since then, more people who may benefit from metformin are able to take it.

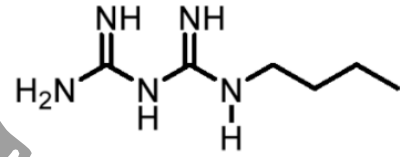
Metformin is effective for T2DM



Metformin
J. Sterne. 1957



Phenformin
G. Ungar. 1957

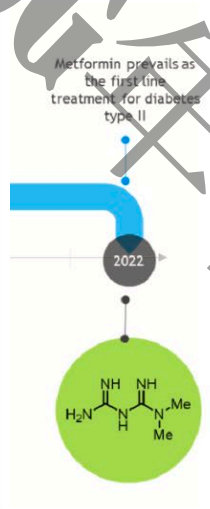


Buformin
A. Beringer. 1958

2016 後
控制糖尿病 metformin第一線用藥
目前T2D使用率: UK 86%, USA 77%

Table 1 Summary of the Pharmacokinetics Characteristics of Metformin

Pharmacokinetics Parameters	Values
Absolute bioavailability	50–60% in healthy individuals
Time to reach Cmax (Tmax)	2.5 hours
Kinetics of metformin absorption	Non-linear
At scheduled and recommended doses time to reach steady state plasma concentration	24–48 hours
Steady state plasma concentration	Less than 1 μg/mL
Mean volume of distribution (Vd)	Ranged between 63–276 L
Selective distribution	Red blood cells most likely represent a secondary compartment of distribution
Excretion	Unchanged in urine
Renal clearance	>400mL/min (indicating glomerular filtration and tubular secretion
Apparent terminal elimination half-life	Approximately 6.5 hours



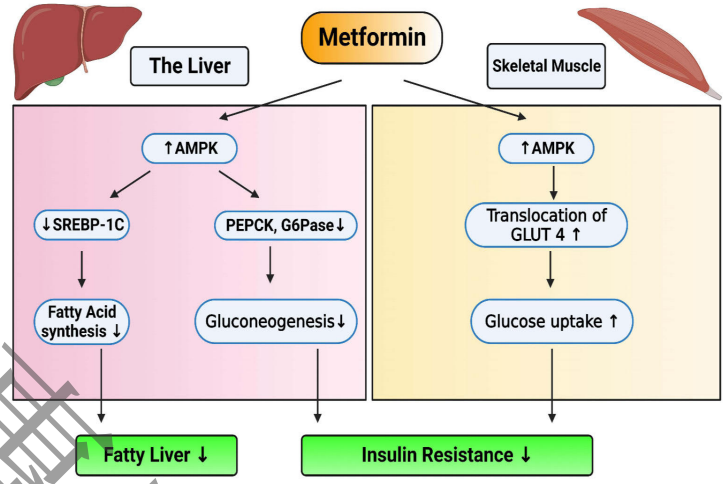
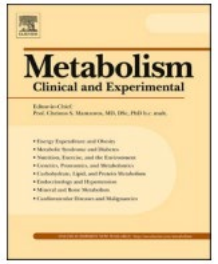


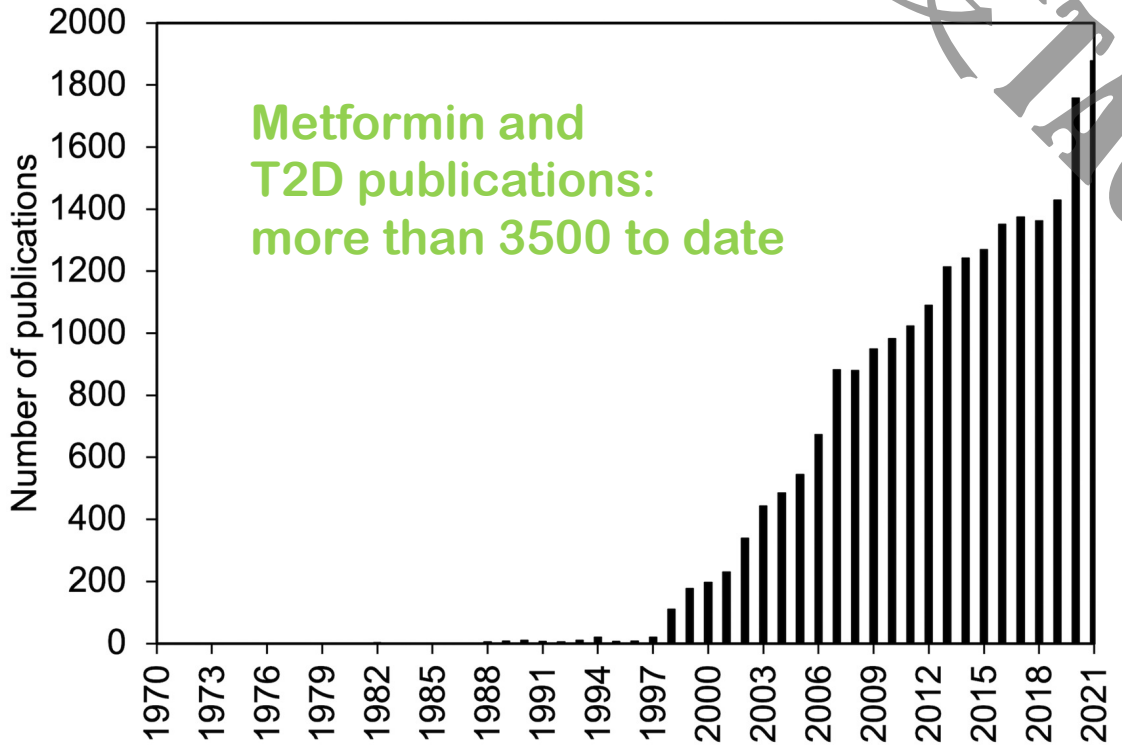
Figure 2 Beneficial effects of metformin. AMPK- adenosine monophosphate-activated protein kinase; SREBP-1C: sterol regulatory element-binding protein 1; PEPCK-Phosphoenolpyruvate carboxy kinase; G6Pase- glucose 6-phosphatase; GLUT4- Glucose transporter 4. This figure was created using the premium version of BioRender (https://biorender.com/) with License No.: MT250DY0DR. Created with BioRender.com.

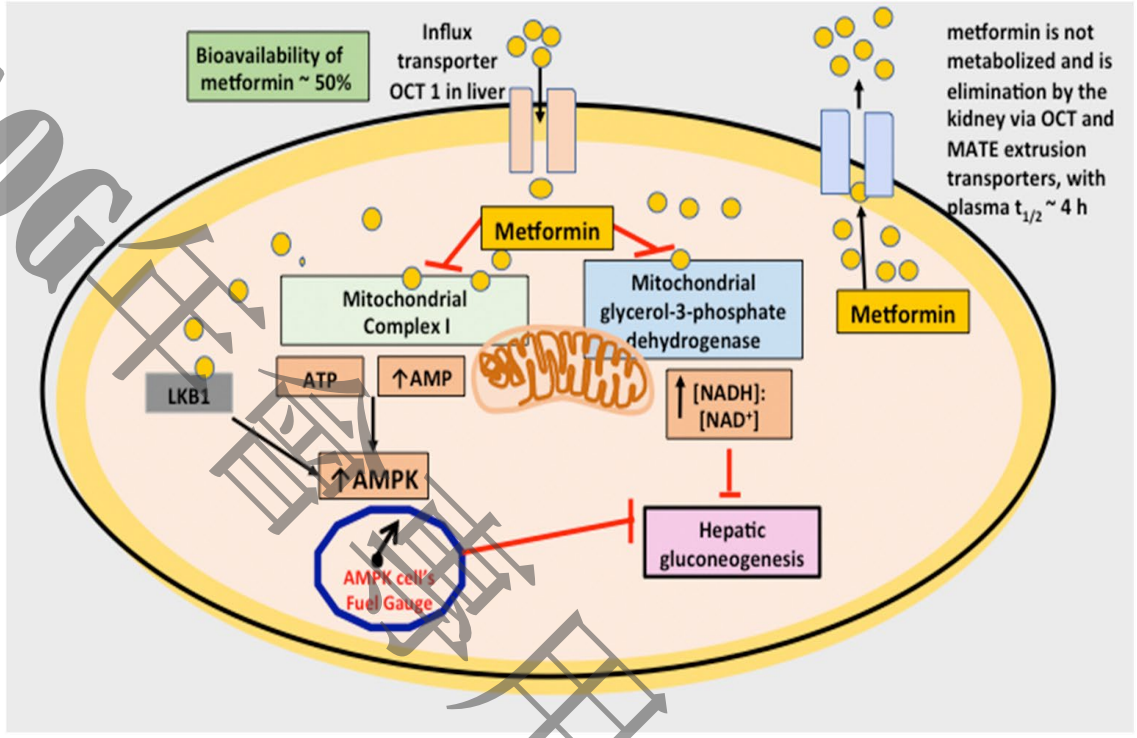
Metformin: Is it a drug for all reasons and diseases?



有預防老化和和百病均醫的藥嗎？

Metformin : cellular mechanisms, preclinical & clinical studies --> 抗糖 抗炎 防癌 抗癌 防老 全身皆沾邊

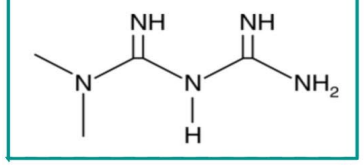




Metabolism - Clinical and Experimental Volume 133 (August 2022)

Metformin's cardiovascular benefits

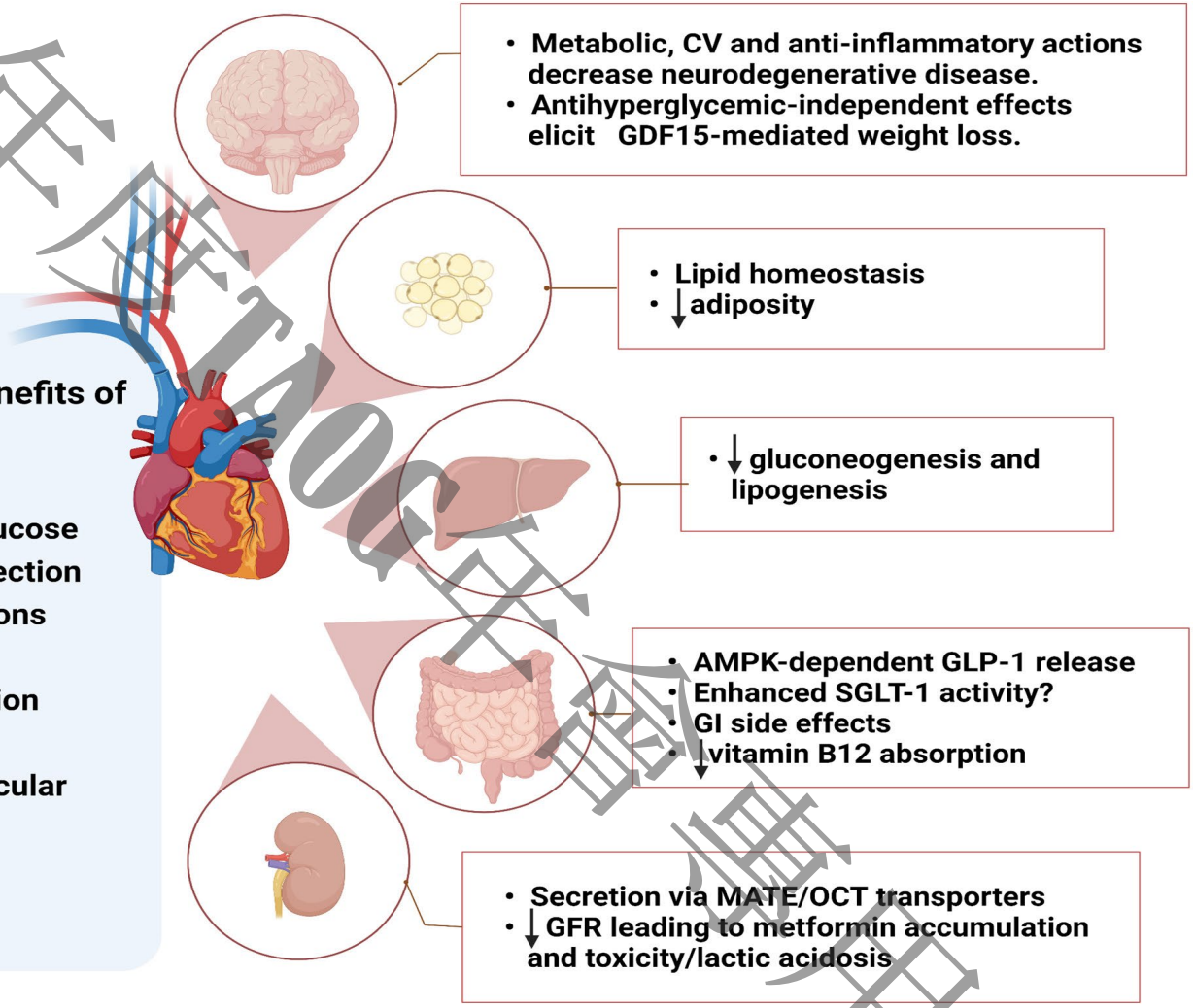
Metformin



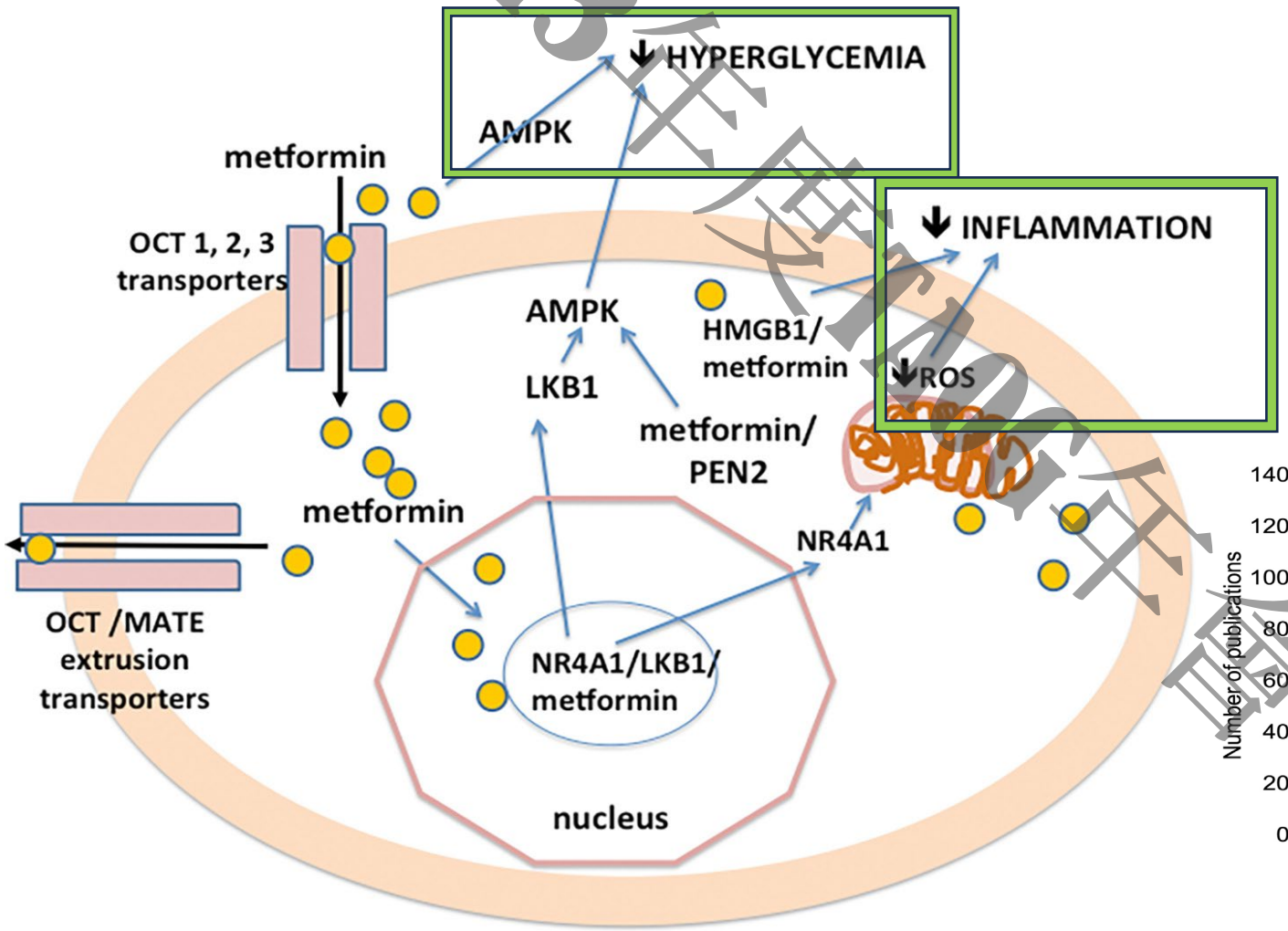
Galega officinalis

Cardiovascular benefits of metformin

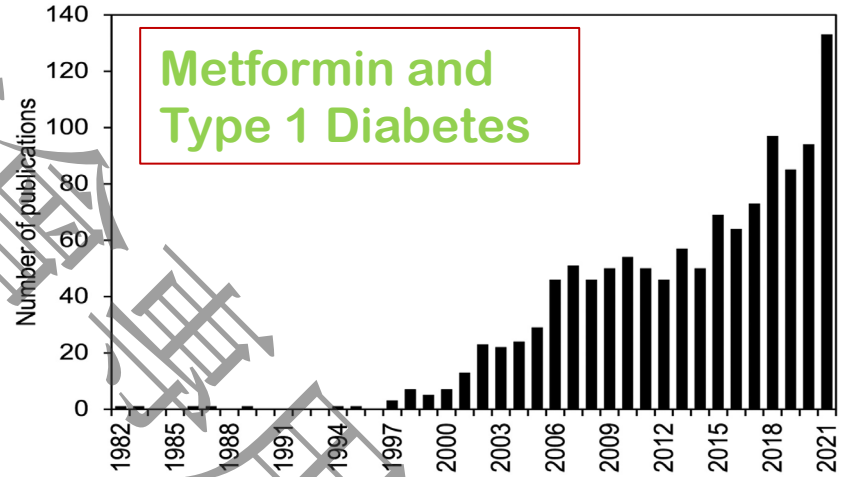
- Lowered blood glucose
- Endothelium protection
- Antioxidative actions
- ↓inflammation
- ↓leukocyte adhesion
- ↓blood pressure
- ↓micro/macrovascular complications



Metformin for type I Diabetes



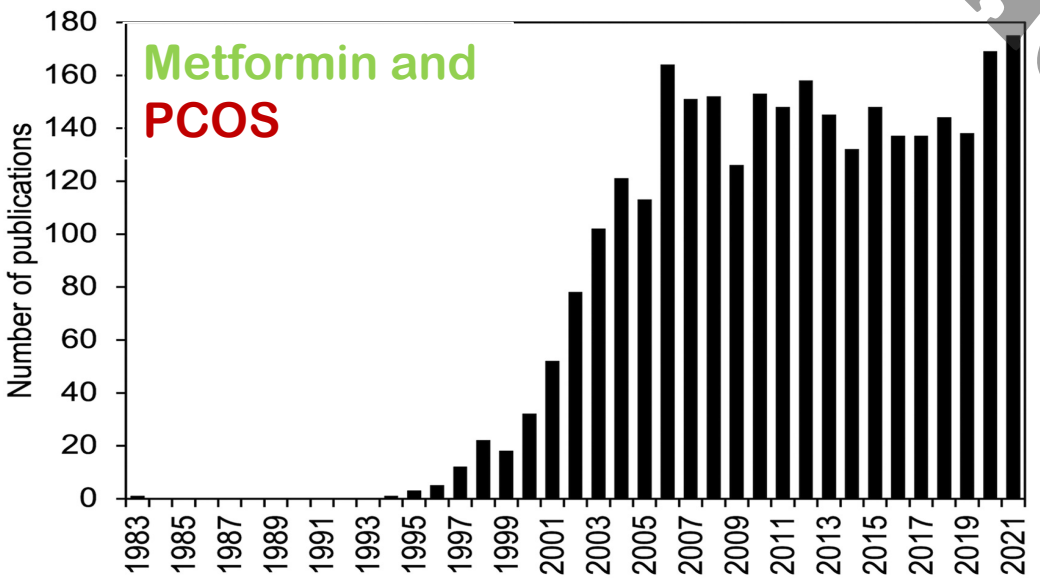
Metformin works by reducing insulin dosage



Metformin for polycystic ovary syndrome (PCOS)

Metformin * regulates insulin resistance

PCOS * alpha-1 AMPK gene expression affects metformin effects



PCOS

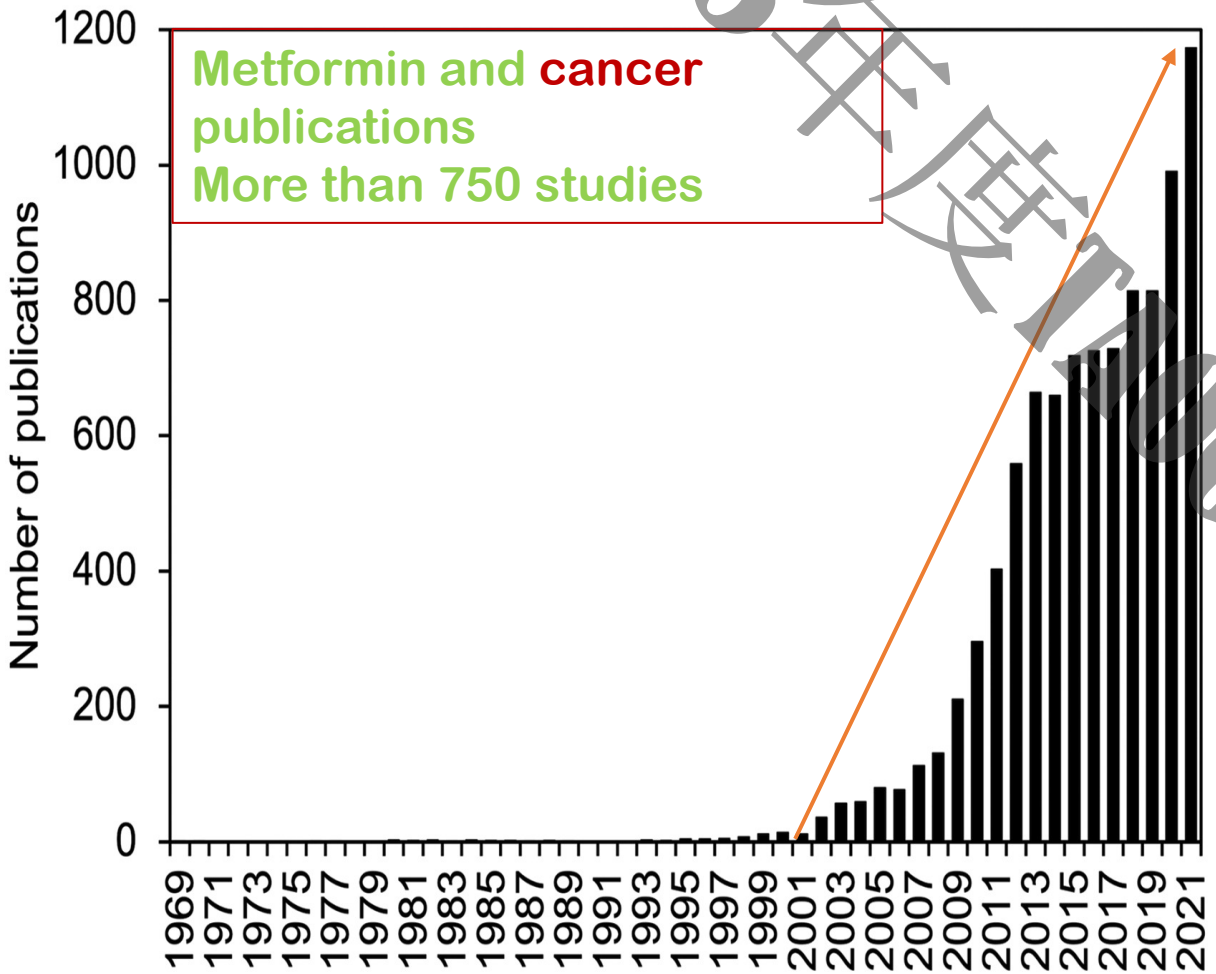
Oligomenorrhea/ammenorrhea, hirsutism, acne, infertility;

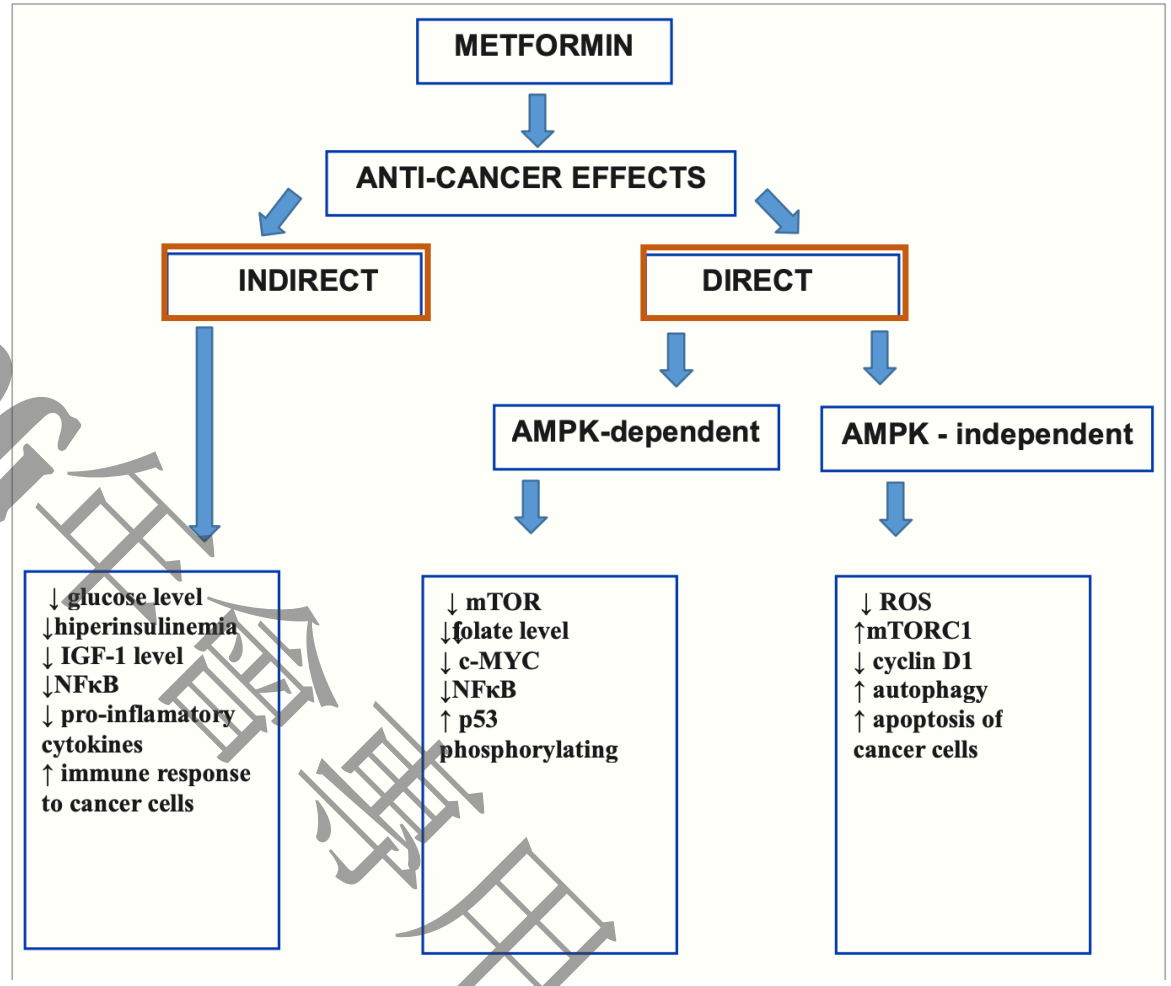
testosterone > 0.8ng/ml, DHEAS > 20ug/dL, fasting insulin > 17mU/L

Metformin 500 mg tid -> PCOS

- ✓ Lower serum insulin and insulin resistance
- ✓ Improve regularity of menstrual cycle
- ✓ Inhibition of ovarian androgen production
- ✓ Less abortion and less GDM
- ✓ Control body weight and may decrease BMI 1.4-4.5
- ✓ Lower risk for T2D

Metformin adjunct to cancer management

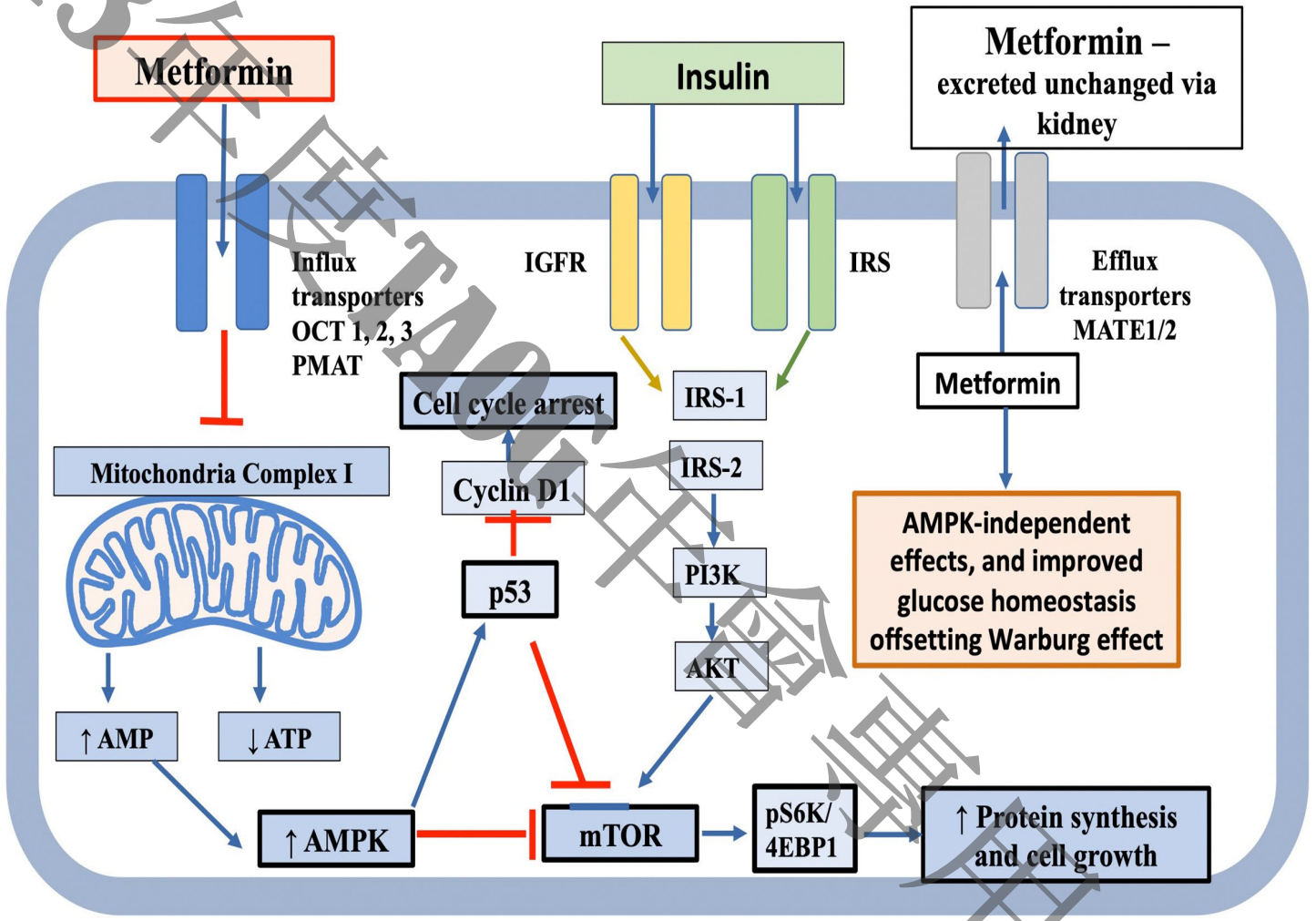




Metformin: Is it a drug for all reasons and diseases?

Cellular mechanism on anti-cancer

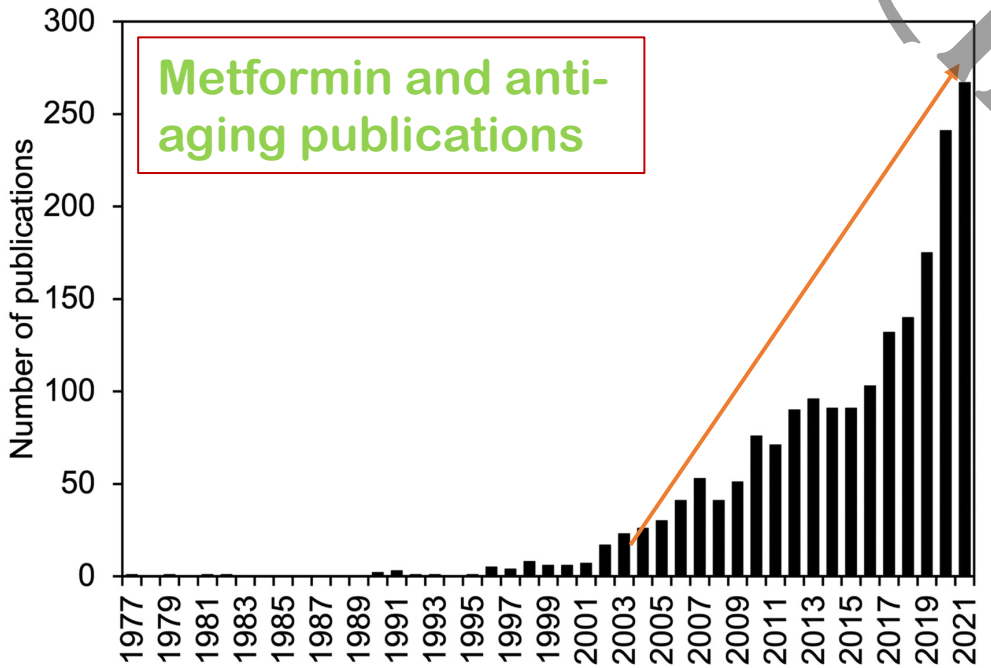
- ✓ Cell cycle arrest
- ✓ Reduce protein synthesis & cell growth

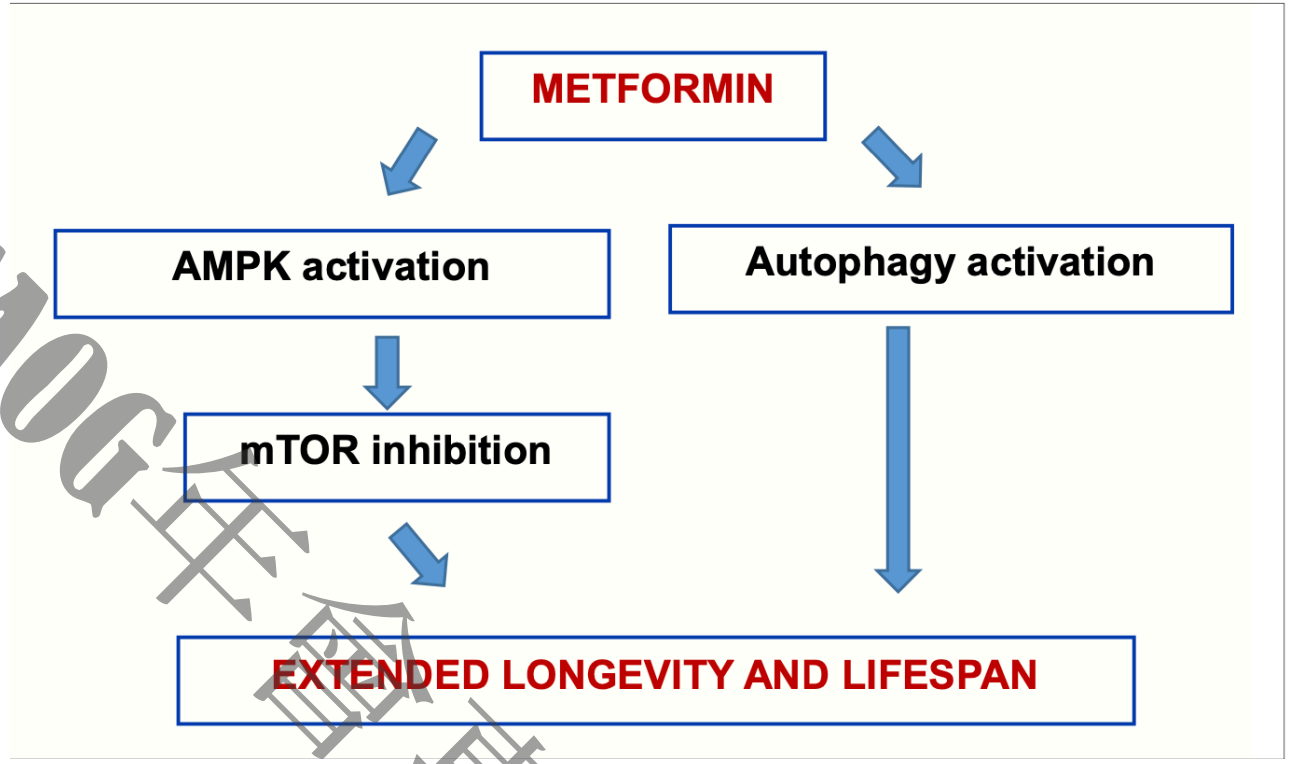


Metformin: Is it a drug for all reasons and diseases?

有預防老化和和百病均醫的藥嗎？

Clinical studies on
*Neurodegenerative disease
*neuroprotective actions
Focus on anti-aging benefits





Equal number of supportive and questionable publications

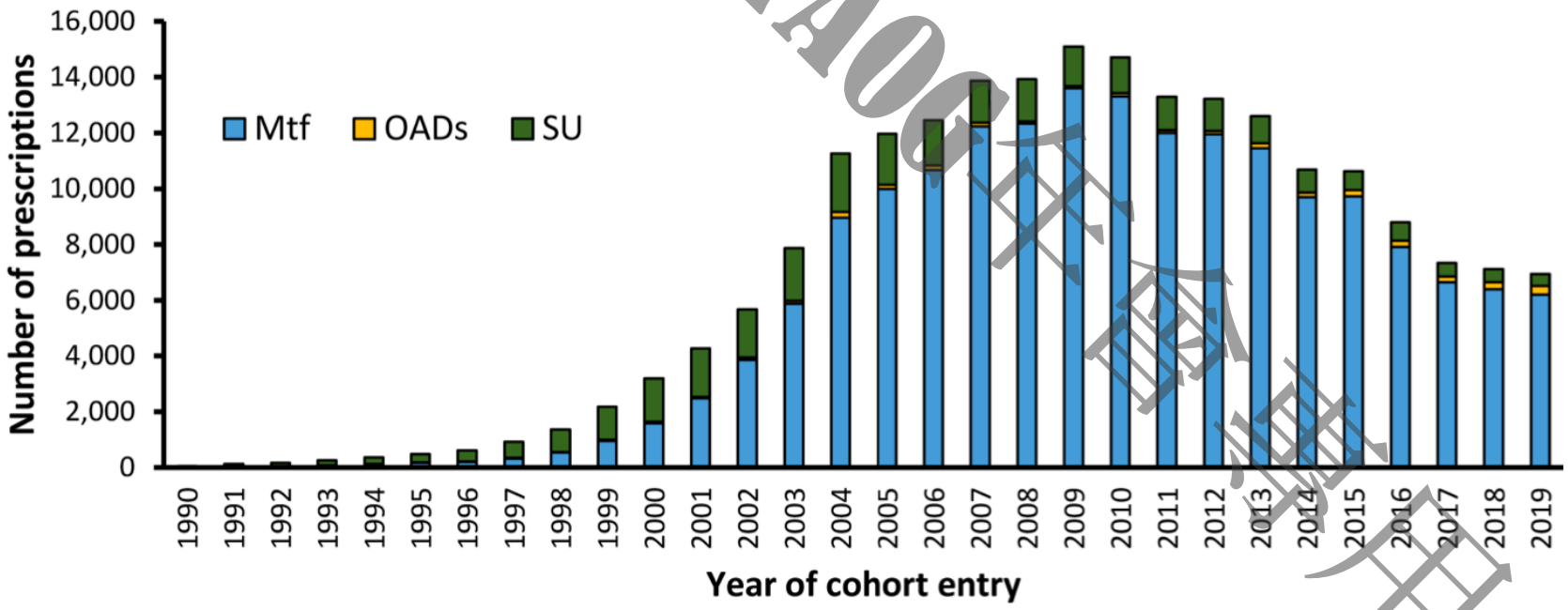
Metformin Dementia

Open access Original research

BMJ Open Diabetes Research & Care

Incident dementia risk among patients with type 2 diabetes receiving metformin versus alternative oral glucose-lowering therapy: an observational cohort study using UK primary healthcare records

Epidemiology/Health services research



BMJ Open Diab Res Care 2024;**12**:e003548. doi:10.1136/

Metformin - Demetia and Mild cognition impairement

- **Women life : 青少女 生育生殖 更年期 銀髮期**

Table 2 Associations of metformin versus alternative GLT with dementia and MCI

Exposure	N persons	N events	HR (95% CI)	SE	RMSE	P value
Dementia						
Age-adjusted						
Other GLTs	32 063	1650	1 (ref)		0.162	
Mtf	179 333	4992	1.01 (0.96 to 1.07)	0.029		0.653
Minimally adjusted (adjusted by age, sex and calendar time)						
Other GLTs	32 063	1650	1 (ref)		0.046	
Mtf	179 333	4992	0.83 (0.79 to 0.88)	0.024		<0.001
Fully adjusted*						
Other GLTs	16 547	713	1 (ref)		0.044	
Mtf	130 336	3282	0.87 (0.79 to 0.94)	0.038		0.001
MCI						
Age-adjusted						
Other GLTs	32 063	2438	1 (ref)		0.086	
Mtf	179 333	8366	1.00 (0.95 to 1.05)	0.023		0.98
Minimally adjusted (adjusted by age, sex and calendar time)						
Other GLTs	32 063	2438	1 (ref)		0.024	
Mtf	179 333	8366	0.92 (0.87 to 0.96)	0.022		<0.001
Fully adjusted*						
Other GLTs	16 547	1105	1 (ref)		0.035	
Mtf	130 336	5814	0.92 (0.86 to 0.99)	0.032		0.017

Excludes ethnicity.
*Adjusted for age, sex, calendar time, IMD, body mass index, smoking status, alcohol excess, statin use, antihypertensive use, hypertension, asthma, COPD, liver disease, coronary heart disease, peripheral vascular disease, stroke, diabetic retinopathy, neuropathy, brain injury, depression, autoimmune disease, CKD, heart failure, skin and soft tissue infection, urinary tract infection, lower respiratory tract infection, sepsis and baseline HbA1c.
CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; GLT, glucose-lowering therapy; HbA1c, hemoglobin A1c; IMD, Index of Multiple Deprivation; MCI, mild cognitive impairment; Mtf, merformin; RMSE, root mean-squared error.

Aging period

Chronic diseases

Disability

Infection

Dementia

MCI
Mild cognition impairment

Metformin ~ Dementia & MCI ~ T2D

Supportive vs Questionable

Less than 80y

Table 3 Associations of metformin versus alternative GLT with dementia and MCI stratified by age group and sex

	Exposure	N persons	N events	HR (95% CI)	P value
Dementia					
Age					
<80	Other GLTs	14 339	277	1 (ref)	
	Mtf	122 441	1542	0.78 (0.68 to 0.89)	<0.001
80+	Other GLTs	4725	436	1 (ref)	
	Mtf	21 401	1740	0.93 (0.83 to 1.03)	0.173
Sex					
Male	Other GLTs	5791	257	1 (ref)	
	Mtf	44 853	1256	0.87 (0.77 to 0.99)	0.03
Female	Other GLTs	3558	270	1 (base)	
	Mtf	31 499	1334	0.86 (0.76 to 0.97)	0.011
MCI					
Age					
<80	Other GLTs	14 339	623	1 (ref)	
	Mtf	122 441	3863	0.83 (0.76 to 0.91)	<0.001
80+	Other GLTs	4839	482	1 (ref)	
	Mtf	22 060	1951	1.05 (0.95 to 1.17)	0.35
Sex					
Male	Other GLTs	9986	587	1 (ref)	
	Mtf	75 587	2995	0.89 (0.81 to 0.98)	0.018
Female	Other GLTs	6561	518	1 (ref)	
	Mtf	54 749	2819	0.95 (0.86 to 1.05)	0.32

Interaction tests: dementia–age: p=0.03; dementia–sex: p=0.37; MCI–age: 0.0014; MCI–sex: 0.58.
GLT, glucose-lowering therapy; MCI, mild cognitive impairment; Mtf, metformin.

Metformin was better than other GLTs

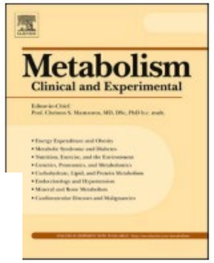
Table 4 Sensitivity analyses*

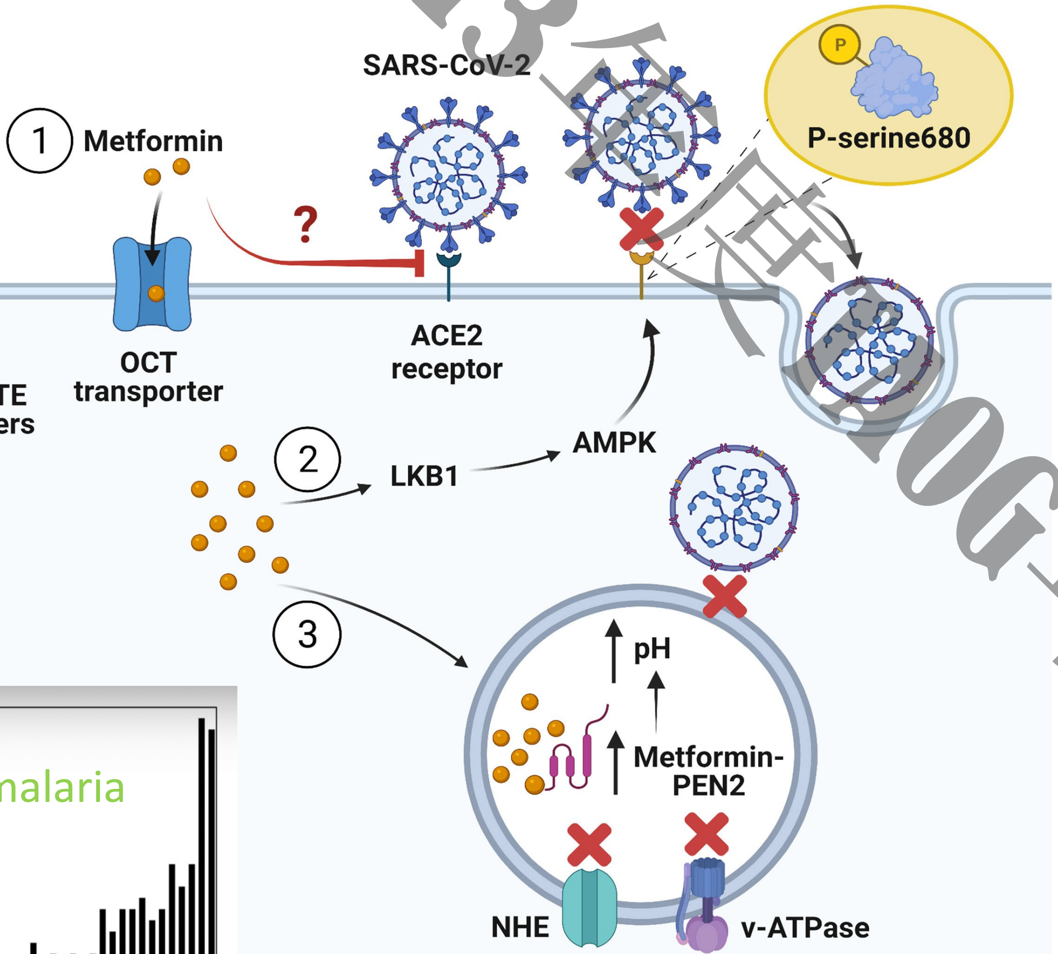
Exposure	N persons	N events	HR (95% CI)	P value
(1) (a) Lagged analysis excluding dementia diagnoses in first 3 months				
Other GLTs	16 042	697	1 (ref)	
Metformin	127 249	3239	0.88 (0.81 to 0.96)	0.004
(b) Excluding dementia diagnoses in first 6 months				
Other GLTs	15 498	679	1 (ref)	
Metformin	123 699	3182	0.88 (0.81 to 0.97)	0.008
(c) Excluding dementia diagnoses in first year				
Other GLTs	14 531	658	1 (ref)	
Metformin	116 211	3050	0.88 (0.80 to 0.96)	0.003
(d) Excluding dementia diagnoses in first 2 years				
Other GLTs	12 863	595	1 (ref)	
Metformin	102 177	2780	0.88 (0.81 to 0.97)	0.01
(2) Subgroup with entry post-2004				
Other GLTs	14 070	540	1 (ref)	
Metformin	124 374	2982	0.88 (0.80 to 0.97)	0.008
(3) Subgroup with entry post-2012				
Other GLTs	5261	106	1 ref)	
Metformin	54 989	681	0.88 (0.71 to 1.10)	0.26
(4) Restricted to those with HES linkage				
Other GLTs	7922	369	1 (ref)	
Metformin	60 692	1453	0.80 (0.71 to 0.90)	<0.001
(5) 'As-treated' analysis				
Other GLTs	16 539	713	1 (ref)	
Metformin	130 278	3282	0.90 (0.83 to 0.98)	0.021

*Confounder adjustment as per fully adjusted models in table 2.
GLTs, glucose-lowering therapies; HES, Hospital Episode Statistics.

BMJ Open Diab Res Care 2024;**12**:e003548. doi:10.1136

Metformin: Is it a drug for all reasons and diseases?





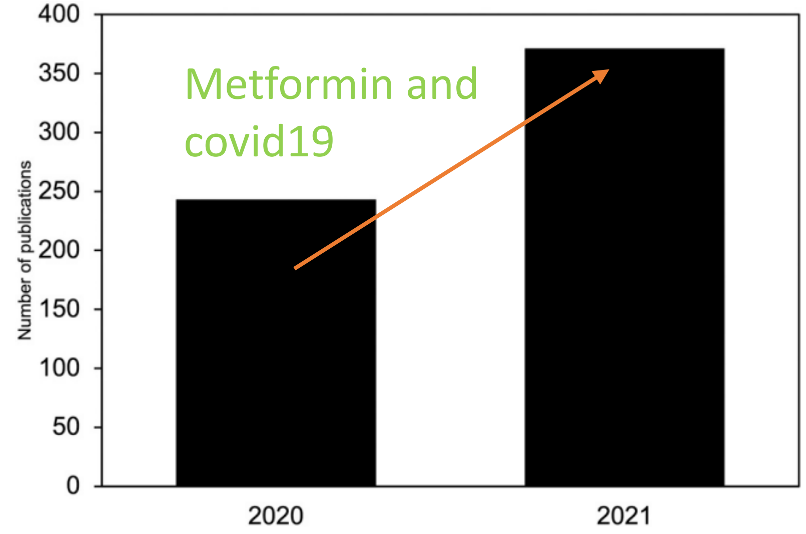
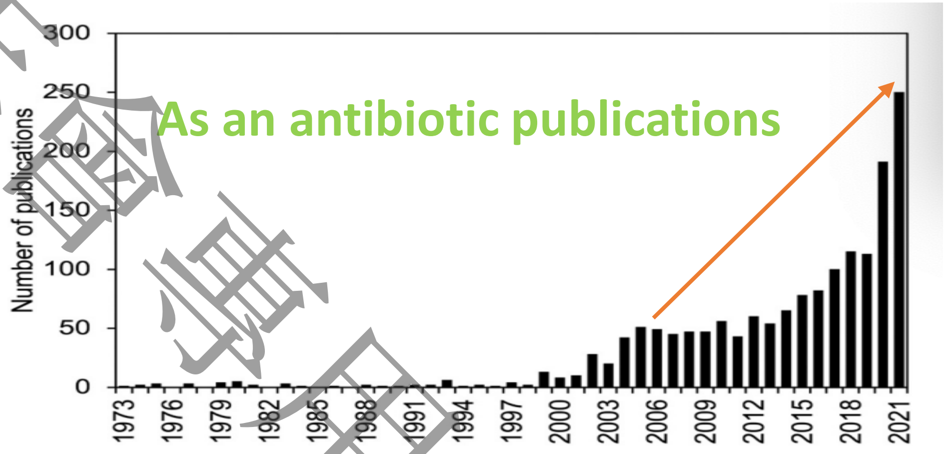
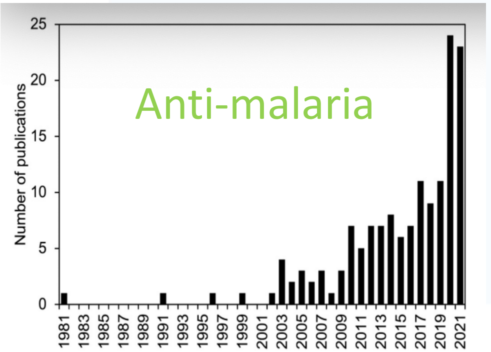


Fig. 13. Publications mentioning metformin and COVID-19. Data obtained





Metformin: Is it a drug for all reasons and diseases?

Dose-dependent effects of metformin on healthspan and lifespan in mice treated with 0.1% metformin (w/w supplement in diet) proving beneficial, whereas 1% proving toxic [335].

In older rodents calorie restriction, but not metformin, has been reported to extend average lifespan [338-342].

The UKPDS data [18, 24] with metformin highlight the CV benefits of reducing insulin resistance and hyperglycemia that also reduces the risk and impact of age-related diseases including cancer and neurodegenerative diseases, thereby improving healthspan.

Several studies have demonstrated that exposure of nematodes to metformin delays aging and enhances lifespan [45, 331, 332].

Metformin

Data from MASTERS (Metformin to Augment Strength Training Effective Response in Seniors) indicated that treatment of healthy female and males over 65 of age blunted the positive effects of exercise on skeletal muscle [42].

Metformin reduces lifespan in older nematodes and linked to reduced numbers of mitochondria [333].

No studies reported on effects of metformin on larvae of fruit flies.

Metformin activates AMPK but does not extend lifespan in either female or male fruit flies [334].

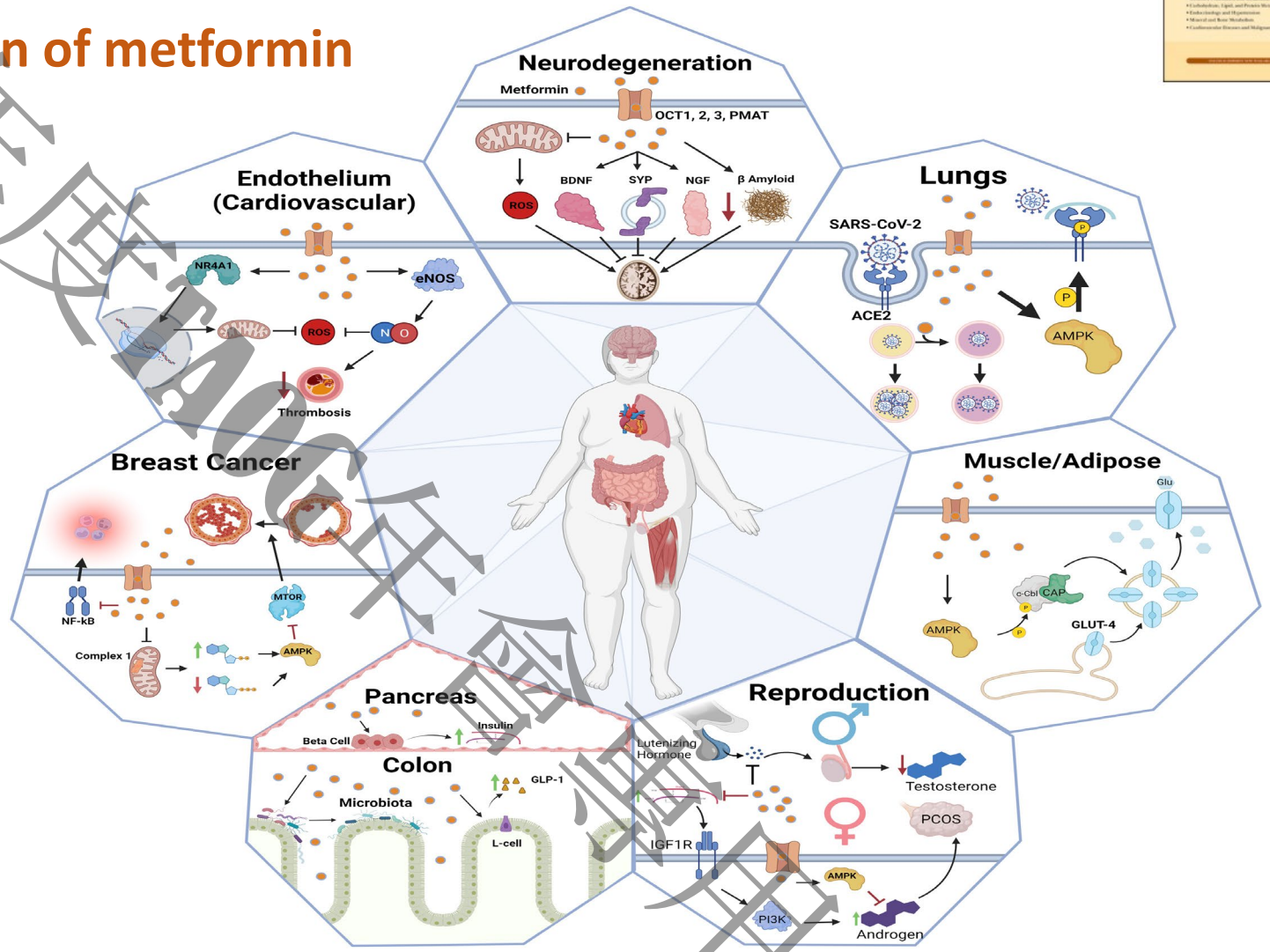
Controversial:

- life span
- dosage
- Elderly skeletal muscle

Metformin: Is it a drug for all reasons and diseases?

Potential targets for the action of metformin

- Neurodegeneration
- Lung
- Muscle/adipose
- Reproduction
- Pancreas/colon
- Breast cancer
- Endothelium/ CVD
- …



Metformin promotes woman health

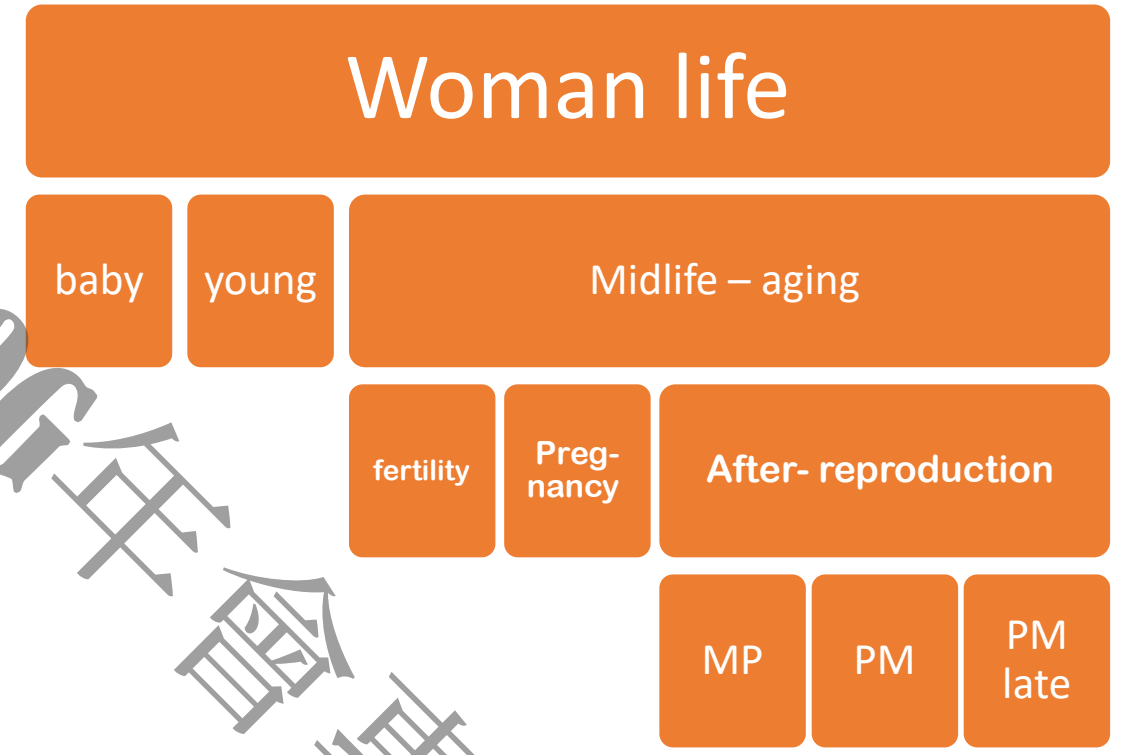
- **Woman life -** 青少女 生育生殖 更年期 銀髮期

	Menarche						FMP (0)			
Stage	-5	-4	-3b	-3a	-2	-1	+1 a	+1b	+1c	+2
Terminology	REPRODUCTIVE				MENOPAUSAL TRANSITION		POSTMENOPAUSE			
	Early	Peak	Late		Early	Late	Early			Late
					Perimenopause					
Duration	*variable*				*variable*	1-3 years	2 years (1+1)	3-6 years		*Remaining lifespan*
PRINCIPAL CRITERIA										
Menstrual Cycle	Variable to regular	Regular	Regular	Subtle changes in Flow/ Length	*Variable Length* Persistent ≥7- day difference in length of consecutive cycles	Interval of amenorrhea of >=60 days				
SUPPORTIVE CRITERIA										
Endocrine FSH AMH Inhibin B			Low Low	Variable* Low Low	↑ Variable* Low Low	↑ >25 IU/L** Low Low	↑ Variable Low Low	Stabilizes Very Low Very Low		
Antral Follicle Count			Low	Low	Low	Low	Very Low	Very Low		
DESCRIPTIVE CHARACTERISTICS										
Symptoms						Vasomotor symptoms *Likely*	Vasomotor symptoms *Most Likely*			*Increasing* symptoms of urogenital atrophy

* Blood draw on cycle days 2-5 ↑ = elevated

**Approximate expected level based on assays using current international pituitary standard[67-69]

J Clin Endocrinol Metab. 2012;97(4):1159.



Metformin promotes woman health ~ Reproduction ~

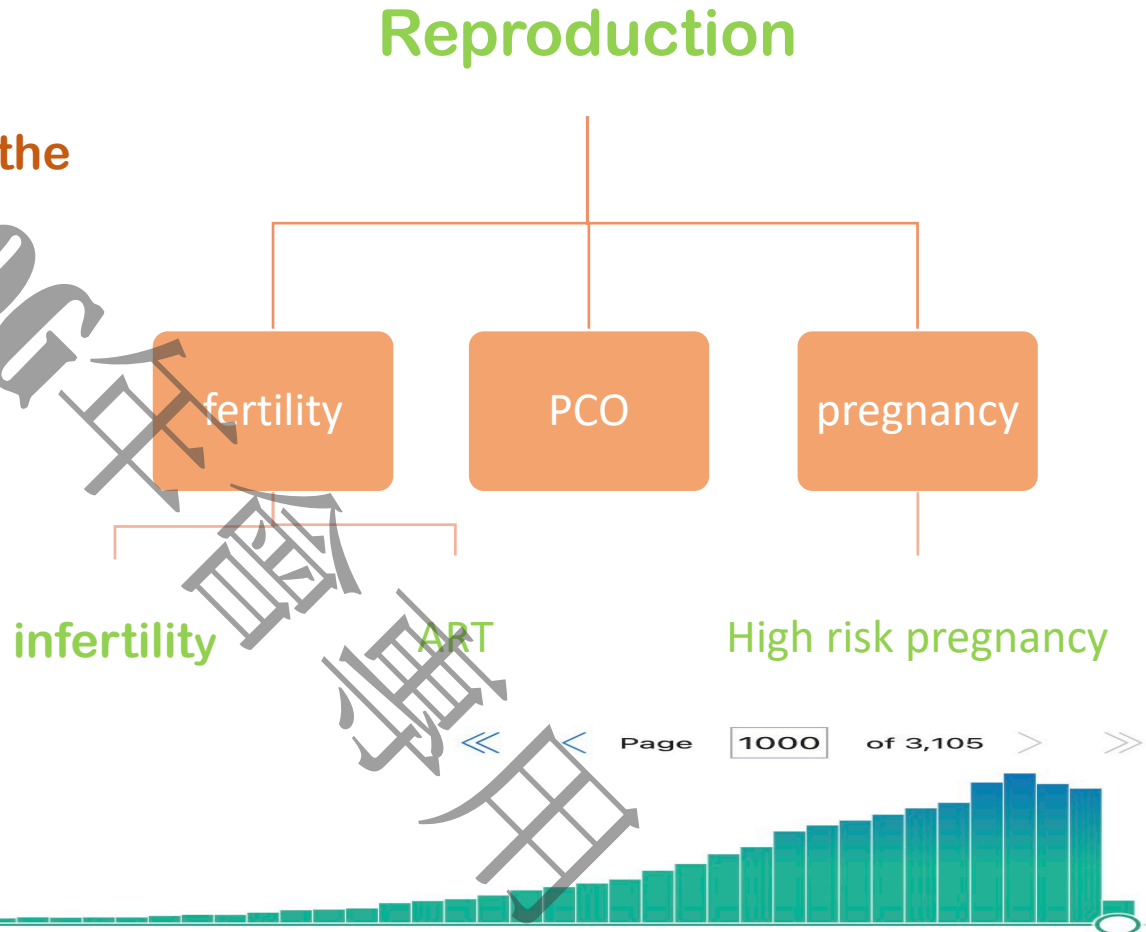
- Women life : 青少女 生育生殖 更年期 銀髪期

✓ 2023 Recommendations
International evidence–based guideline for the assessment and management of PCOS

✓ Metformin for Diabetes in Pregnancy
Are we closer to defining its role?

Metformin Plus Insulin for preexisting Diabetes or Gestational diabetes in early pregnancy

The MOMPOD Randomized Clinical trial
JAMA 2023; 330(22):2182-90



Metformin and PCOS -1

Recommendations from the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome†

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建議等級與品質

EBR >CR > PP

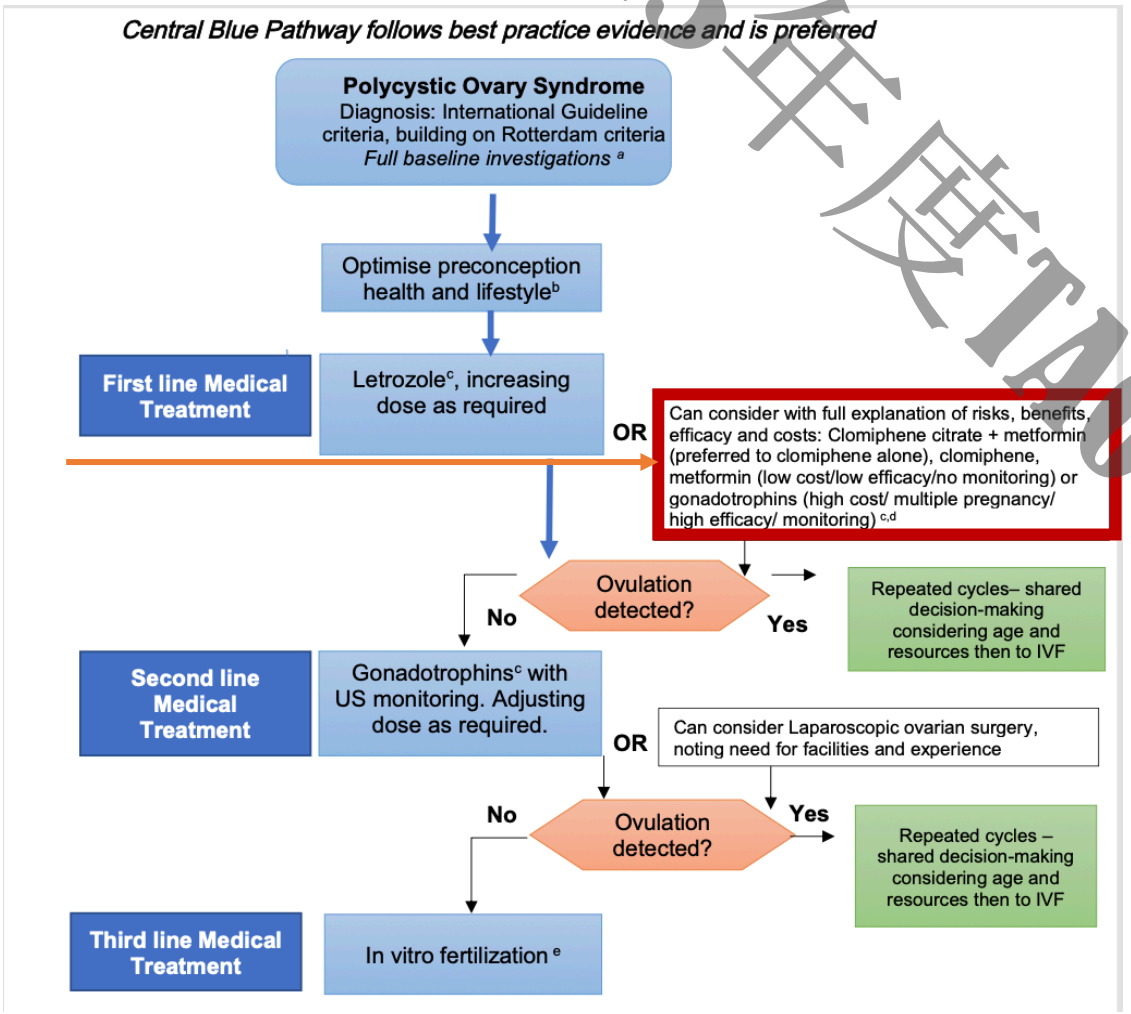
Categories of PCOS guideline recommendations

EBR	Evidence Based Recommendations: Evidence sufficient to inform a recommendation made by the guideline development group.
CR	Consensus Recommendations: In the absence of adequate evidence, a consensus recommendation has been made by the guideline development group, also informed by evidence from the general population.
PP	Practice Points: Evidence not sought. A practice point has been made by the guideline development group where important issues arose from discussion of evidence-based or consensus recommendations.

PCOS, polycystic ovary syndrome.

Teede. International PCOS Guideline 2023. Fertil Steril 2023.

Metformin and PCOS -2



a. Baseline investigations (see narrative):
   i. Diagnosis of PCOS - Endocrine profile and pelvic ultrasound scan
   ii. Assessment of BMI, BP & glycemic status (OGTT / HbA1c)
   iii. Routine preconception assessments (Rubella immunity, infection screen etc..), advice and supplementation.
   iv. Additional investigations: semen analysis and consider tubal patency assessment
b. Healthy lifestyle encompassing healthy eating and regular physical activity should be recommended in all those with PCOS to limit adverse impacts on fertility and fertility treatment outcomes and to optimize health during pregnancy
c. Off label prescribing: Letrozole, metformin and other pharmacological treatments are generally off label in PCOS, as pharmaceutical companies have not applied for approval in this condition. However, recommended off label use is evidence-based and allowed in many countries. Where it is allowed, health professionals should inform women and discuss the evidence, possible concerns and side effects of treatment.
d. Compared to letrozole, metformin has lower efficacy, cost and multiple pregnancy rate and gonadotrophins have higher efficacy, cost and multiple pregnancy rate. Both may be an alternative first line choice for informed women.
e. In vitro fertilization (IVF) - Third line unless other infertility factors (e.g. male, tubal). PCOS specific protocols to minimise risk of ovarian hyperstimulation syndrome, consider invitro maturation if available.

Metformin and PCOS -3

Quality (certainty) of evidence categories (adapted from GRADE)

High	⊕⊕⊕⊕	Very confident that the true effect lies close to that of the estimate of the effect.
Moderate	⊕⊕⊕◯	Moderate confidence in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is different.
Low	⊕⊕◯◯	Limited confidence in the effect estimate. The true effect may be substantially different from the estimate of the effect.
Very Low	⊕◯◯◯	Very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect.

GRADE, Grading of Recommendations, Assessment, Development, and Evaluation.

Teede. International PCOS Guideline 2023. Fertil Steril 2023.

The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework recommendation strength

❖	Conditional recommendation against the option.
❖❖	Conditional recommendation for either the option or the comparison.
❖❖❖	Conditional recommendation for the option.
❖❖❖❖	Strong recommendation for the option.

Teede. International PCOS Guideline 2023. Fertil Steril 2023.

⊕ Quality of evidence

◆ Recommendation for the option

Metformin and PCO - 4

Quality of evidence

5.4		**Clomiphene citrate and metformin**		
5.4.1		**Metformin versus placebo**		
5.4.1.1	EBR	Metformin could be used alone, in women with PCOS with anovulatory infertility and no other infertility factors, to improve clinical pregnancy and live birth rates, whilst informing women that there are more effective ovulation agents.	❖❖❖ ⊕⊕◯◯	Metformin vs placebo Conditional recommendation For the option
5.4.1.2	PP	Women should be counselled as to potential mild gastrointestinal side-effects with metformin.		
5.4.1.3	PP	Healthcare and resource burden including monitoring, travel and costs are lower with metformin.		Low Quality of evidence
5.4.1.4	PP	Consideration of age and screening for other fertility factors needs to be discussed before prescribing metformin.		
5.4.2		**Clomiphene citrate verses metformin**		
5.4.2.1	EBR	Clomiphene citrate could be used in preference to metformin in women with PCOS with anovulatory infertility and no other infertility factors, to improve ovulation, clinical pregnancy and live birth rates.	❖❖❖ ⊕⊕◯◯	CC vs Metformin
5.4.2.2	PP	The risk of multiple pregnancy is increased with clomiphene citrate use (alone or in combination with metformin) and therefore clomiphene cycles may require ultrasound monitoring.		
5.4.3		**Clomiphene citrate and metformin verses clomiphene citrate alone**		
5.4.3.1	EBR	Clomiphene citrate combined with metformin could be used rather than clomiphene citrate alone in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation and clinical pregnancy rates.	❖❖❖ ⊕⊕◯◯	CC+Metformin vs CC
5.4.4		**Clomiphene citrate and metformin versus metformin alone**		
5.4.4.1	EBR	Clomiphene citrate combined with metformin could be used rather than metformin alone in women with PCOS with anovulatory infertility and no other infertility factors to improve live birth rates.	❖❖❖ ⊕⊕◯◯	CC+metformin vs metformin
5.4.4.2	PP	Monitoring of combined cycles will need to be equivalent to clomiphene citrate alone.		

Fertility and Sterility® 2024

Metformin and PCO -IVF

5.7.5		**Adjunct metformin**	
5.7.5.1	EBR	Adjunct metformin therapy could be used before and/or during FSH ovarian stimulation in women with PCOS undergoing IVF/ICSI treatment with GnRH agonist long protocol, to reduce the risk of developing ovarian hyperstimulation syndrome and miscarriage.	❖❖❖ ⨁⨁○○
5.7.5.2	PP	Good practice in PCOS and IVF is the use of a GnRH antagonist protocol as it gives the flexibility of using a GnRH agonist trigger, freeze all strategy to reduce the risk of ovarian hyperstimulation syndrome. However, if using a GnRH agonist long protocol then metformin could be considered. If using metformin, the following could be considered: • Commence metformin at the start of GnRH agonist treatment. • Gradually titrate metformin up to a dose of between 1000mg to 2500mg daily in order to minimize side effects. • Stopping metformin therapy at the time of the pregnancy test or period, unless the metformin therapy is otherwise indicated.	

Adjunct metformin
Conditional recommendation
For the option
Low evidence

- **1000-2500 mg**
- **Add B12 ; Reduce the risk of OHSS**

Metformin & Weight loss

Time course and dose effect of metformin on weight in patients with different disease states

Table 2. Parameter estimates of final model and 90% confidential interval.

Model	Parameter	Estimate	Simulation (n = 1000) median	90% confidence interval
i	E_{max}, %	−6.86	−6.86	[−6.86, −6.86]
	ET_{50}, week	107	127	[2, 155]
	ω_{Emax}	15.427	15.427	[0.003, 29.715]
	ω_{ET50}	0.381	0.315	[0.003, 207.605]
	ε	0.316	0.316	[0.010, 1.860]
ii	E_{max}, %	−8.82	−8.82	[−8.82, −8.82]
	ET_{50}, week	45.5	46.7	[27.8, 219.3]
	ω_{Emax}	16.793	15.684	[8.189, 98.951]
	ω_{ET50}	0.048	0.073	[0.003, 16.188]
	ε	1.217	1.175	[0.522, 1.825]
iii	E_{max}, %	−4.14	−4.14	[−4.14, −4.14]
	ET_{50}, week	15.1	12.7	[0.5, 57.0]
	ω_{Emax}	2.198	1.480	[0.003, 2.988]
	ω_{ET50}	0.003	0.003	[0.003,45.497]
	ε	0.01	0.01	[0.01, 0.01]

90% confidential interval was displayed as the 5th, 95th percentile of Monte Carlo simulations. i, patients with type 2 diabetes mellitus; ii, patients with antipsychotic induced weight gain; iii, patients with obesity; E_{max}, the maximal effects; ET_{50}, the treatment duration to reach half of the the maximal effects; ω_{Emax}, inter-study variability of E_{max}; ω_{ET50}, inter-study variability of ET_{50}; ε, residual error.

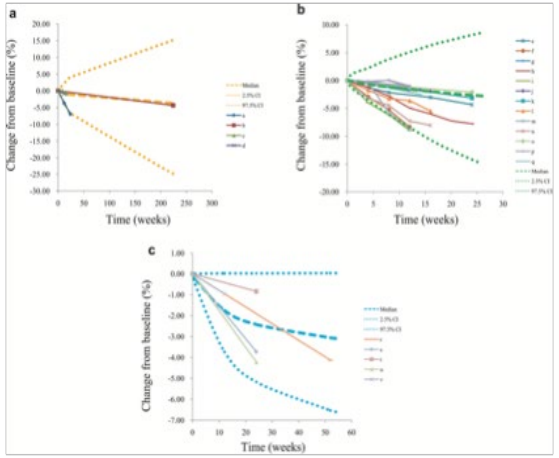


Figure 2. Prediction-corrected visual predictive check plots.

(a) Patients with type 2 diabetes mellitus, (b) patients with antipsychotic induced weight gain, and (c) patients with obesity; Median, 2.5% CI and 97.5% CI were simulated by Monte Carlo (n = 1000); CI, confidence interval; a, Lee et al. [16]; (b) Out et al. [17]; (c) Wu et al. [18]; (d) Esteghamati et al. [19]; (e) Chen et al. [20]; (f) Wu et al. [21]; (g) Baptista et al. [22]; (h) Wu et al. [23]; (i) Wang et al. [24]; (j) Jarskog et al. [25]; (k) Rado et al. [26]; (l) Klein et al. [27]; (m) Wu et al. [28]; (n) Peng et al. [29]; (o) Wu et al. [30]; (p) Chiu et al. [31]; (q) Carrizo et al. [32]; (r) Yanovski et al. [33]; (s) Pastor-Villaescusa et al. [34]; (t) Pastor-Villaescusa et al. [34]; (u) Mauras et al. [35]; (v) Lim et al. [36].

maximum efficacy; and (e) for patients with obesity, a dose of 1000 mg/day metformin is required for 15.1 weeks to play a better effect, 61 weeks to achieve maximum efficacy.

As is well-known, current evidence shows that the effects of metformin on weight are likely to be a decrease in caloric intake and direct and indirect effects on appetite regulation

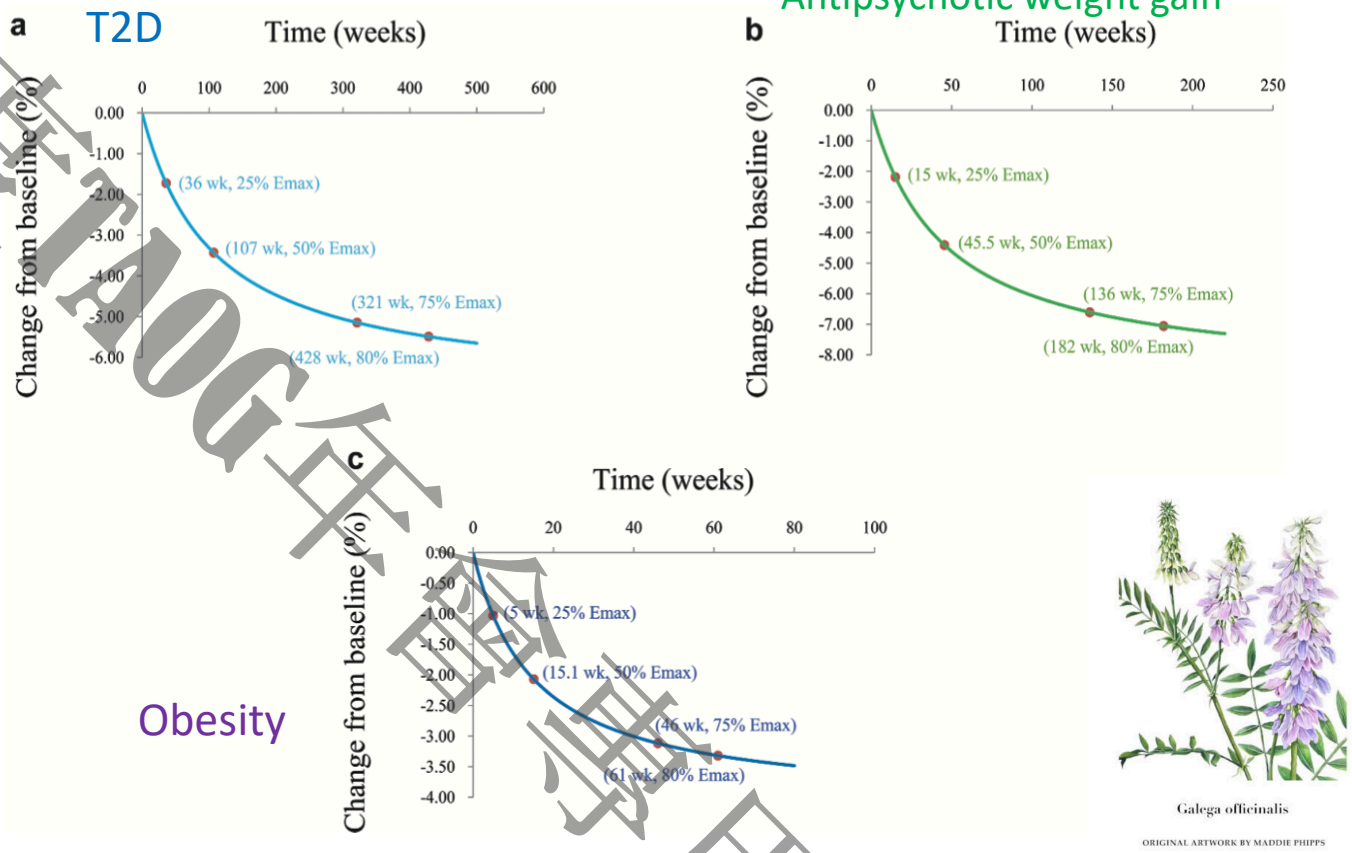


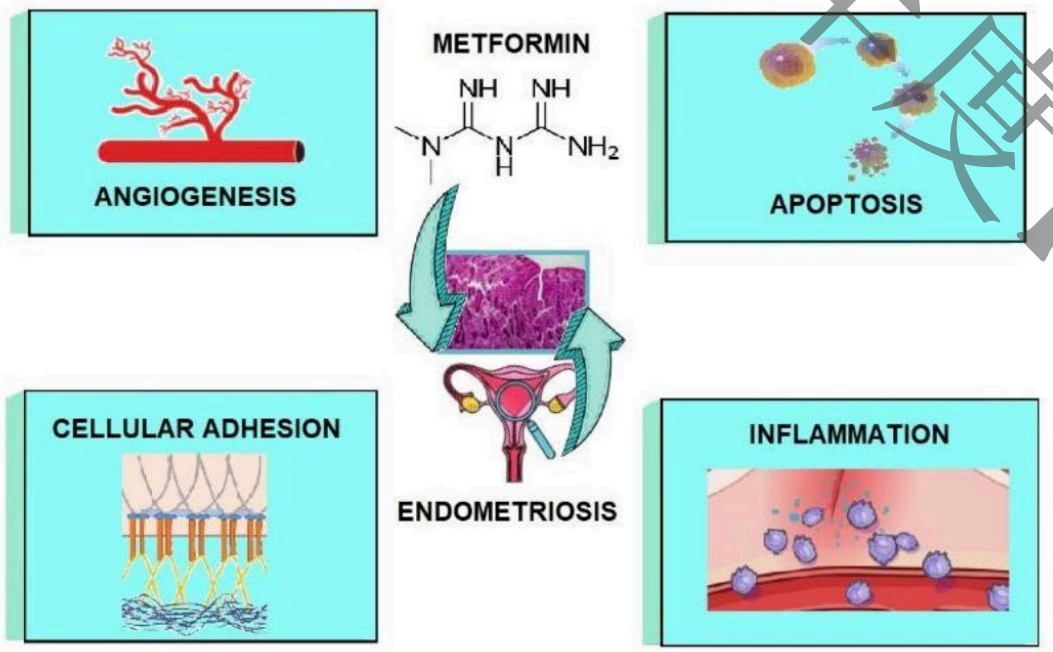
Figure 3. Model prediction.

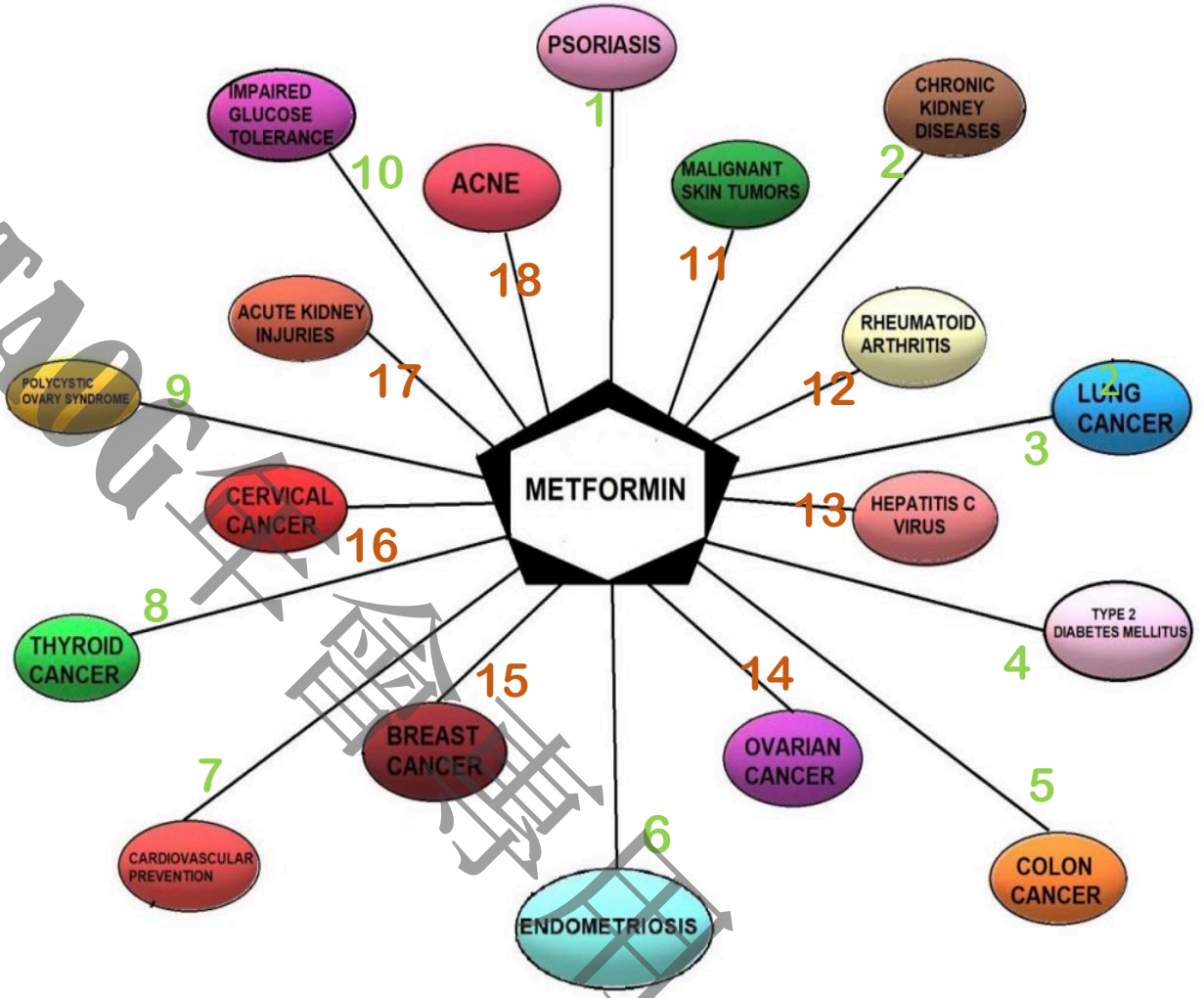
(a) Patients with type 2 diabetes mellitus, (b) patients with antipsychotic induced weight gain, and (c) patients with obesity; wk, weeks.

Metformin & Endometriosis

Review

Metformin as a Potential Treatment Option for Endometriosis





- ✓ Apoptosis
- ✓ Inflammation
- ✓ Cellular adhesion
- ✓ angiogenesis

Cancers 2022, 14, 577. https://doi.org/10.3390/cancers14030577

Metformin pregnancy

JAMA | Original Investigation

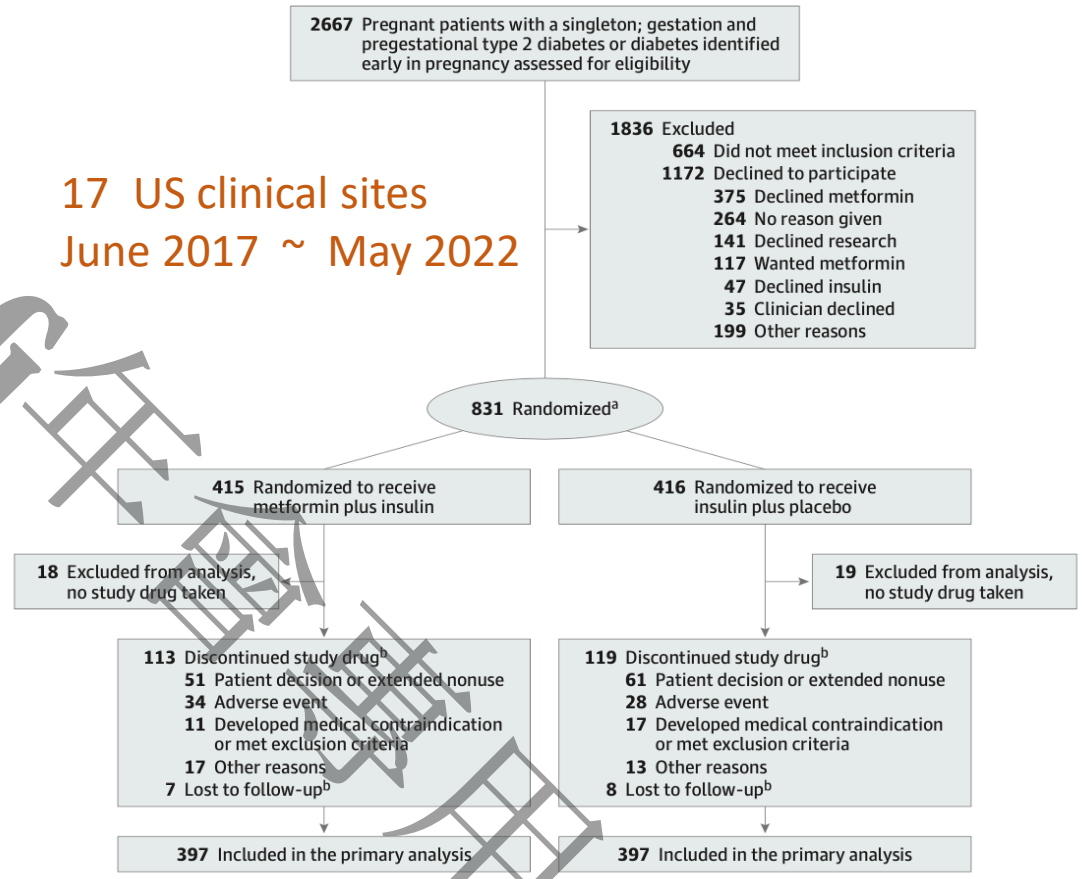
Metformin Plus Insulin for Preexisting Diabetes or Gestational Diabetes in Early Pregnancy
The MOMPOD Randomized Clinical Trial (1)

Table 1. Study Participant Baseline Characteristics (continued)

	No. (%)[a]	
	Metformin plus insulin (n = 397)	Insulin plus placebo (n = 397)
Gestational age at enrollment, wk[f]		
18 to <23	162 (41)	165 (42)
<18	235 (59)	232 (58)
HbA_{1c} % at enrollment[d]	n = 361	n = 361
Mean (SD)	7.7 (2.02)	7.7 (1.97)
Median (IQR)	7.2 (6.0-9.1)	7.3 (6.1-9.1)
Gestational age at HbA_{1c} measurement, mean (SD), wk	11.1 (4.4)	10.6 (5.4)
Gestational age at HbA_{1c} measurement, median (IQR), wk	10.3 (7.9-14.1)	10.3 (7.4-13.7)

17 US clinical sites
June 2017 ~ May 2022

Figure. MOMPOD Study Flow Diagram



Metformin pregnancy

JAMA | Original Investigation

Metformin Plus Insulin for Preexisting Diabetes or Gestational Diabetes in Early Pregnancy
The MOMPOD Randomized Clinical Trial (2)

Table 1. Study Participant Baseline Characteristics

	No. (%)[a]	
	Metformin plus insulin (n = 397)	Insulin plus placebo (n = 397)
Demographics		
Age, mean (SD), y	32.8 (5.5)	33.1 (5.7)
Race[b]		
American Indian or Alaska Native	3 (1)	1 (0)
Asian	10 (3)	13 (3)
Black or African American	119 (30)	115 (29)
Native Hawaiian or Other Pacific Islander	2 (1)	2 (1)
White	55 (14)	57 (14)
≥ 2 Races	8 (2)	2 (1)
Not reported or declined to report	95 (24)	97 (24)
Hispanic ethnicity[b]		
No	194 (49)	188 (47)
Yes	203 (51)	209 (53)
Diabetes characteristics		
Preexisting type 2 diabetes requiring medical therapy prior to pregnancy	311 (78)	313 (79)
Diagnosis of diabetes early in pregnancy	86 (22)	84 (21)
Use of diabetes medication prior to pregnancy	174 (44)	181 (46)
Metformin used earlier in pregnancy	162 (41)	175 (44)
Criteria to diagnose diabetes early in pregnancy[c]	n = 86	n = 84
HbA_{1c} ≥6.5%[d]	25 (29)	22 (26)
Fasting blood glucose ≥126 mg/dL	5 (6)	5 (6)
1-h OGTT≥200 mg/dL[d]	18 (21)	24 (29)
2-Step method positive	25 (29)	20 (24)
1-Step method positive	12 (14)	12 (14)
Other clinical characteristics and laboratory results		
Chronic hypertension requiring medication	103 (26)	86 (22)
Smoking during pregnancy	28 (7)	32 (8)
Body mass index at enrollment[e]	n = 383	n = 379
Mean (SD)	36.4 (8.0)	36.3 (8.9)
Median (IQR)	35.2 (31.2-41.1)	34.4 (29.6-41.5)
Distribution		
<30	76 (19)	105 (26)
30 to <40	198 (50)	164 (41)
≥40	109 (27)	110 (28)

Asian population was samll
Hispanic ethinity: 51%

Preexisiting T2D : 78%

Metformin used earlier in pregancy: 41, 44%

Chronic hypertension requireing medication 26,22%

BMI : 36.4, 36.3

JAMA. Dec. 12. 2023;330(22):2182-2190. doi:10.1001/jama.2023.22949

Metformin pregnancy

JAMA | Original Investigation

Metformin Plus Insulin for Preexisting Diabetes or Gestational Diabetes in Early Pregnancy
The MOMPOD Randomized Clinical Trial (3)

Table 2. Primary Composite Neonatal Outcome and Components

	Metformin plus insulin (n = 397)[a]	Insulin plus placebo (n = 397)[a]	Unadjusted absolute difference (95% CI)	Adjusted odds ratio (95% CI)[b]
Composite primary outcome[c]	280 (71)	292 (74)	−3.95 (−11.49 to 3.99)	0.86 (0.63 to 1.19)
Live births[d]	386 (97)	384 (97)		
Fetal and neonatal death	11 (3)	13 (3)	−4.30 (−24.54 to 15.95)	0.83 (0.36 to 1.89)
Miscarriage <20 wk	7 (2)	4 (1)		
Stillbirth ≥20 wk	3 (1)	7 (2)		
Neonatal death <28 d	1 (<1)	2 (1)		
Preterm birth <37 wk	130 (34)	143 (37)	−3.89 (−11.27 to 3.49)	0.86 (0.64 to 1.16)
Neonatal hypoglycemia	152 (39)	162 (42)	−2.91 (−10.09 to 4.28)	0.89 (0.67 to 1.19)
Birth trauma	16 (4)	16 (4)	−0.14 (−17.83 to 17.56)	1.02 (0.50 to 2.07)
Umbilical artery pH <7.05	9 (2)	9 (2)		
Shoulder dystocia	7 (2)	7 (2)		
Hyperbilirubinemia requiring phototherapy	87 (23)	92 (24)	−1.99 (−10.35 to 6.37)	0.93 (0.66 to 1.30)
Large for gestational age (>90th percentile)	100 (26)	137 (36)	−11.46 (−19.04 to −3.88)	0.63 (0.46 to 0.86)
Small for gestational age (<10th percentile)	30 (8)	26 (7)	3.71 (−9.86 to 17.28)	1.17 (0.68 to 2.02)
Low birth weight (<2500 g)	81 (21)	73 (19)	3.08 (−5.73 to 11.90)	1.14 (0.80 to 1.63)

Metformine plus insulin has no increased risk than Insulin pregants

Metformine plus insulin has lesser large for gestational age (>90th percentile)

JAMA. 2023;330(22):2182-2190. doi:10.1001/jama.2023.22949

Metformin for woman health after reproduction

Woman life: 更年期　銀髪期

Lower cancer risk &
Increase survival through better treatment

Reduce chronic diseases
Weight loss
Proper lifestyle

Mental health - anti-aging
⬇ Neurodegenerative
⬆ Neuroprotection

✓ Breast cancer
- ◆With T2D
- ◆Without T2D
- ◆Residual cancer

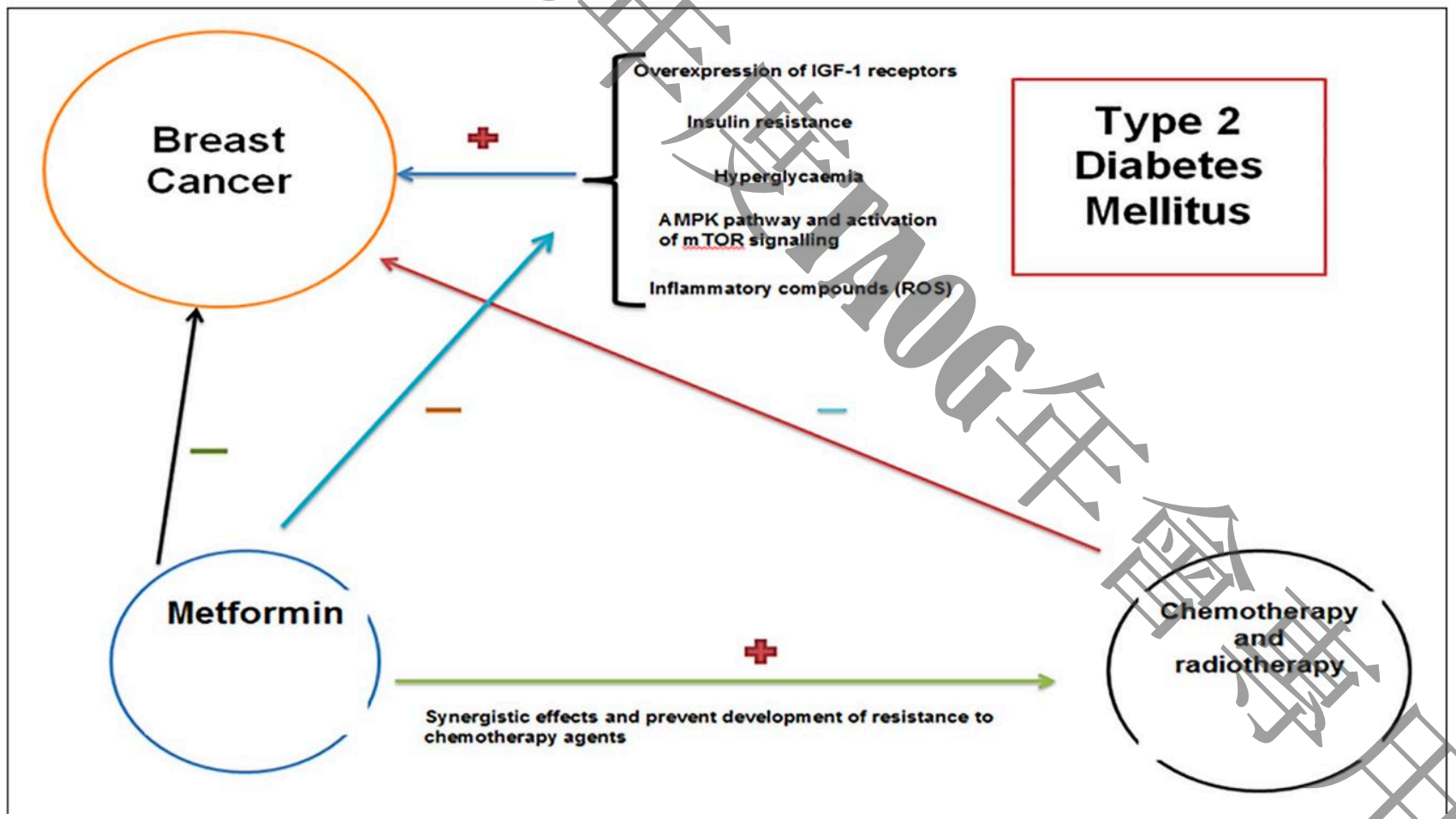
✓ Endometrial cancer
Endometrial hyperplasia

1959 2024

Metformin as an adjuvant in breast cancer treatment

SAGE Open Medicine
Volume 7: 1–16

DOI: 10.1177/2050312119865114
journals.sagepub.com/home/smo



Metformin
850 mg bid

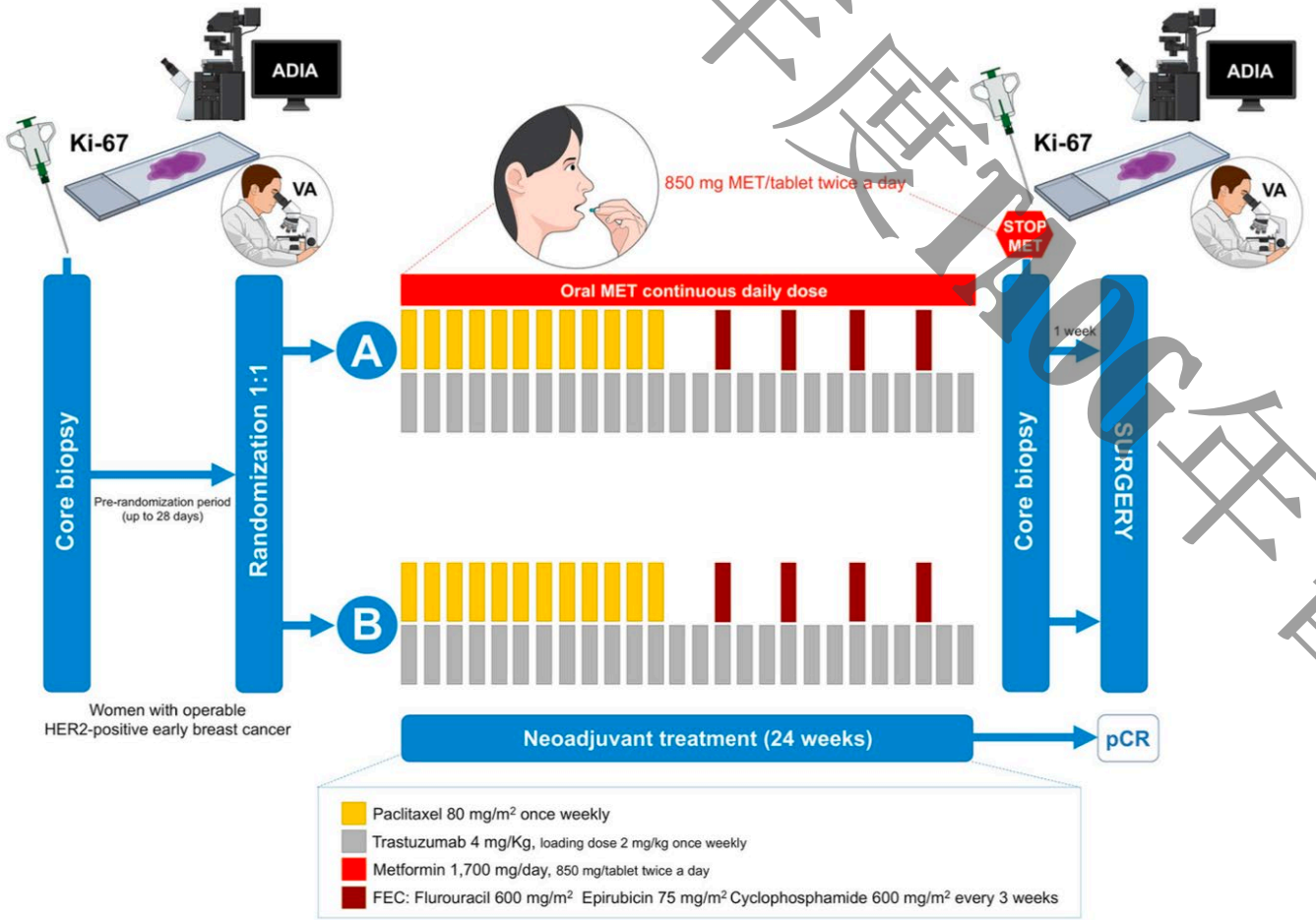
Before surgery
Before chemotherpy

Metformin BRCA

Communication

Neoadjuvant Metformin Added to Systemic Therapy Decreases the Proliferative Capacity of Residual Breast Cancer

Prospective pre-sx treatment



Metformin 850 mg bid

⬇proliferative ⬇遠端轉移

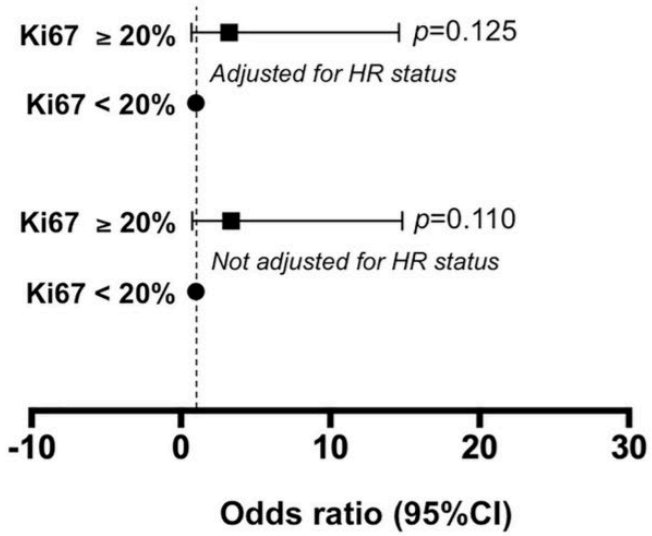
Abstract: The proliferative capacity of residual breast cancer (BC) disease indicates the existence of partial treatment resistance and higher probability of tumor recurrence. We explored the therapeutic potential of adding neoadjuvant metformin as an innovative strategy to decrease the proliferative potential of residual BC cells in patients failing to achieve pathological complete response (pCR) after pre-operative therapy. We performed a prospective analysis involving the intention-to-treat population of the (Metformin and Trastuzumab in Neoadjuvancy) METTEN study, a randomized multicenter phase II trial of women with primary, non-metastatic (human epidermal growth factor receptor 2) HER2-positive BC evaluating the efficacy, tolerability, and safety of oral metformin (850 mg twice-daily) for 24 weeks combined with anthracycline/taxane-based chemotherapy and trastuzumab (arm A) or equivalent regimen without metformin (arm B), before surgery. We centrally evaluated the proliferation marker Ki67 on sequential core biopsies using visual assessment (VA) and an (Food and Drug Administration) FDA-cleared automated digital image analysis (ADIA) algorithm. ADIA-based pre-operative values of high Ki67 (≥20%), but not those from VA, significantly predicted the occurrence of pCR in both arms irrespective of the hormone receptor status ($p = 0.024$ and 0.120, respectively). Changes in Ki67 in residual tumors of non-pCR patients were significantly higher in the metformin-containing arm ($p = 0.025$), with half of all patients exhibiting high Ki67 at baseline moving into the low-Ki67 (<20%) category after neoadjuvant treatment. By contrast, no statistically significant changes in Ki67 occurred in residual tumors of the control treatment arm ($p = 0.293$). There is an urgent need for innovative therapeutic strategies aiming to provide the protective effects of decreasing Ki67 after neoadjuvant treatment even if pCR is not achieved. Metformin would be evaluated as a safe candidate to decrease the aggressiveness of residual disease after neoadjuvant (pre-operative) systemic therapy of BC patients.

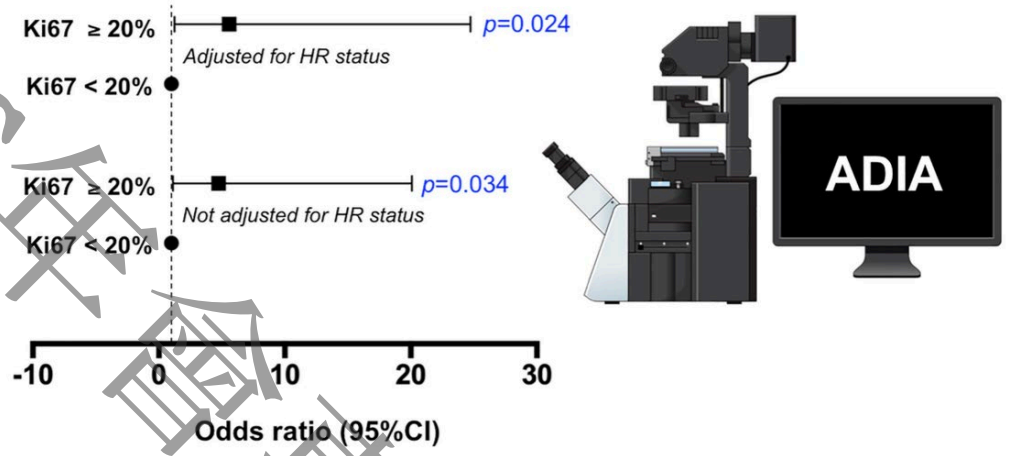
Keywords: metformin; Ki67; breast cancer; residual disease

Metformin BRCA

Communication

Neoadjuvant Metformin Added to Systemic Therapy Decreases the Proliferative Capacity of Residual Breast Cancer

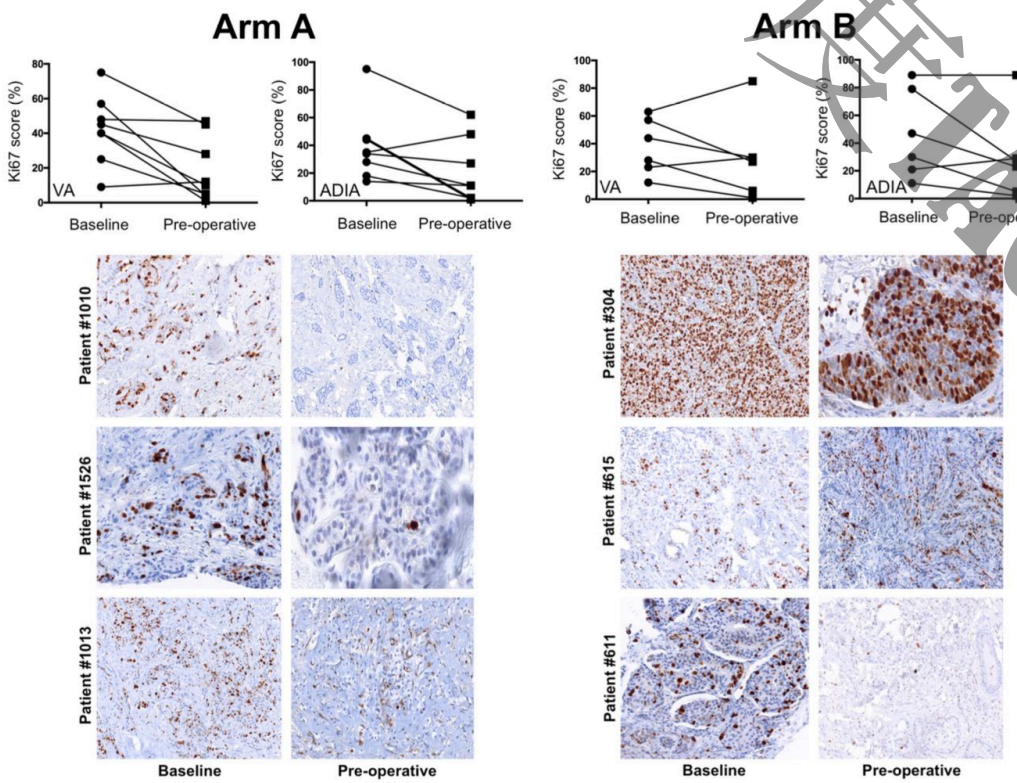




Metformin BRCA

Communication

Neoadjuvant Metformin Added to Systemic Therapy Decreases the Proliferative Capacity of Residual Breast Cancer



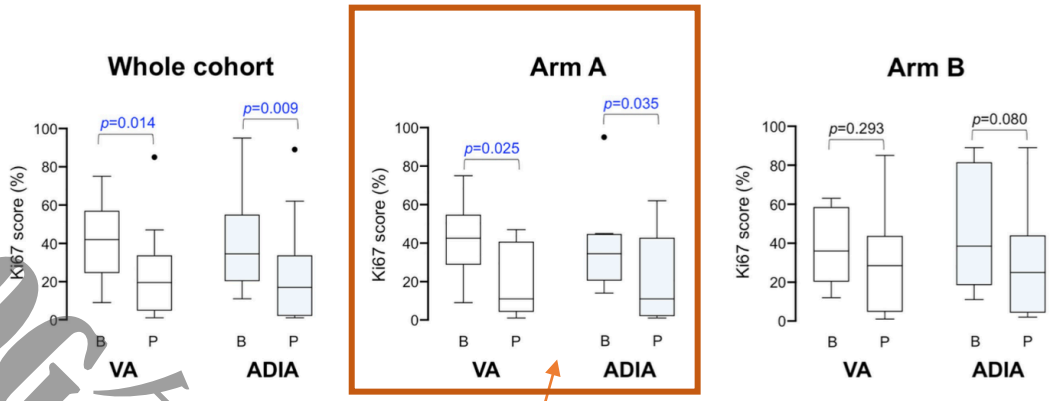


Figure 4. Global changes in Ki67 scores among METTEN study patients with a residual tumor after neoadjuvant treatment. Box plots showing the distribution of Ki67 values in baseline (B) and pre-operative (P) core biopsies in the whole population and stratified by treatment arms. The figure shows the median values (horizontal bars within boxes) and 25th and 75th percentile (lower and upper horizontal lines of the boxes); whiskers extend 1.5 times the interquartile range from the 25th and 75th percentiles. Circles: outliers.

More Ki67 difference
Was showed on Arm A

Arm A- metformin (+)
Arm B - metformin (-)

Metformin RCT non-T2D BRCA

JAMA | Original Investigation

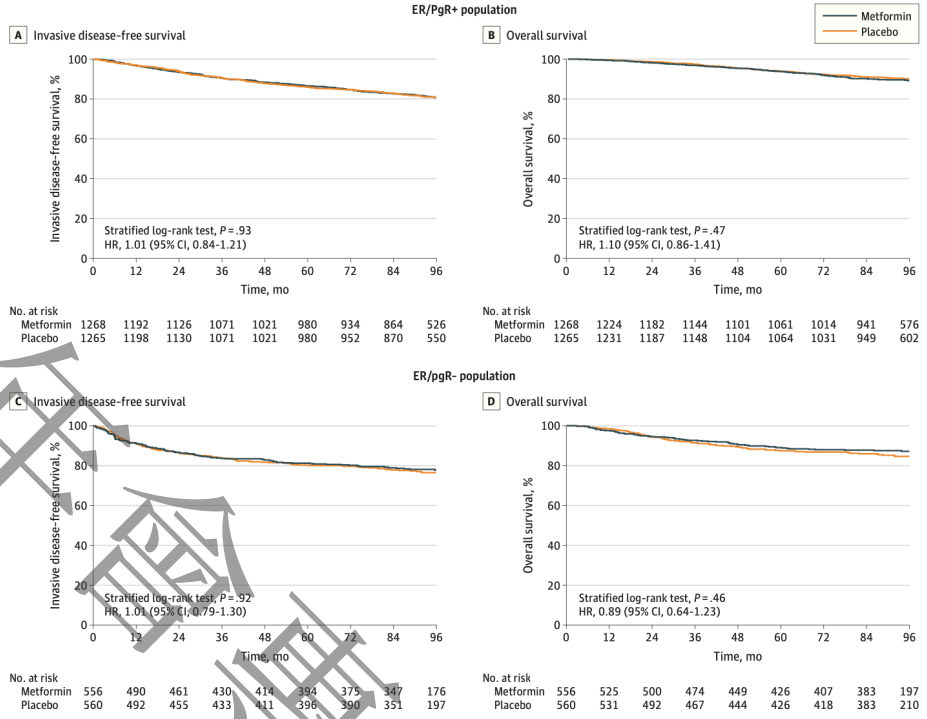
Effect of Metformin vs Placebo on Invasive Disease-Free Survival in Patients With Breast Cancer
The MA.32 Randomized Clinical Trial

2010~2020
95-96 months follow up

Table 2. Breakdown of Invasive Disease-Free Survival and Overall Survival Events in Patients With Breast Cancer Without Diabetes[a,b]

	No. (%)			
	ER/PgR+ population		ER/PgR- population	
	Metformin (n = 1268)	Placebo (n = 1265)	Metformin (n = 556)	Placebo (n = 560)
Patients with an invasive disease-free survival event	234 (18.5)	231 (18.3)	122 (21.9)	123 (22.0)
Event type for first event				
Distant recurrence	127 (10.0)	129 (10.2)	55 (9.9)	67 (12)
Local or regional recurrence	32 (2.5)	39 (3.1)	27 (4.9)	29 (5.2)
Invasive contralateral breast tumor	15 (1.2)	9 (0.7)	10 (1.8)	9 (1.6)
New primary (non-breast cancer) malignancy	49 (3.9)	48 (3.8)	25 (4.5)	12 (2.1)
Death (breast cancer)	0	0	0	1 (0.2)
Death (other primary malignancy)	0	1 (0.1)	0	0
Death (primary cardiovascular disease)	3 (0.2)	1 (0.1)	0	0
Death (other and unknown)	8 (0.6)	4 (0.4)	5 (0.9)	5 (0.9)
Patients with a death at any time (before or after an invasive disease-free survival event)	131 (10.3)	119 (9.4)	70 (12.6)	79 (14.1)
Cause of death				
Breast cancer	99 (7.8)	91 (7.2)	56 (10.1)	69 (12.3)
Other primary malignancy	15 (1.2)	15 (1.2)	6 (1.1)	4 (0.7)
Cardiovascular disease	4 (0.3)	2 (0.2)	0	0
Other condition	13 (1.0)	11 (0.9)	8 (1.4)	6 (1.1)

Figure 2. Effect of Metformin vs Placebo on Invasive Disease-Free Survival and Overall Survival



The median duration of follow-up was 96 months (IQR, 86-102) for treatment groups of patients with estrogen receptor and/or progesterone positive (ER/PgR+) breast cancer and was 94 months (IQR, 86-101) for both treatment groups of patients with ER/PgR− breast cancer.

A, Invasive disease-free survival (events include breast cancer recurrence, new primary cancers, or death).

B, Overall survival.

C, Invasive disease-free survival (events include breast cancer recurrence, new primary cancers, or death).

D, Overall survival.

Metformin RCT non-DM BRCA

JAMA | Original Investigation

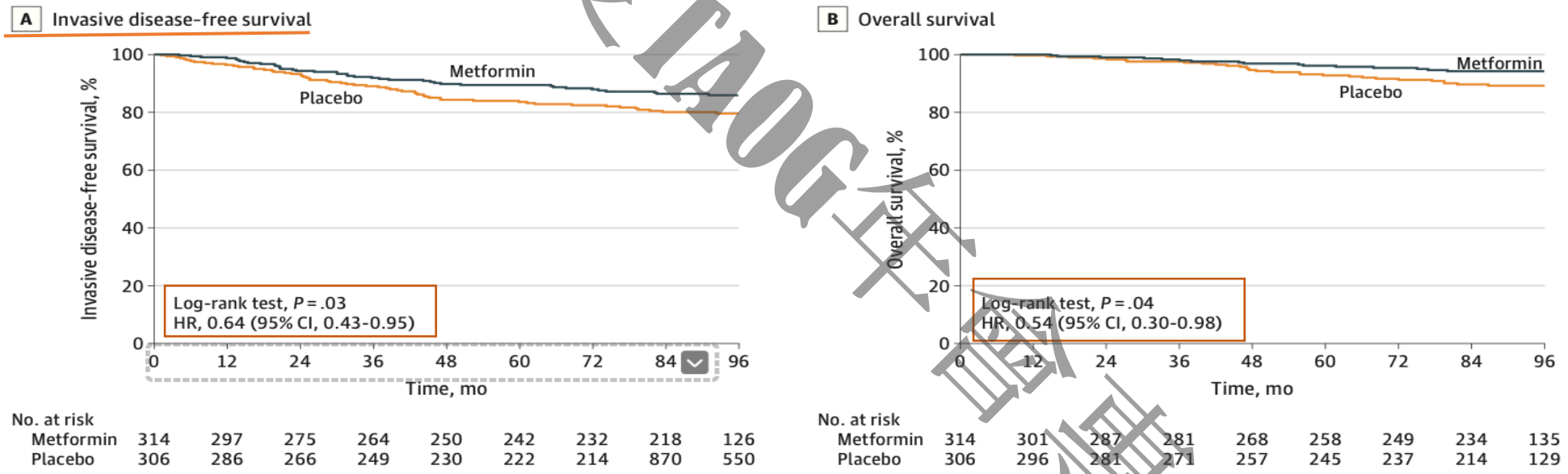
Effect of Metformin vs Placebo on Invasive Disease-Free Survival in Patients With Breast Cancer

The MA.32 Randomized Clinical Trial

UK USA Canada Switzerland

Figure 3. Exploratory Analysis of the Effect of Metformin vs Placebo on Invasive Disease-Free and Overall Survival in the Patients With *ERBB2*-Positive Breast Cancer

HER-2 NEU positive BC - free survival (FS)and over all survival



The median duration of follow-up was 96 months (IQR, 85-101) for both treatment groups of patients with human epidermal growth factor receptor 2 (*ERBB2*, formerly *HER2 or HER2/neu*).

A, Invasive disease-free survival (events include breast cancer recurrence, new primary cancers, or death).
B, Overall survival.

Metformin and breast cancer: where are we now?

Study Designation	Phase	Intervention	Outcome
METTEN study **N = 84**	II	Neoadjuvant treatment in HER-2 positive BC (weekly paclitaxel + trastuzumab followed by 4 cycles of 3-weekly FEC + trastuzumab) plus metformin (850 mg bid)/pbo	pCR in metformin 65.5%, (95% CI: 47.3–80.1) vs control arm 58.6%, (95% CI: 40.7–74.5) OR 1.34 [95% CI: 0.46–3.89], $p = 0.589$
NCIC MA.32 **(NCT01101438)** **N = 3649**	III	Adjuvant treatment with Metformin (850 mg bid)/pbo for 5 years in non-diabetic population.	ER positive/HER-2 negative patients DFS (HR = 1.01; 95% CI, 0.84–1.21) OS (HR = 1.1; 95% CI, 0.86–1.41) ER negative/HER-2 negative patients DFS (HR = 1.01; 95% CI, 0.79–1.3) OS (HR = 0.89; 95% CI, 0.64–1.23) HER-2 positive regardless ER status DFS (HR = 0.64; 95% CI, 0.43–0.95) OS (HR = 0.53; 95% CI, 0.3–0.98)
MYME trial **(NCT01885013)** **N = 126**	II	Chemotherapy regimen in metastatic BC with 8 cycles of non-pegylated liposomal doxorubicin plus cyclophosphamide plus metformin 1000 mg bid/control	PFS 9.4 m. (95% CI 7.8–10.4) in metformin vs. 9.9 m. control arm (95% CI 7.4–11.5 $p = 0.651$) OS 34.4 m. (95% CI 19.3–37.2) metformin vs. 26.8 m. control arm (95% CI 19.4–37.9) HR 0.81, 95% CI 0.50–1.30, $p = 0.382$ No difference in metformin effects (OS and PFS) in HOMA <2.5 and ≥2.5
NCT01310231 **N = 40**	II	Chemotherapy regimen in metastatic setting (anthracyclines, platinum, taxanes or capecitabine) plus metformin 850 mg bid	PFS 5.4 m metformin vs. 6.3 m control arm. HR 1.2 (95% CI 0.63–2.31). OS 20.2 m metformin vs. 24.2 m. control arm HR 1.68 (95% CI 0.79–3.55).

As neoadjuvant HER-2 BC
Metformin 850 mg bid

- difference on DFS
  ER + HER-2(-) BC
+ difference on DFS
  HER-2 (+) BC

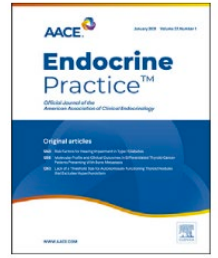
Galega officinalis

ORIGINAL ARTWORK BY MADDIE PHIPPS

Int. J. Mol. Sci. 2022, 23, 2705. https://doi.org/10.3390/ijms23052705

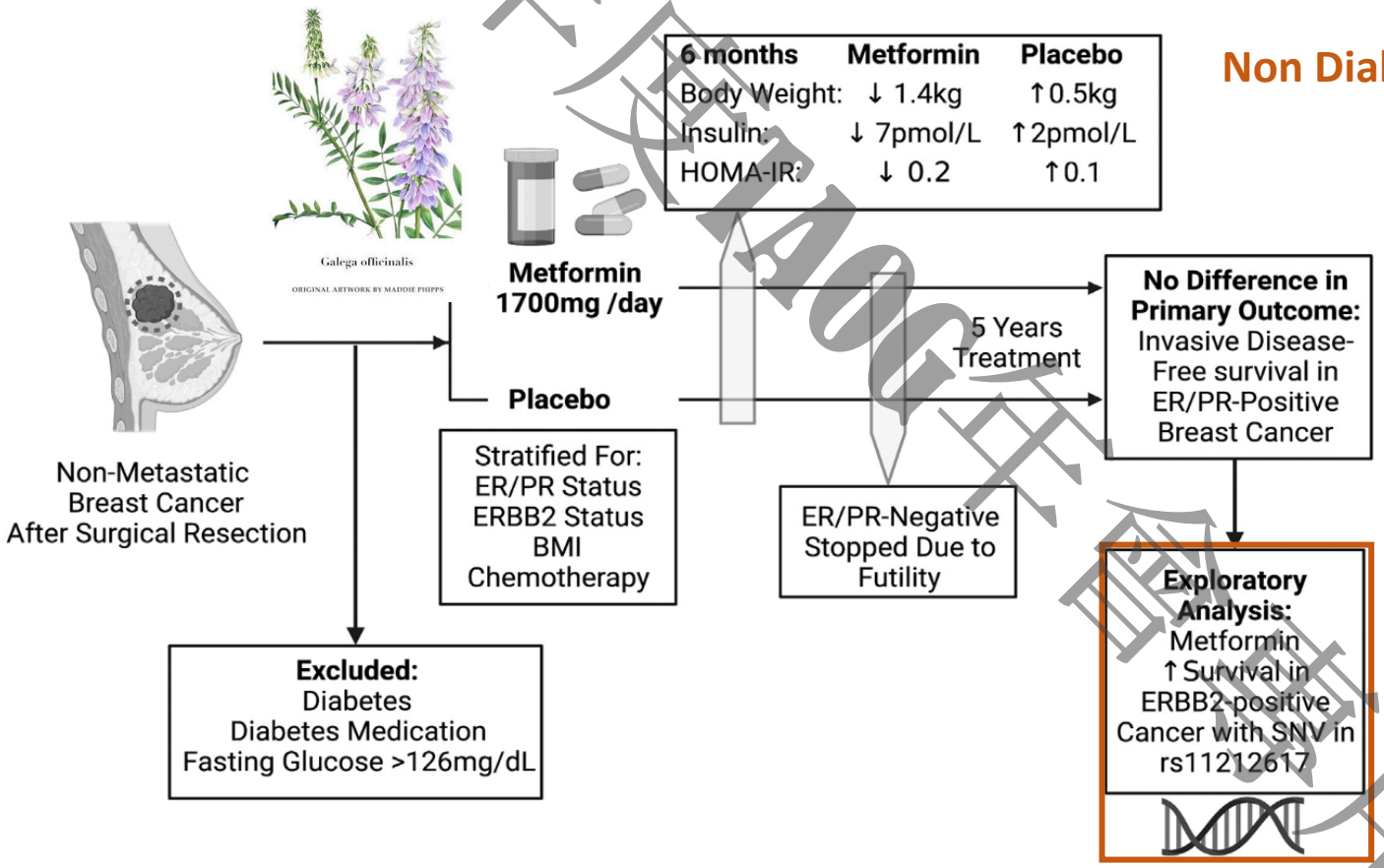
Commentary

Metformin and Cancer: Is This the End?



E.J. Gallagher, N.G. Kase, N.A. Bickell et al.

Endocrine Practice 28 (2022) 832–834



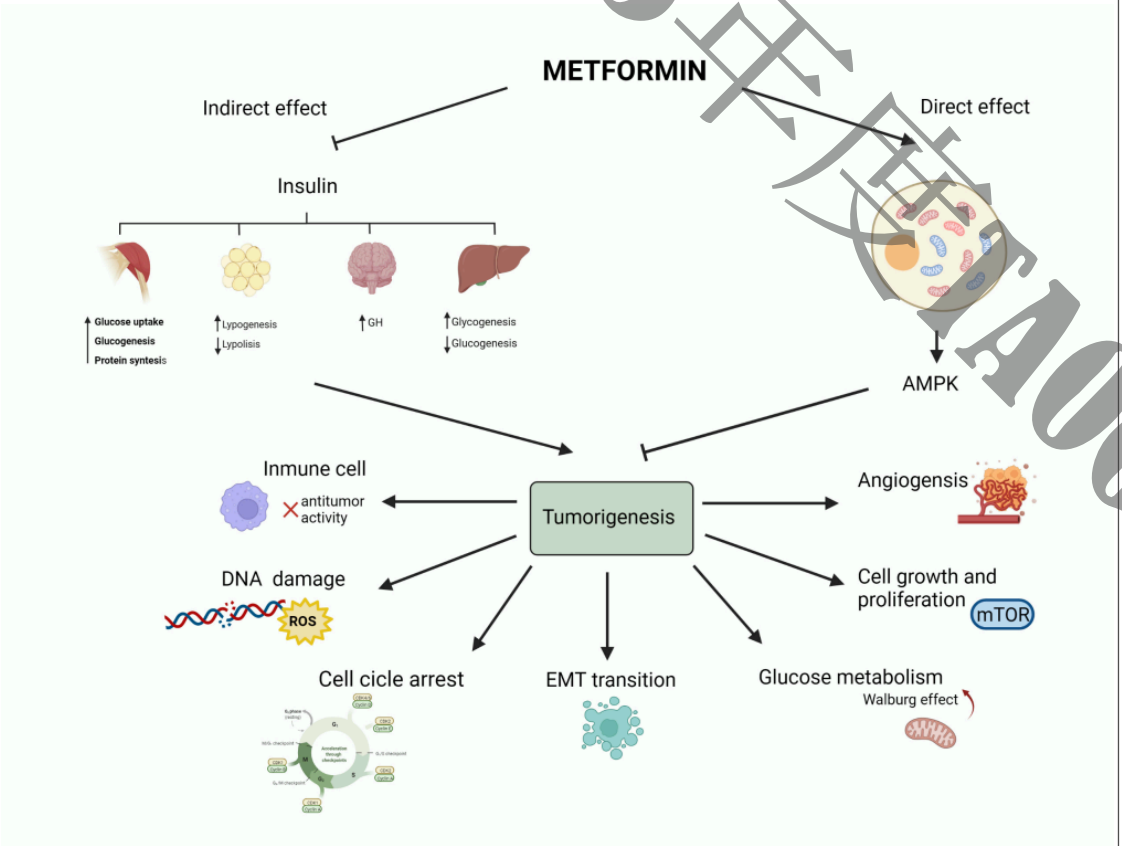
Non Diabetic population

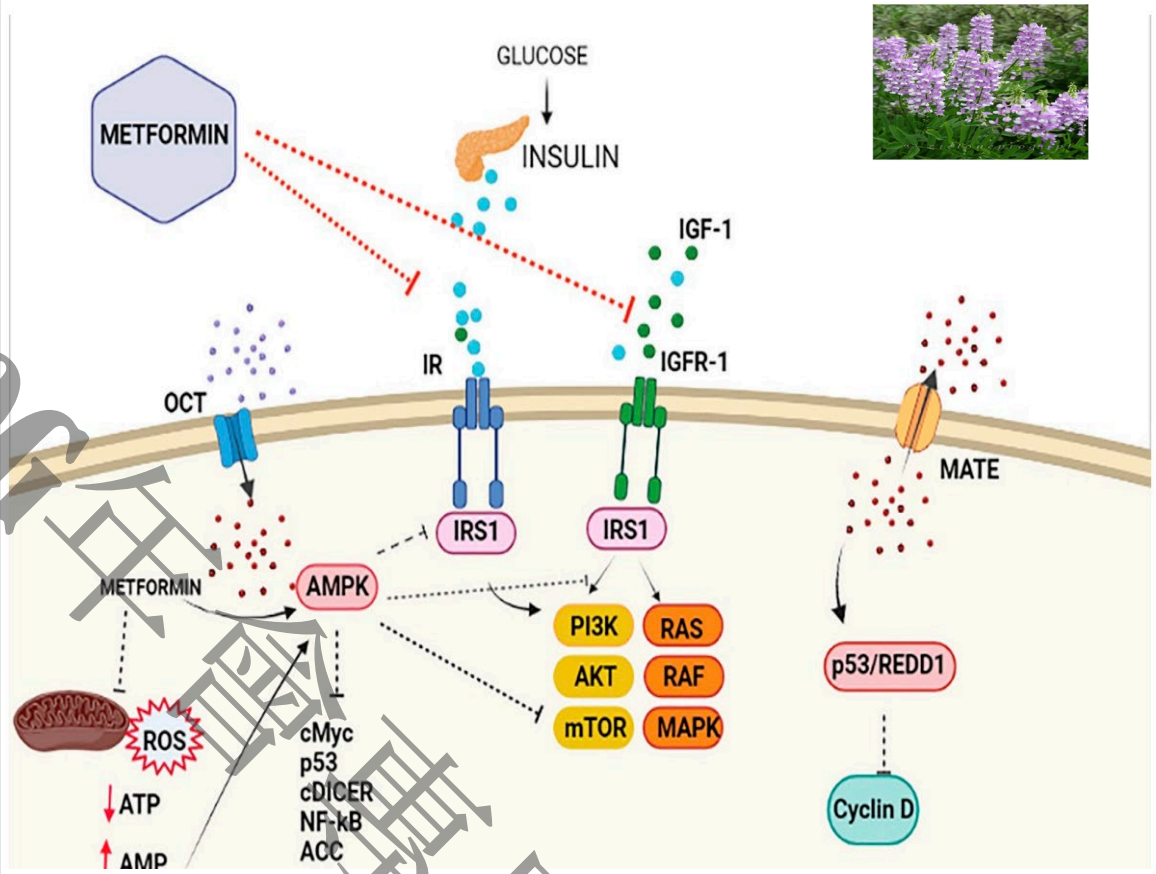
ER/PR (+) BRCA
FS 無明顯差別

Survival ↑ ERBB2 (+) BC
SNV rs11212617

Endocrine Practice 28 (2022) 832e834

Metformin and breast cancer: where are we now?





Int. J. Mol. Sci. 2022, 23, 2705. https://doi.org/10.3390/ijms23052705

Metformin and breast cancer: where are we now?

Study Designation	Phase	N	Clinical Setting	Study Medication	End Point
NCT04559308 (Recruiting)	II	80	Neoadjuvancy	4 cycles of EC followed by weekly paclitaxel plus metformin (1000 mg bis)/control	Clinical benefit rate (tumor size)
NCT04387630 (Recruiting)	II/III	120	Neoadjuvancy	Neoadjuvant treatment as physician's choice plus metformin (from 850 mg–2550 mg/day)/pbo	Clinical response rate T-cell cytotoxic markers
NCT01589367 (Completed)	II	208	Neoadjuvancy	Letrozole plus metformin (1000 mg bis)/pbo up to 24 weeks prior to surgery	Clinical response rate
NCT01929811 (Active, not recruiting)	II	92	Neoadjuvancy	TEC plus metformin(500 mg/day)/control	pCR
NCT04248998 (Recruiting)	II	90	Neoadjuvancy in TN breast cancer	4 cycles of AC followed by weekly paclitaxel + FMD +metformin (850 mg bis)/pbo	pCR
NCT02488564 (Completed)	II	49	Neoadjuvancy in HER-2 positive breast cancer	Liposomal doxorubicin in combination with Docetaxel and Trastuzumab plus Metformin (1000 mg bis)	pCR
NCT05023967 (Recruiting)	II	120	Localized BC not tributary to neoadjuvant treatment	Fast for ≥16 h plus metformin (1500 mg/day) vs. observation for 4–6 weeks prior to surgery	Ki67 levels Incidence of adjacent DCIS Toxicity
NCT04143282 (Completed)	II	250	Metastatic breast cancer	Standard chemotherapy plus metformin (1000 mg bis)	Radiologic response rate OS, DFS

Onging... Pathologic complete response (pCR)

Int. J. Mol. Sci. 2022, 23, 2705. https://doi.org/10.3390/ijms23052705

Metformin and ovarian cancer : where are we now?

The Relationship between Metformin Consumption and Cancer Risk: An Updated Umbrella Review of Systematic Reviews and Meta-Analyses

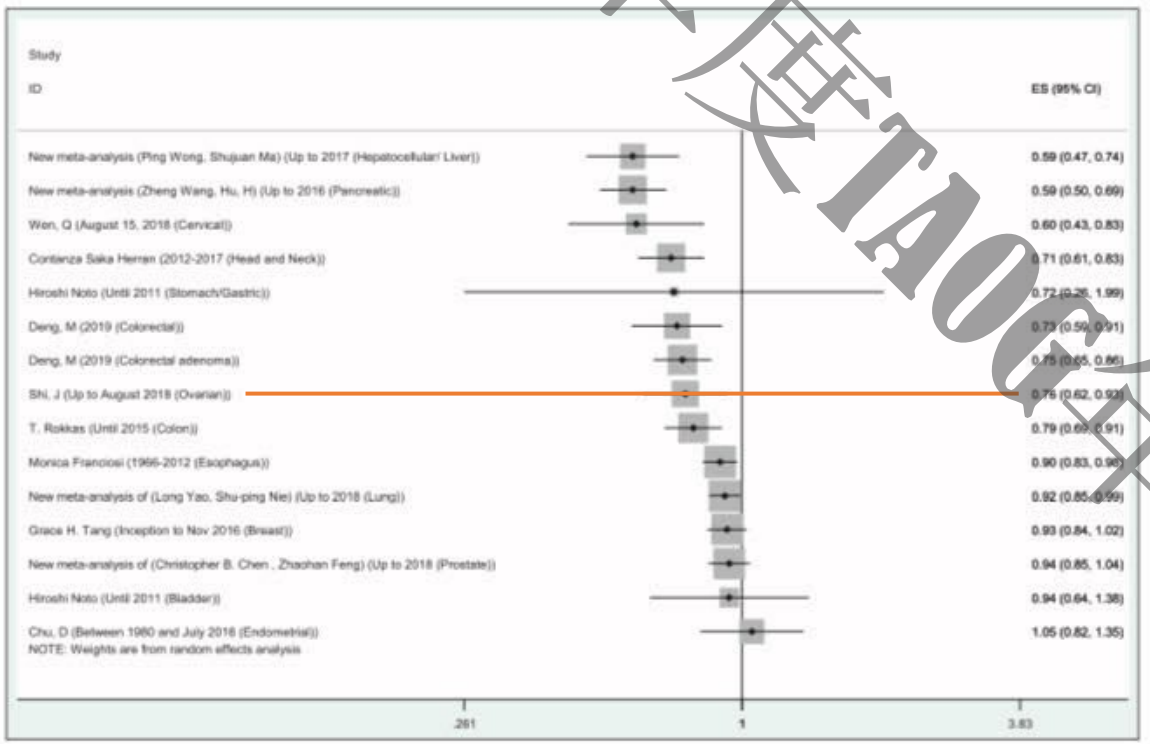


Figure 2: Relationship between metformin use and the risk of cancer worldwide. The midpoint of each segment estimates the odds ratio and length of the segment, showing the 95% confidence interval in each study

~2017 Hepatocellular /live
~2016 Pancreatic
~2018 Cervical cancer
~2017 Head and Neck
~ 2011 Stomac/ gastric
~2019 Colorectoal
~2018 Ovarian
~2015 Colon
~2012 Esophagus
~2018 Lung
~2016 Breast
~2018Prostate
~2011 Bladder

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DOI: 10.4103/ijpvm.ijpvm_62_21
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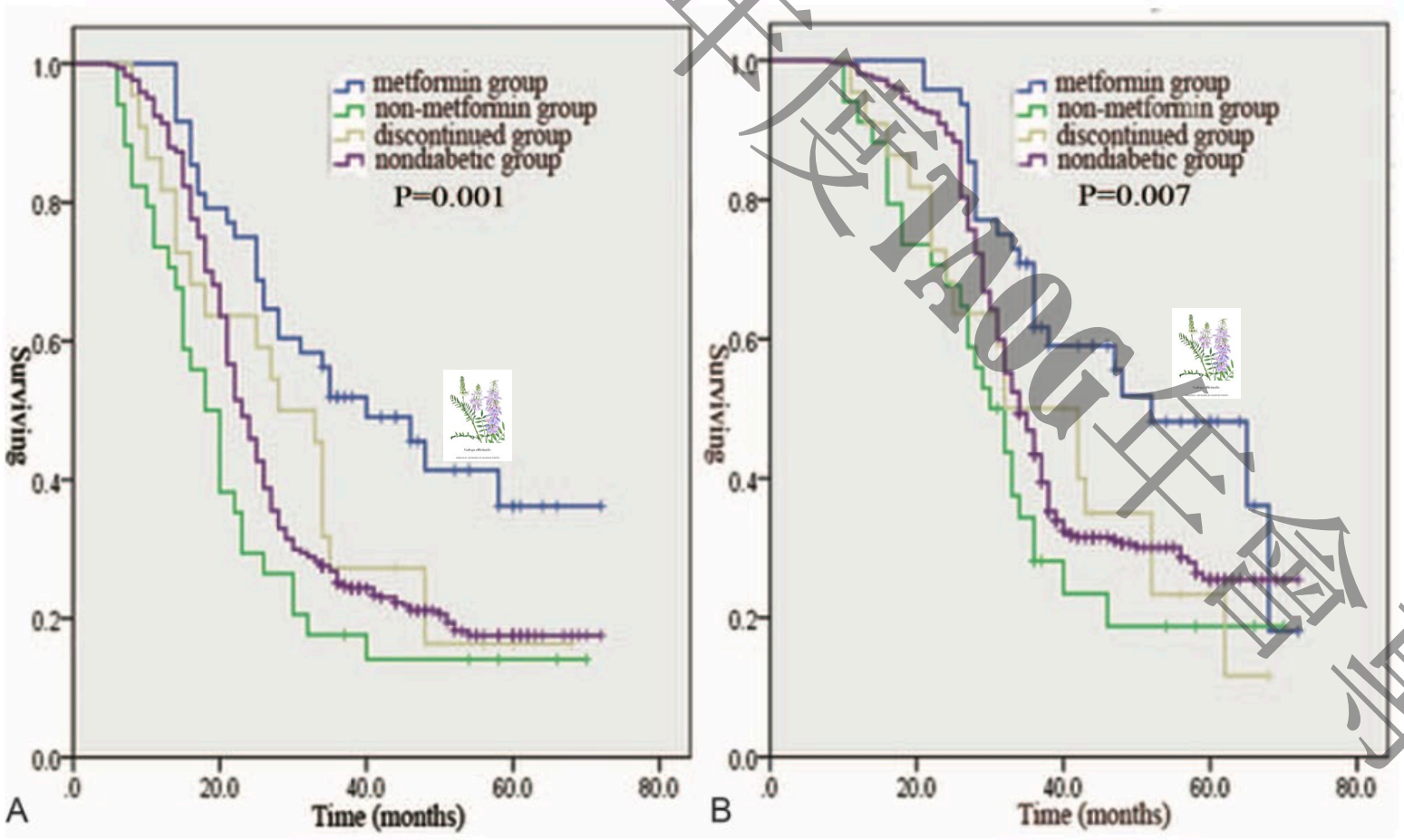
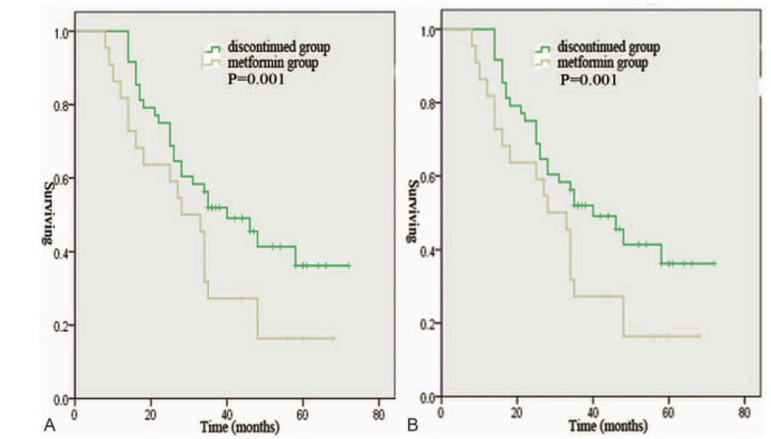
International Jounal of preventive medicine 2023, 14:90

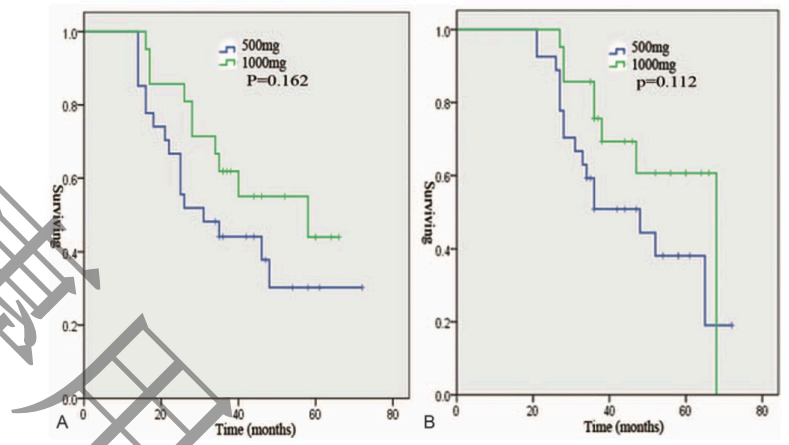
Metformin and ovarian cancer : where are we now?

Continuous use of metformin can improve survival in type 2 diabetic patients with ovarian cancer

A retrospective study

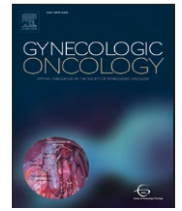


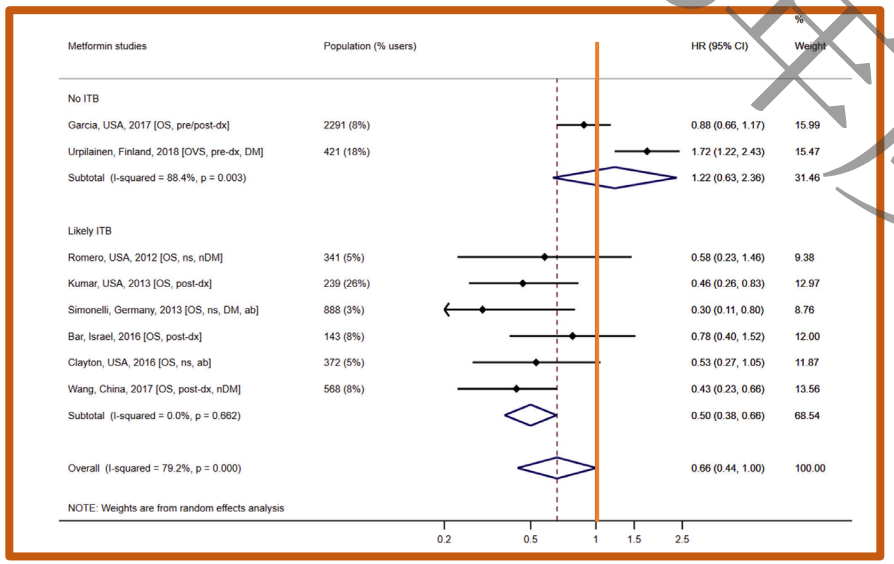


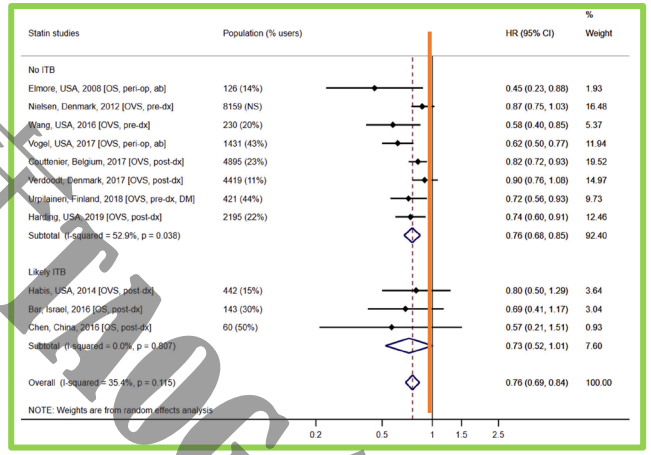


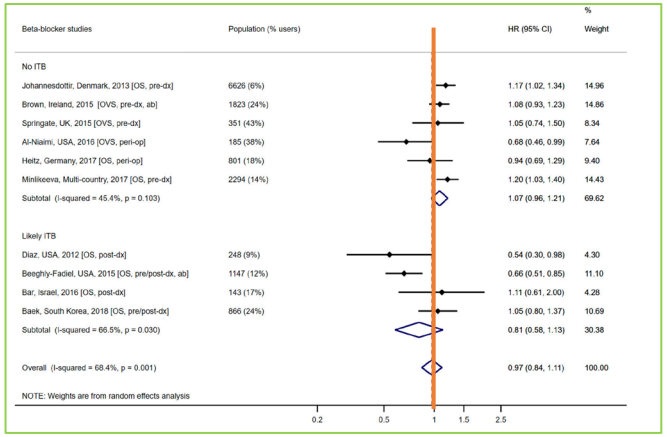
Medicine (2017) 96:29(e7605)

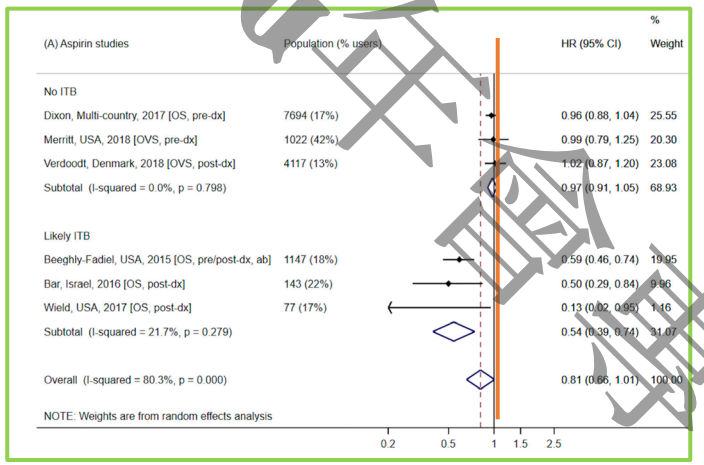
Common medications and survival in women with ovarian cancer: A systematic review and meta-analysis

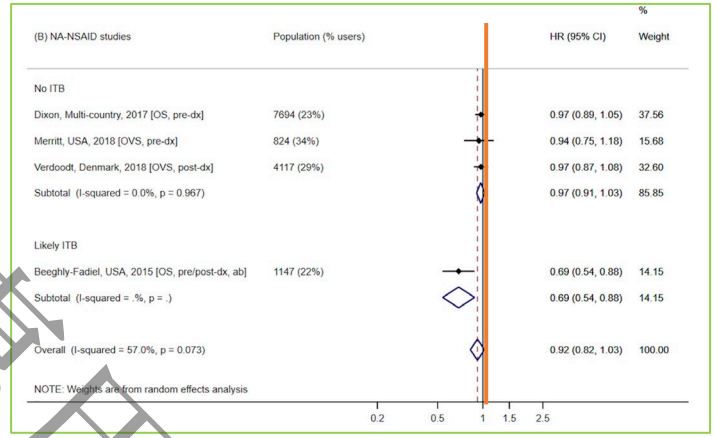












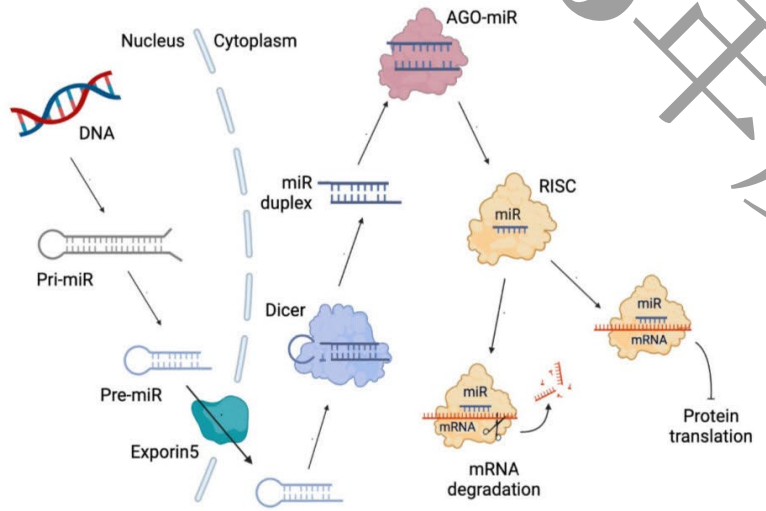
Metformin VS Statin beta bloker Aspin NSAID

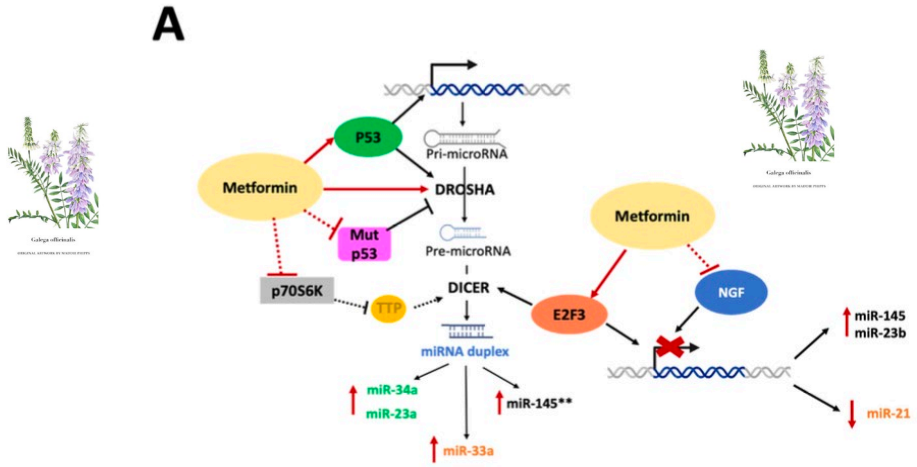
A. Majidi et al. / Gynecologic Oncology 157 (2020) 678–685

Review

Mechanisms of Regulation of the Expression of miRNAs and lncRNAs by Metformin in Ovarian Cancer

pharmaceuticals





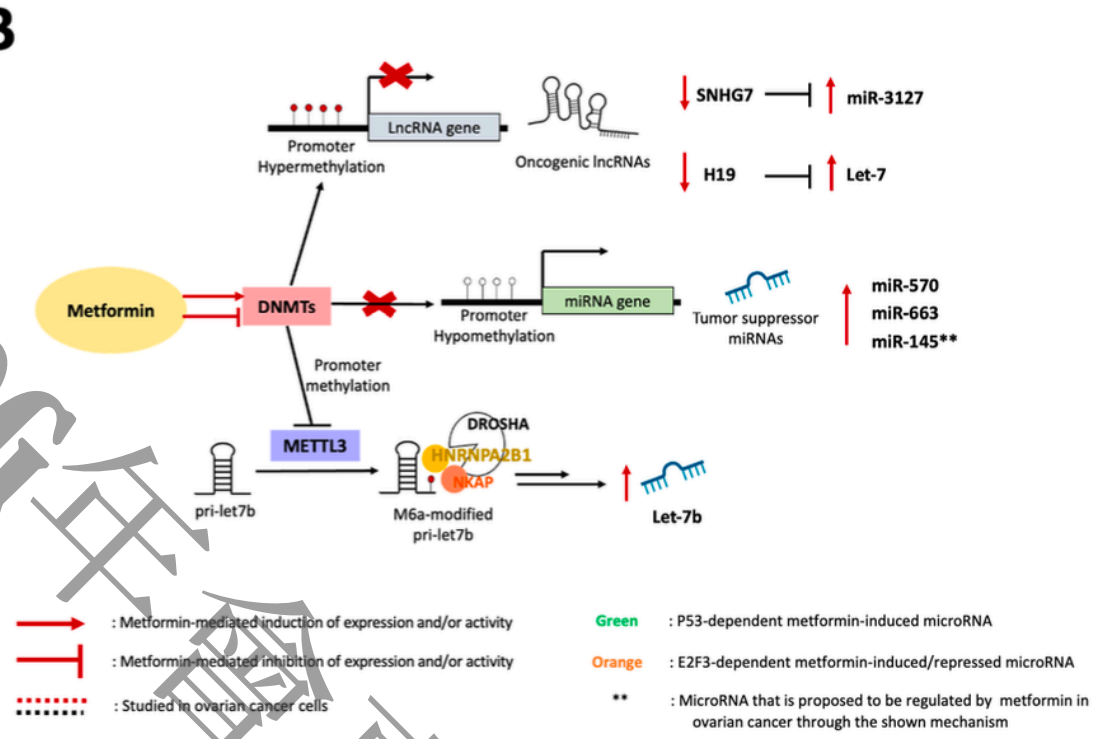


Figure 1. Diagram of microRNA (miRNA) biosynthesis. miR duplex: miRNA duplex comprising two strands. pri-miRNA: primary miRNA. Pre-miRNA: precursor miR. mRNA: messenger RNA. Dicer: RNase III double-stranded RNA nuclease. AGO-miR: Argonaute bound to miRNA. RISC: RNA-induced silencing complex.

Metformin and ovarian cancer : where are we now?

Molecular targets of metformin against ovarian cancer based on network pharmacology

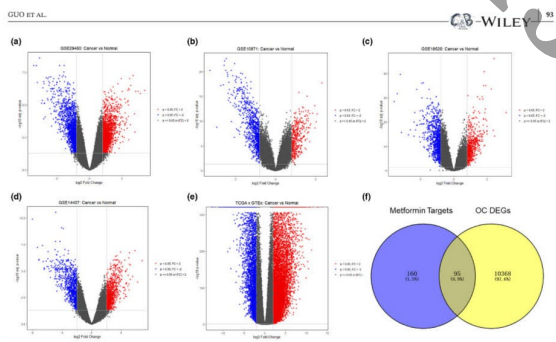


FIGURE 2 Visualization of ovarian cancer-related target gene (differentially expressed genes) screening in datasets by volcano plots. Volcano plot visualization for DEGs from GSE29450 (a), GSE10971 (b), GSE18520 (c), GSE14407 (d), and TCGA+GTEx (e). (f) Venn diagram for the common targets of metformin and ovarian cancer. TCGA, the Cancer Genome Atlas; GTEx, Genotype-Tissue Expression.

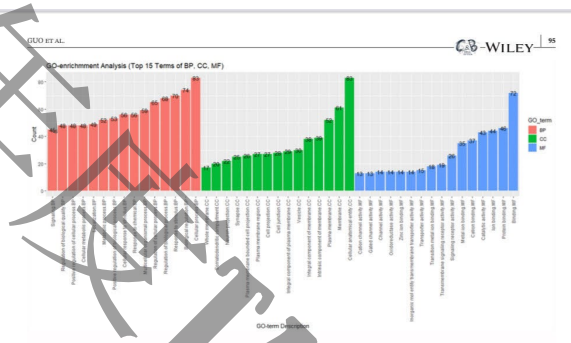


FIGURE 4 GO enrichment plot for the common targets of metformin and OC. GO enrichment analysis for the main biological processes, cellular components, and molecular functions of the common targets of metformin and OC (15 high-ranking one). GO, gene ontology.

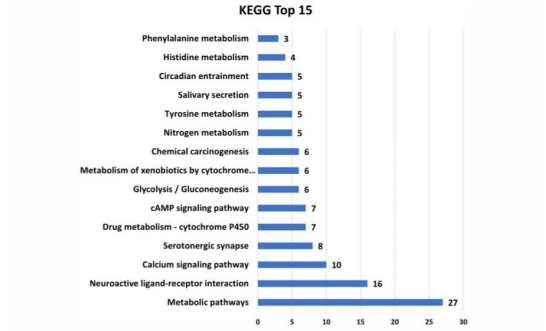
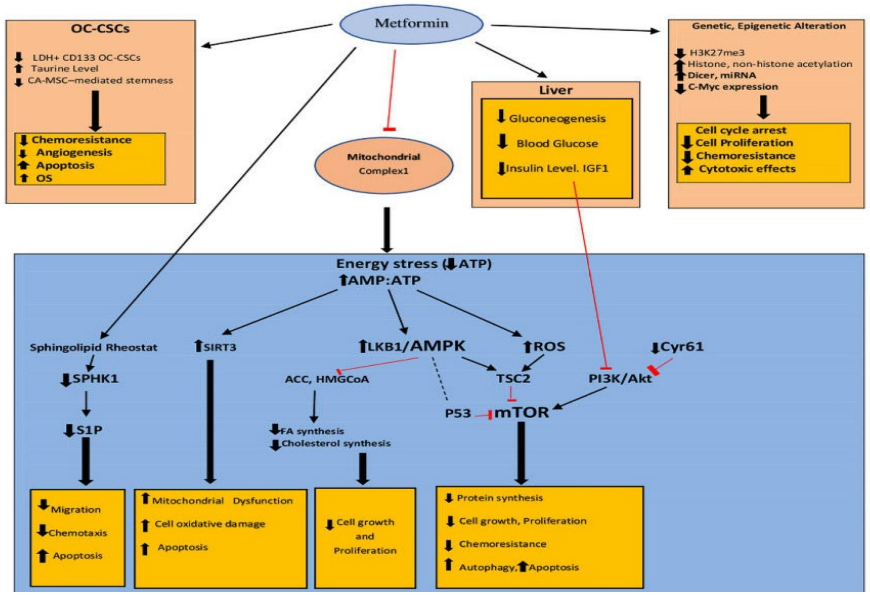


FIGURE 5 KEGG pathway enrichment analysis for the common targets of metformin and OC (15 high-ranking targets). KEGG: Kyoto Encyclopedia of Genes and Genomes.



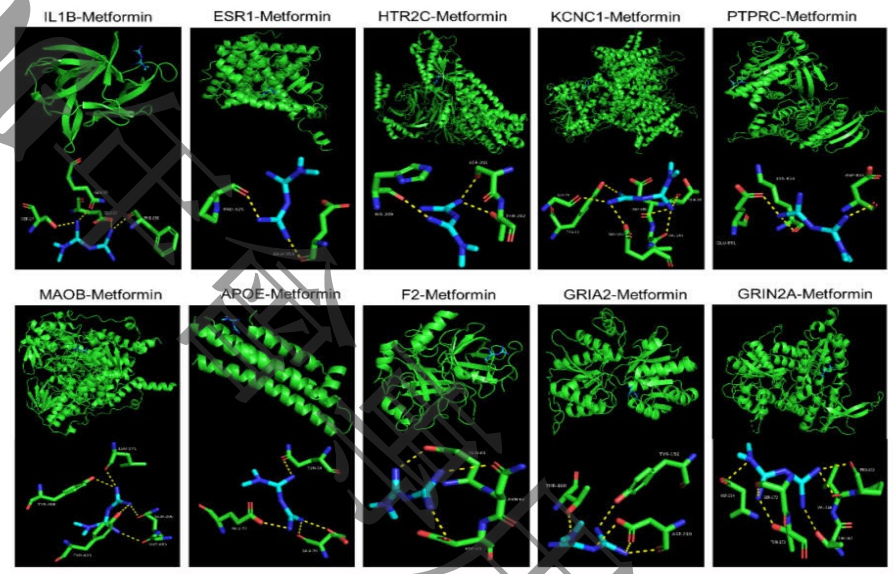
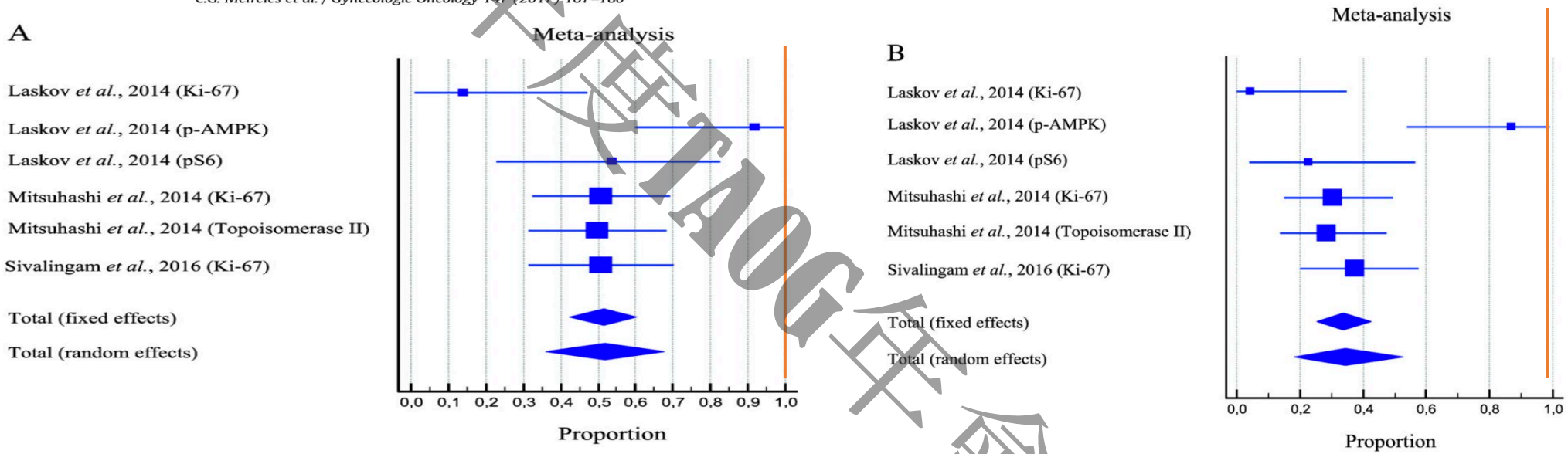


FIGURE 6 Molecular docking patterns of metformin with IL1B, ESR1, HTR2C, KCNC1, PTPRC, MAOB, APOE, F2, GRIA2, GRIN2A shown as 3D diagrams.

Review Article

Effects of metformin on endometrial cancer: Systematic review and meta-analysis



Proportion of cell proliferation biomarker staining before (A) and after (B) treatment with metformin in patients with endometrial cancer (samples, n = 123).

Results from two types of meta-analysis: **fixed and random effect.**

Meta-analysis was performed using MedCalc. **A. I^2 (inconsistency) = 68.22%. B. I^2 = 75.93%.**

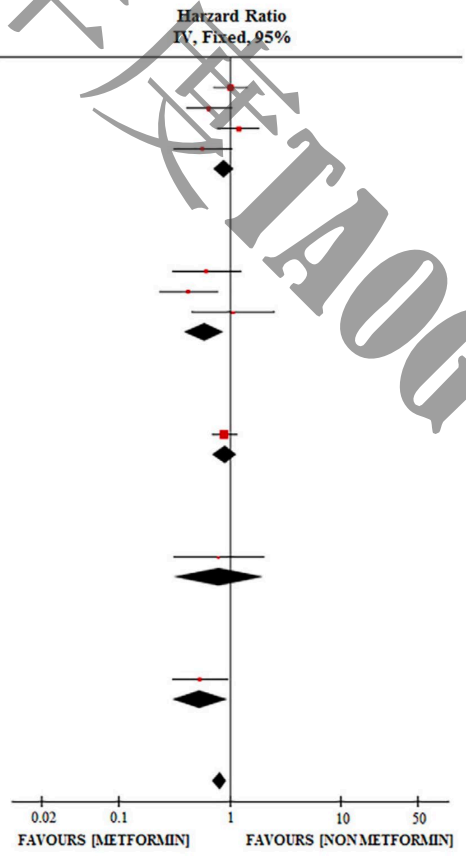
Metformin & endometrial cancer

Review Article

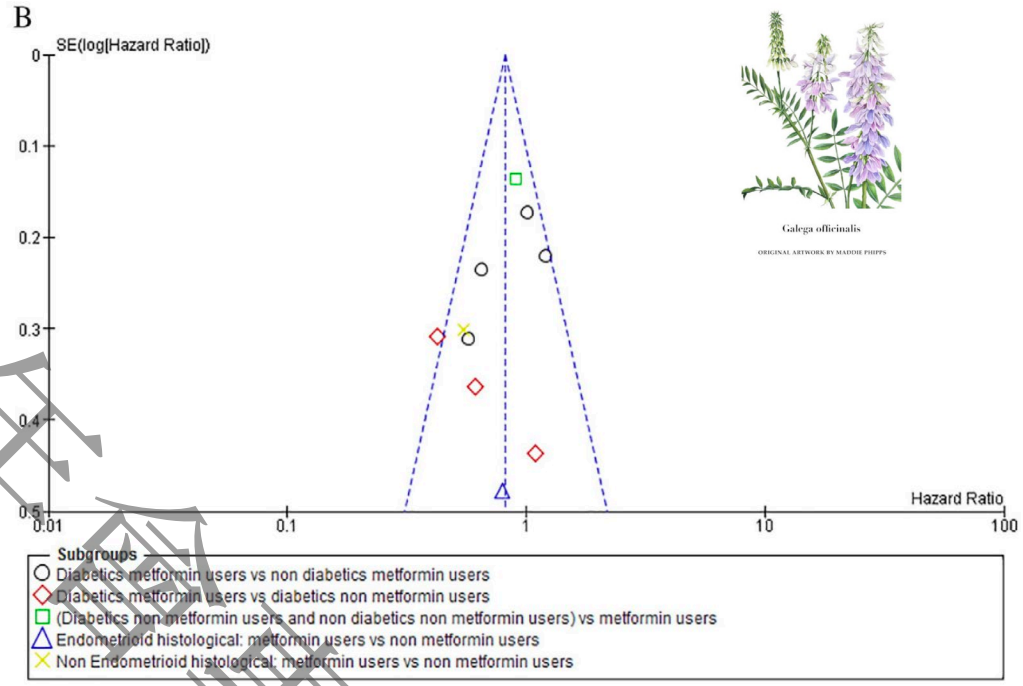
Effects of metformin on endometrial cancer: Systematic review and meta-analysis

A

Study or Subgroup	log[Harzard Ratio]	SE	Weight	Harzard Ratio IV, Fixed, 95%
Diabetics metformin users *vs* non diabetics non metformin users				
Al Hilli *et al.*, 2015	0.01	0.1727	19%	1.01 [0.72, 1.42]
Ezewuiro *et al.*, 2015	-0.4308	0.2351	10.3%	0.65 [0.41, 1.03]
Ko *et al.*, 2014	0.1823	0.2198	11.8%	1.20 [0.78, 1.85]
Nevadunsky *et al.*, 2014	-0.5621	0.3108	5.9%	0.57 [0.31, 1.05]
Subtotal (95% CI)			**47%**	**0.89 [0.72, 1.11]**
Heterogeneity: Chi²= 6.23, df= 3 (P= 0.10); I²=52%				
Test for overall effect: Z=1.05 (P= 0.30)				
Diabetics metformin users *vs* diabetics non metformin users				
Al Hilli *et al.*, 2015	-0.4943	0.3621	4.3%	0.61 [0.30, 1.24]
Ezewuiro *et al.*, 2015	-0.8675	0.3072	6.0%	0.42 [0.23, 0.77]
Lemanska *et al.*, 2015	0.077	0.4355	3.0%	1.08 [0.46, 2.54]
Subtotal (95% CI)			**13.3%**	**0.59 [0.39, 0.88]**
Heterogeneity: Chi²= 3.16, df= 2 (P= 0.21); I²=37%				
Test for overall effect: Z= 2.59 (P= 0.010)				
(Diabetics non metformin users and non diabetics non metformin users) *vs* metformin users				
Seebacher *et al.*, 2016	-0.1054	0.1356	30.9%	0.90 [0.69, 1.17]
Subtotal (95% CI)			**30.9%**	**0.90 [0.69, 1.17]**
Heterogeneity: Not applicable				
Test for overall effect: Z= 0.78 (P= 0.44)				
Endometrioid histological: metformin users *vs* non metformin users				
Nevadunsky *et al.*, 2014	-0.2357	0.4773	2.5%	0.79 [0.31, 2.01]
Subtotal (95% CI)			**2.5%**	**0.79 [0.31, 2.01]**
Heterogeneity: Not applicable				
Test for overall effect: Z= 0.49 (P= 0.62)				
Non Endometrioid histological: metformin users *vs* non metformin users				
Nevadunsky *et al.*, 2014	-0.6162	0.2999	6.3%	0.54 [0.30, 0.97]
Subtotal (95% CI)			**6.3%**	**0.54 [0.30, 0.97]**
Heterogeneity: Not applicable				
Test for overall effect: Z= 2.05 (P= 0.04)				
Total (95% CI)			**100%**	**0.82 [0.70, 0.95]**
Heterogeneity: Chi²= 15.03, df= 9 (P= 0.09); I²=40%				
Test for overall effect: Z= 2.69 (P= 0.007)				
Test for subgroup differences: Chi²= 5.64, df= 4 (P= 0.23); I²=29.1%				



B



✓ Diabetics metformin

Gynecologic Oncology 147 (2017) 167–180

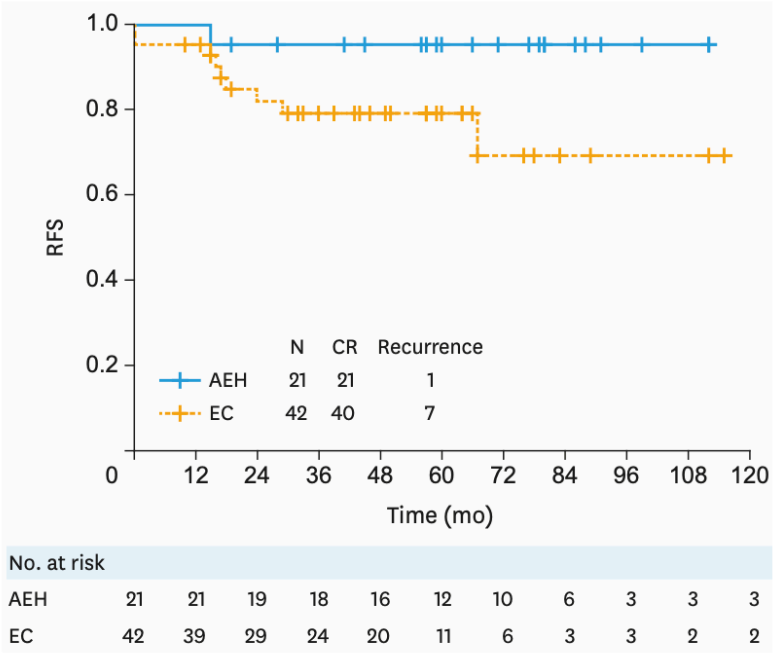
J Gynecol Oncol. 2019 Nov;30(6):e90
https://doi.org/10.3802/jgo.2019.30.e90
pISSN 2005-0380·eISSN 2005-0399

JOURNAL OF GYNECOLOGIC ONCOLOGY

Original Article

Check for updates

Long-term outcomes of progestin plus metformin as a fertility-sparing treatment for atypical endometrial hyperplasia and endometrial cancer patients



EC

No. at risk											
AEH	21	21	19	18	16	12	10	6	3	3	3
EC	42	39	29	24	20	11	6	3	3	2	2

Fig. 1. RFS in 63 patients who underwent fertility-sparing treatment with metformin plus medroxyprogesterone acetate. RFS was measured from the date of initial treatment until the date of event occurrence, defined as recurrence, progression, or not reaching remission.
AEH, atypical endometrial hyperplasia; CR, complete response; EC, endometrial cancer; RFS, relapse-free survival.

MPA and metformin fertility-sparing regimen

Relapse free survival

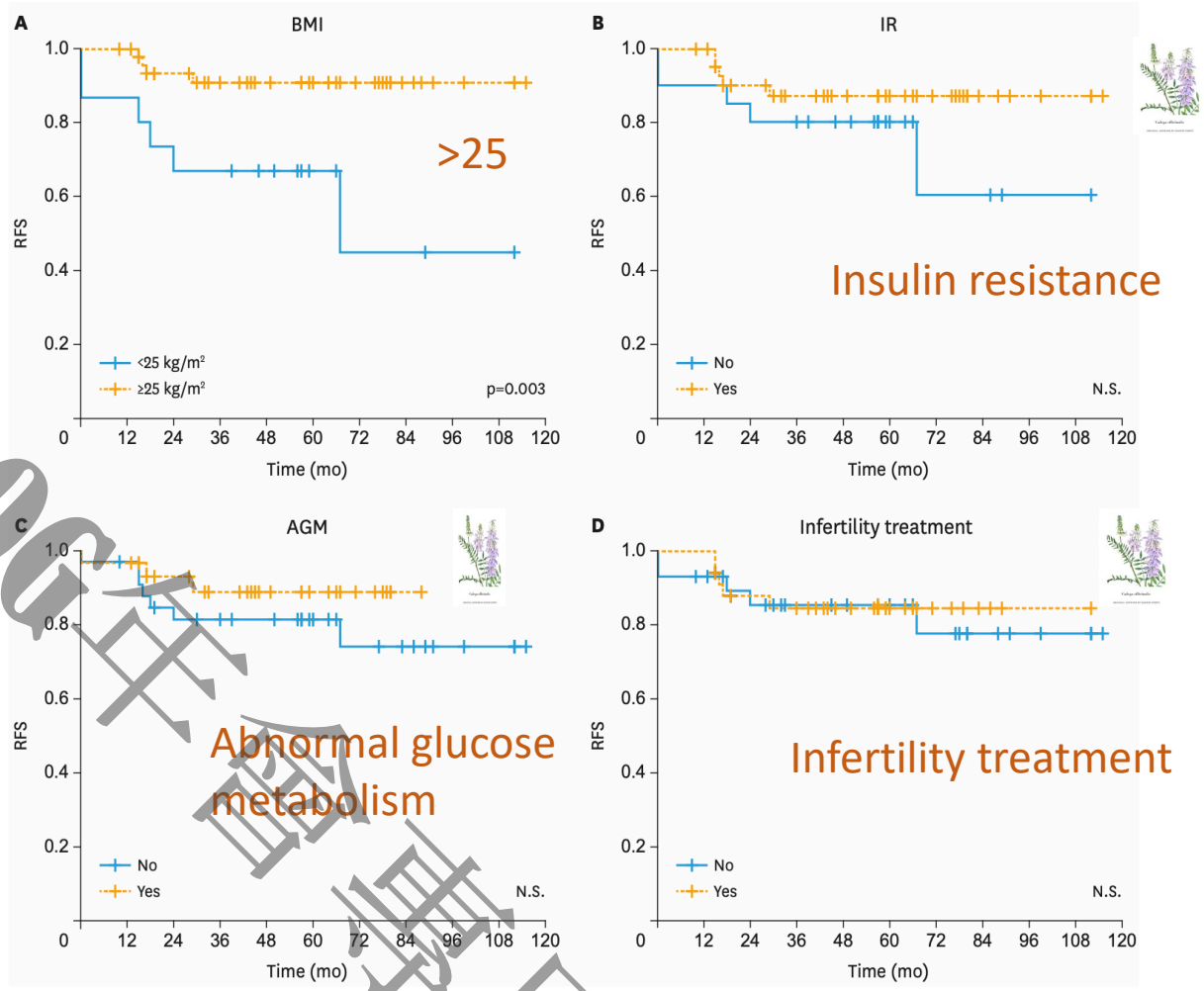


Fig. 2. Relapse-free survival of 63 patients who underwent fertility-sparing treatment with metformin plus medroxyprogesterone acetate, with respect to BMI (A), status of IR (B), AGM (C), and infertility treatment (D).
AGM, abnormal glucose metabolism; BMI, body mass index; IR, insulin resistance; N.S., not significant.

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jgo JOURNAL OF GYNECOLOGIC ONCOLOGY

Original Article

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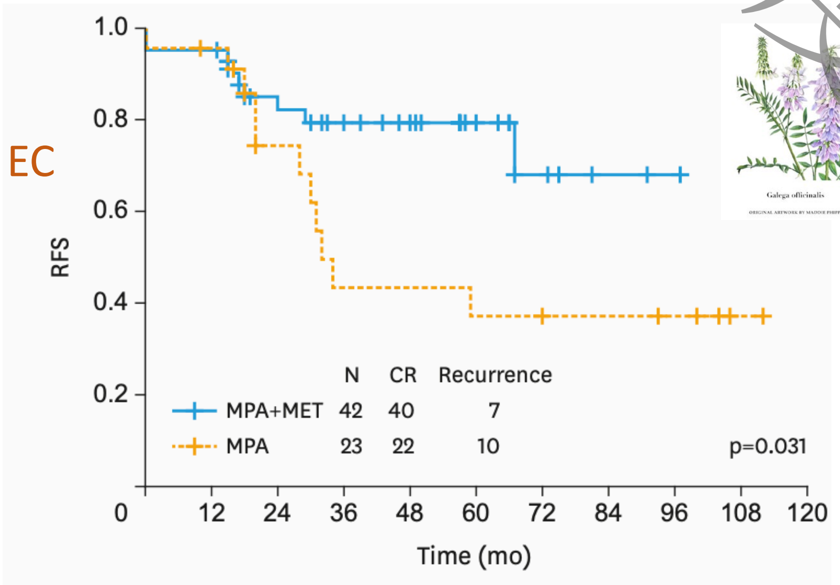
Long-term outcomes of progestin plus metformin as a fertility-sparing treatment for atypical endometrial hyperplasia and endometrial cancer patients

EC



No. at risk											
MPA+MET	42	40	29	24	20	10	5	3	1	0	0
MPA	23	22	12	7	7	6	5	5	4	2	1

Fig. 3. Relapse-free survival of the patients with endometrial cancer treated with metformin plus MPA compared with historical control treated with MPA alone.
CR, complete response; MET, metformin; MPA, medroxyprogesterone acetate.

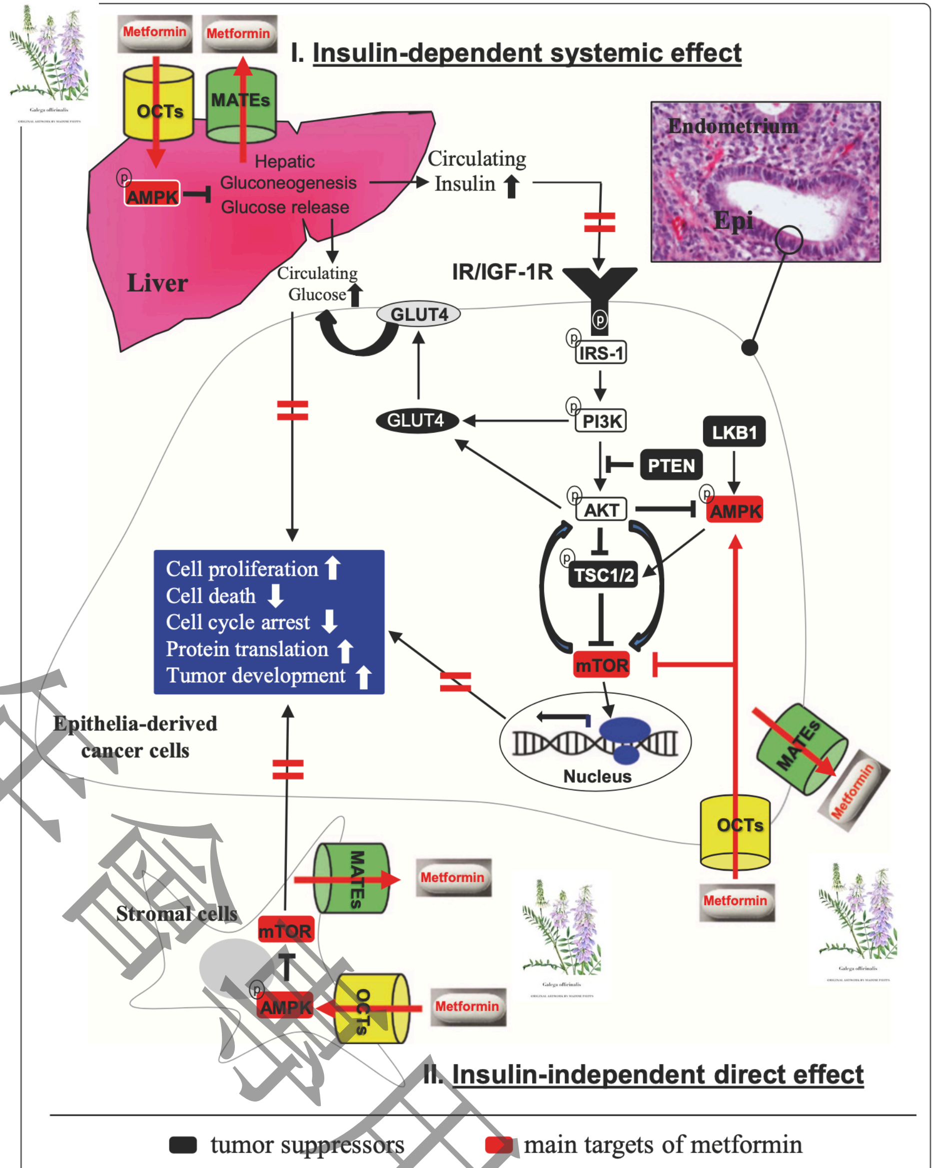
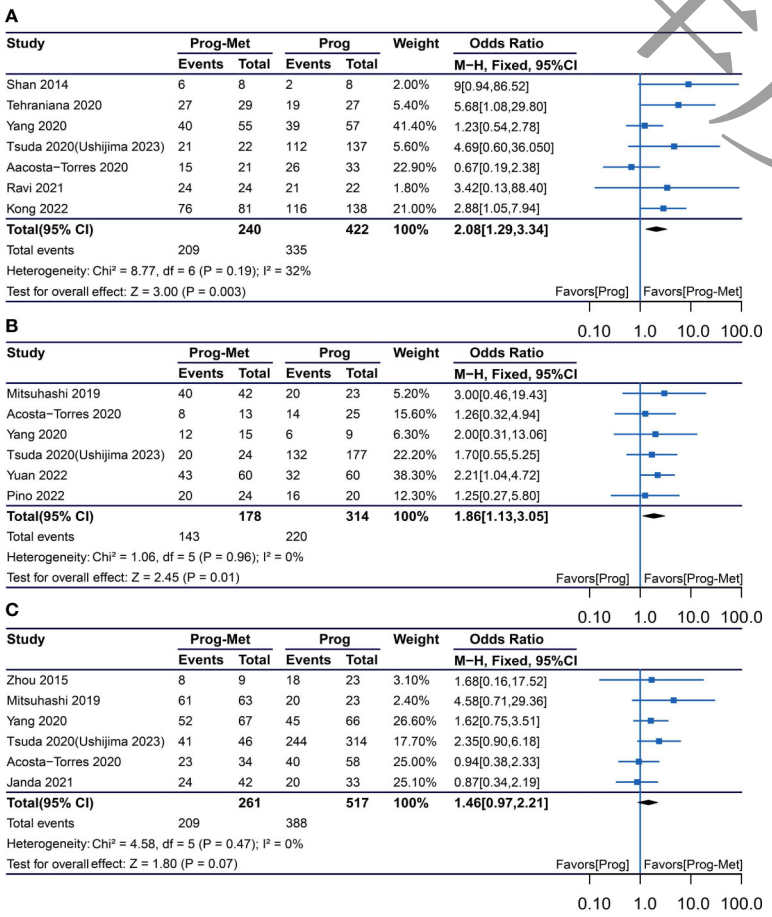


Figure 2 (See legend on next page.)

Progestin plus metformin improves outcomes in patients with endometrial hyperplasia and early endometrial cancer more than progestin alone: a meta-analysis figure 1



Complete response

comparing Prog-Met versus progestin systemically and locally

Subgroups:

(A) Endometrial hyperplasia,

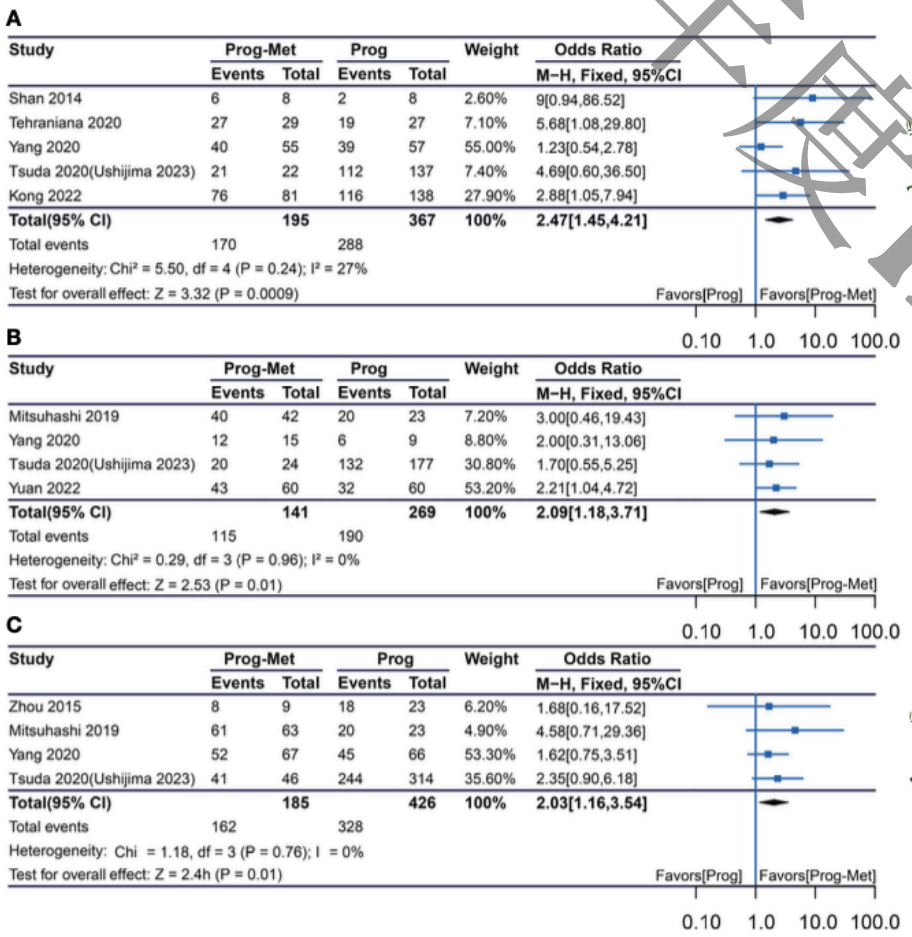
(B) early-stage endometrial cancer,

(C) endometrial hyperplasia and early-stage endometrial cancer.

Effect size is presented as odds ratio with 95% confidence interval.

Odds ratio >1 means that progestin combined with metformin is superior to progestin. Prog, progestin; Met, metformin

Progestin plus metformin improves outcomes in patients with endometrial hyperplasia and early endometrial cancer more than progestin alone: a meta-analysis figure 2



Complete response

comparing Prog-Met versus Prog by administering progestin systemically

Subgroups:

(A) Endometrial hyperplasia,

(B) early-stage endometrial cancer

(C) endometrial hyperplasia and early-stage endometrial cancer

Effect size is presented as odds ratio with 95% confidence interval.

Odds ratio >1 means that progestin combined with metformin is superior to progestin. Prog, progestin;

Met, metformin

Progestin plus metformin improves outcomes in patients with endometrial hyperplasia and early endometrial cancer more than progestin alone: a meta-analysis

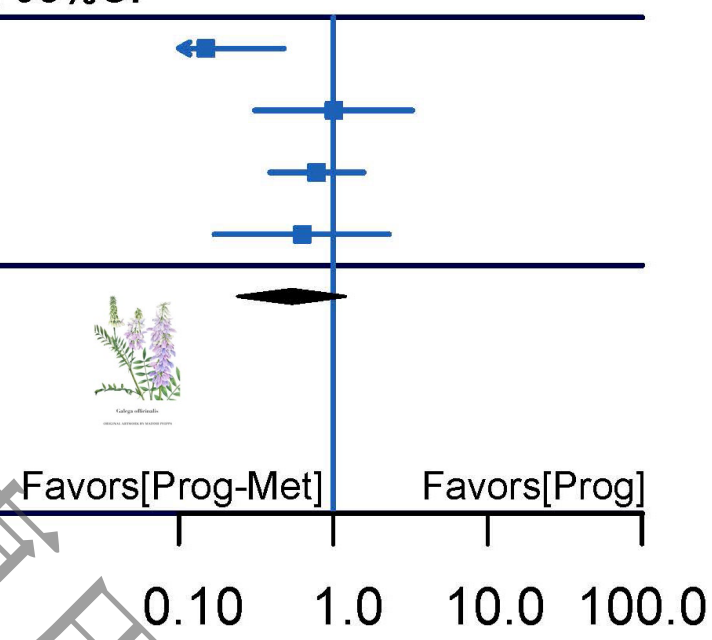
Figure 3

Relapse comparing Prog-Met versus Prog in endometrial hyperplasia andearly-stage endometrial cancer

Study	Prog-Met		Prog		Weight	Odds Ratio
	Events	Total	Events	Total		M−H, Random, 95%CI
Mitsuhashi 2019	8	61	10	20	30.80%	0.15[0.05,0.48]
Yang 2020	7	52	6	45	13.10%	1.01[0.31,3.26]
Tsuda 2020	15	37	119	256	42.00%	0.78[0.39,1.58]
Acosta−Torres 2020	4	23	10	40	14.20%	0.63[0.17,2.30]
Total(95% CI)		**173**		**361**	**100%**	**0.54[0.24,1.20]**
Total events	34		145			

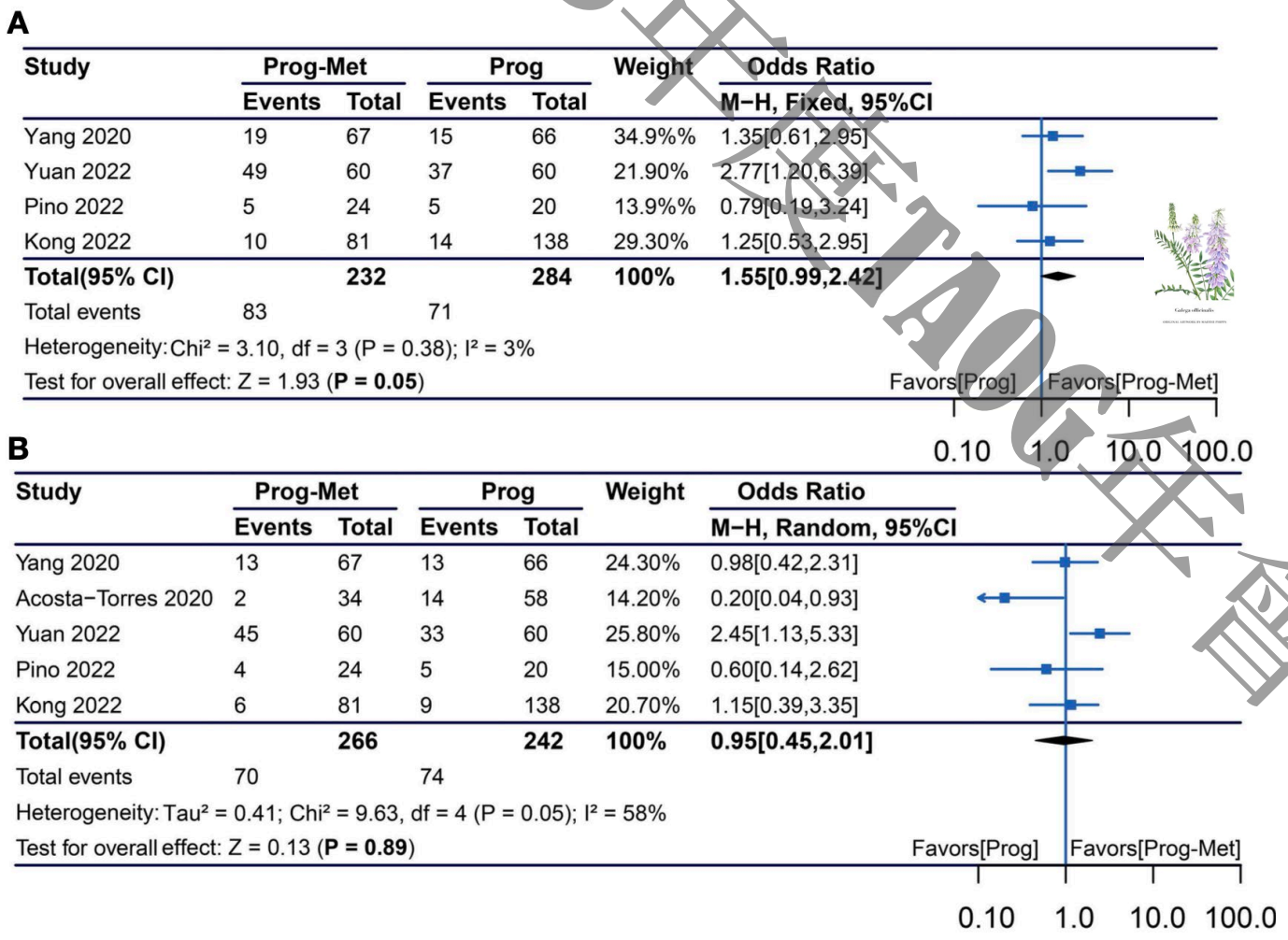
Heterogeneity: Tau² = 0.37; Chi² = 6.87, df = 3 (P = 0.08); I² = 56%

Test for overall effect: Z = 1.51 (P = 0.13)



Odds ratio >1 means that progestin is superior to progestin combined with metformin. Prog, progestin; Met, metformin

Progestin plus metformin improves outcomes in patients with endometrial hyperplasia and early endometrial cancer more than progestin alone: a meta-analysis Fig 4



Obstetric outcomes

comparing Prog-Met versus Prog

Subgroups:

(A) Clinical pregnancy rate

(B) live birth rate

Effect size is presented as odds ratio with 95% confidence interval.

Odds ratio >1 means that progestin combined with metformin is superior to progestin. Prog, progestin; Met, metformin

Metformin
EMCA & other gyn malignancies

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2022, VOL. 30, NO. 4, 359–367
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REVIEW ARTICLE

Perspectives of metformin use in endometrial cancer and other gynaecological malignancies

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ABSTRACT

Insulin resistance and hyperinsulinemia play a key role in type 1 endometrial cancer pathogenesis. Most of these cancers develop on a background of overweight or type 2 diabetes mellitus (T2DM). One of the medications widely used in the treatment of T2DM is biguanide derivative, metformin, which exerts promising anticancer properties principally through activation of adenosine monophosphate kinase (AMPK) and inhibition of mammalian target of rapamycin (mTOR) pathways. Many epidemiological studies on diabetic patients show potential preventative role of metformin in endometrial cancer patients, but data regarding its therapeutic role is still limited. So far, most of attention has been paid to the concept of metformin use in fertility sparing treatment of early-stage cancer. Another investigated alternative is its application in patients with primary advanced or recurrent disease. In this review we present the latest data on clinical use of metformin in endometrial cancer patients and potential underlying mechanisms of its activity. Finally, we present some most important clinical information regarding metformin efficacy in other gynaecological malignancies, mainly breast and ovarian cancer.

ARTICLE HISTORY
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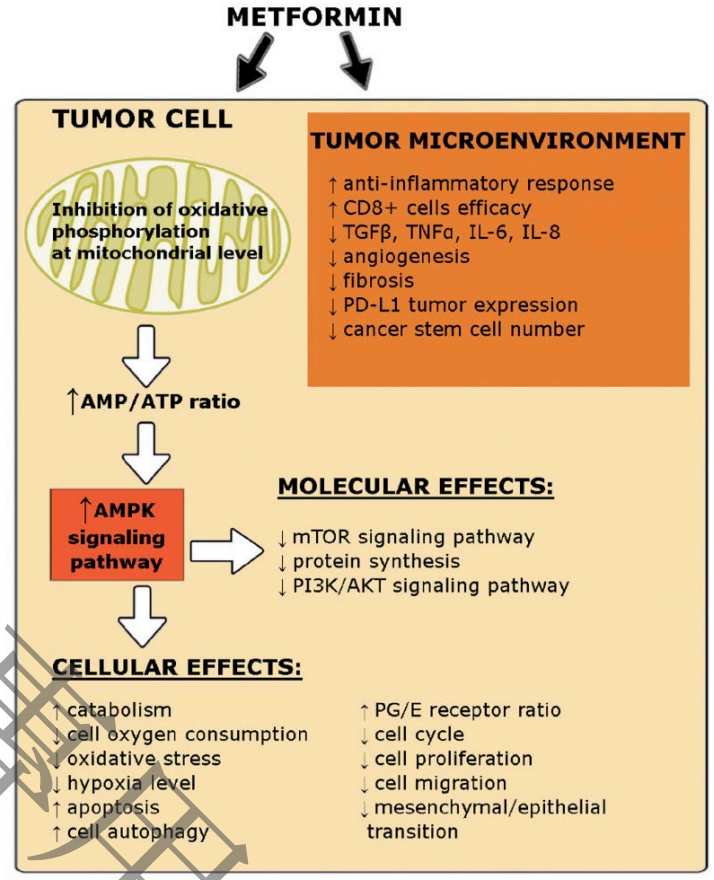
KEYWORDS
Metformin; endometrial cancer; adenosine monophosphate kinase; mammalian target of rapamycin; diabetes mellitus; insulin resistance



Jounal of drug targeting 2022, Vol. 30, No. 4, 359-367

Association of Metformin Use and Survival Outcome in Women With Cervical Cancer

Int J Gynecol Cancer. Author manuscript; available in PMC 2020 September 30.

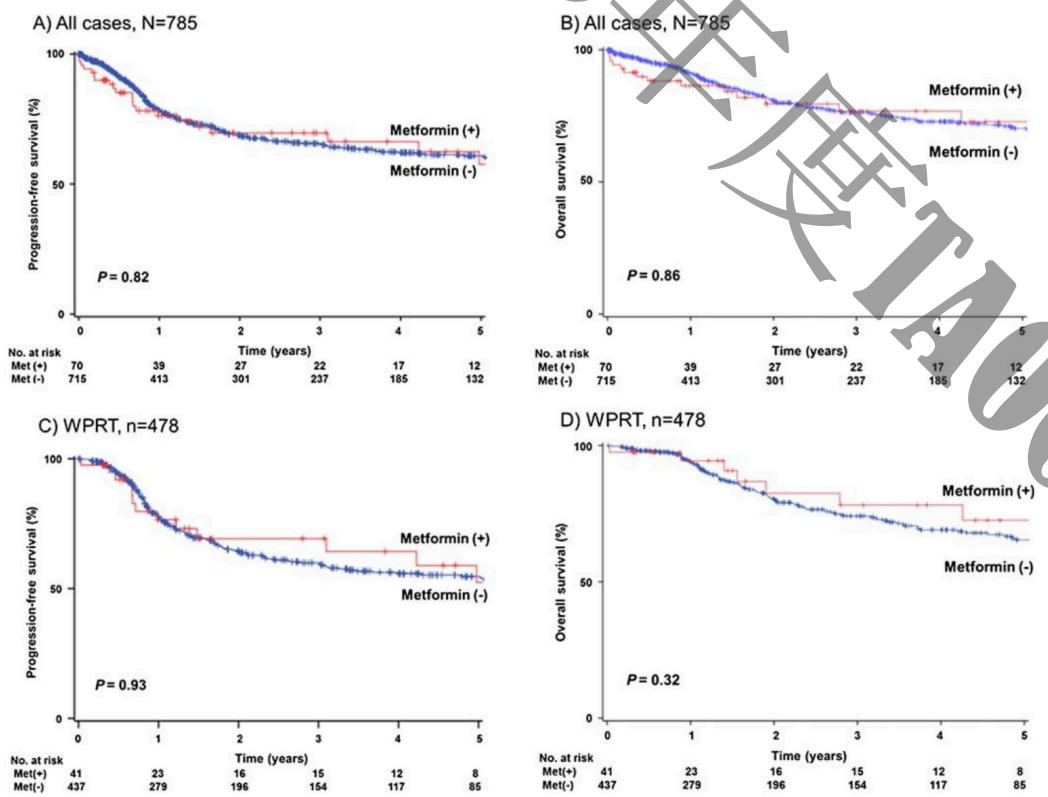


FIGURE 1.
Survival curves of cervical cancer based on metformin use. Log-rank test for *P*-values. Kaplan-Meier methods to construct survival curves were used for (A) PFS for all cases, (B) OS for all cases, (C) PFS for WPRT cases, and (D) OS for WPRT cases. No. indicates number; met, metformin.

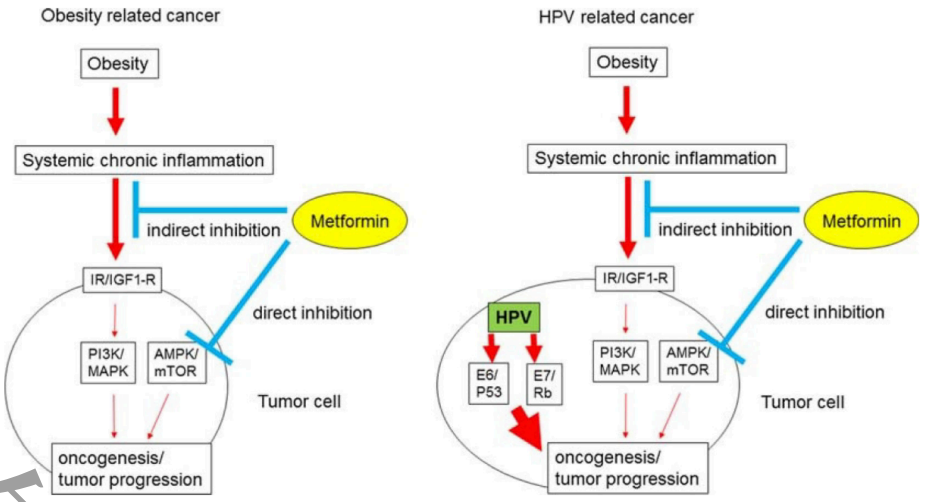


FIGURE 2.
Proposed schematic figure for the mechanism of metformin effects in cervical cancer. Systemic chronic inflammation caused by obesity leads to insulinemia and glycemia, which activate PI3K/MAPK signaling pathway implicated in oncogenesis and tumor progression. The AMPK/mTOR pathway plays a pivotal role in maintaining and promoting cancer cells. In obesity-related cancer, metformin suppresses the proliferation of cancer throughout inhibition of the indirect pathway (PI3K/MAPK signaling pathway) and the direct inhibition pathway (AMPK/mTOR pathway). However, in HPV-related cancer, metformin cannot sufficiently suppress the initiation and progression of cancer, although it may partially have inhibitory function throughout the indirect and direct inhibition pathway. The HPV oncoproteins, E6 and E7, largely overcome negative growth regulation by the host cell proteins, p53 and Rb, and induce genomic instability. The involvement of metformin on this pathway has not been well understood. IR indicates insulin receptor; IFG1-R, insulin-like growth factor-1 receptor; MAPK, mitogen-activated protein-kinase; AMPK, 5′ adenosine monophosphate–activated protein kinase; Rb, retinoblastoma.

DE GRUYTER J Basic Clin Physiol Pharmacol 2023; 34(2): 151–160

Review

Amirreza Naseri, Sarvin Sanaie, Sina Hamzehzadeh, Sepideh Seyedi-Sahebari, Mohammad-Salar Hosseini, Elnaz Gholipour-khalili, Ehsan Rezazadeh-Gavgani, Reza Majidazar, Parya Seraji, Sara Daneshvar and Erfan Rezazadeh-Gavgani*

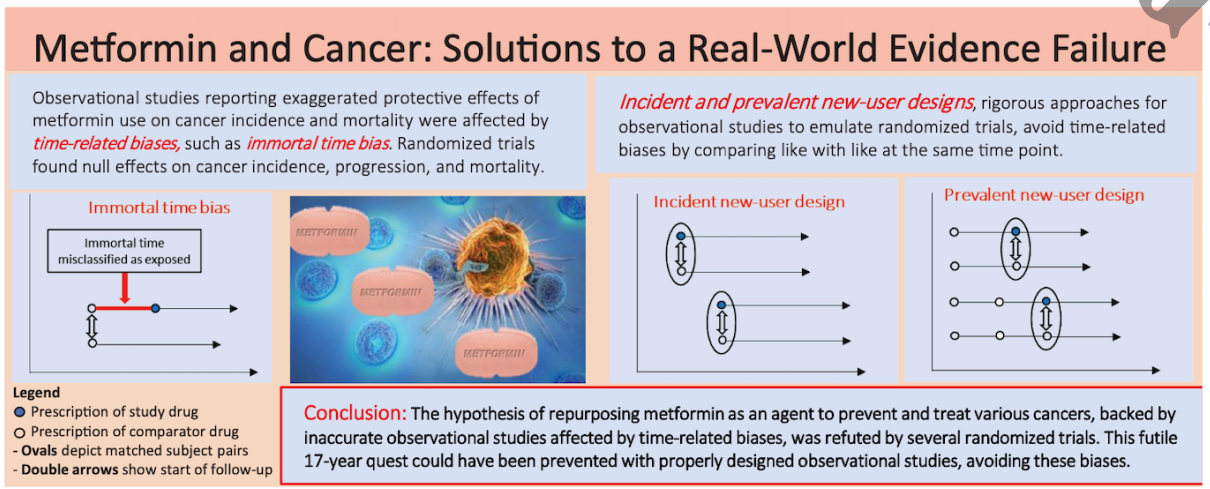
Metformin: new applications for an old drug

Diabetes Care® American Diabetes Association®

Metformin and Cancer: Solutions to a Real-World Evidence Failure

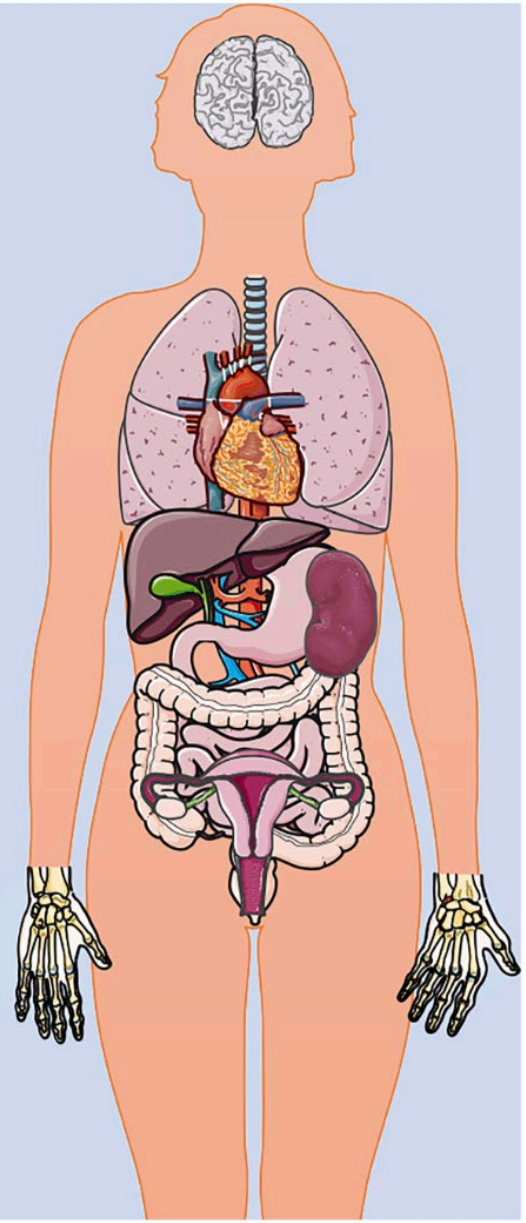
Oriana Hoi Yun Yu and Samy Suissa

Diabetes Care 2023;46(5):904–912 | https://doi.org/10.2337/dci22-0047



Suggested beneficial effects of Metformin;

- Alzheimer's Disease
- Tuberculosis
- COVID-19
- Atherosclerosis
- Heart failure
- Diabetes Mellitus
- Weight loss
- Liver cirrhosis
- Hepatocellular carcinoma
- Diabetic nephropathy
- Polycystic ovary syndrome
- Colorectal cancer
- Prostate cancer
- Osteoarthritis
- Rheumatoid Arthritis



J Basic Clin Physio Pharmacal 2023, 34(2):151-60

Take home message

Metformin Promotes Women Health

- ✓ **It is safe to use metformin to promote women health for each period**
- ✓ Usually, the dosage of Metformin is around 250 ~ 2500 mg
- ✓ **Obesity & Overweight Metabolic syndrome & T2D**
- ✓ Add B12 and watch for side effects such as G-I disturbance / Diarrhea