

Physical and psychological comorbidity of endometriosis

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Outlines of endometriosis comorbidity



1

Introduction



2

**Physical
comorbidity**



3

**Psychological
comorbidity**



4

Conclusions

Outlines of endometriosis comorbidity



1

Introduction



2

**Physical
comorbidity**



3

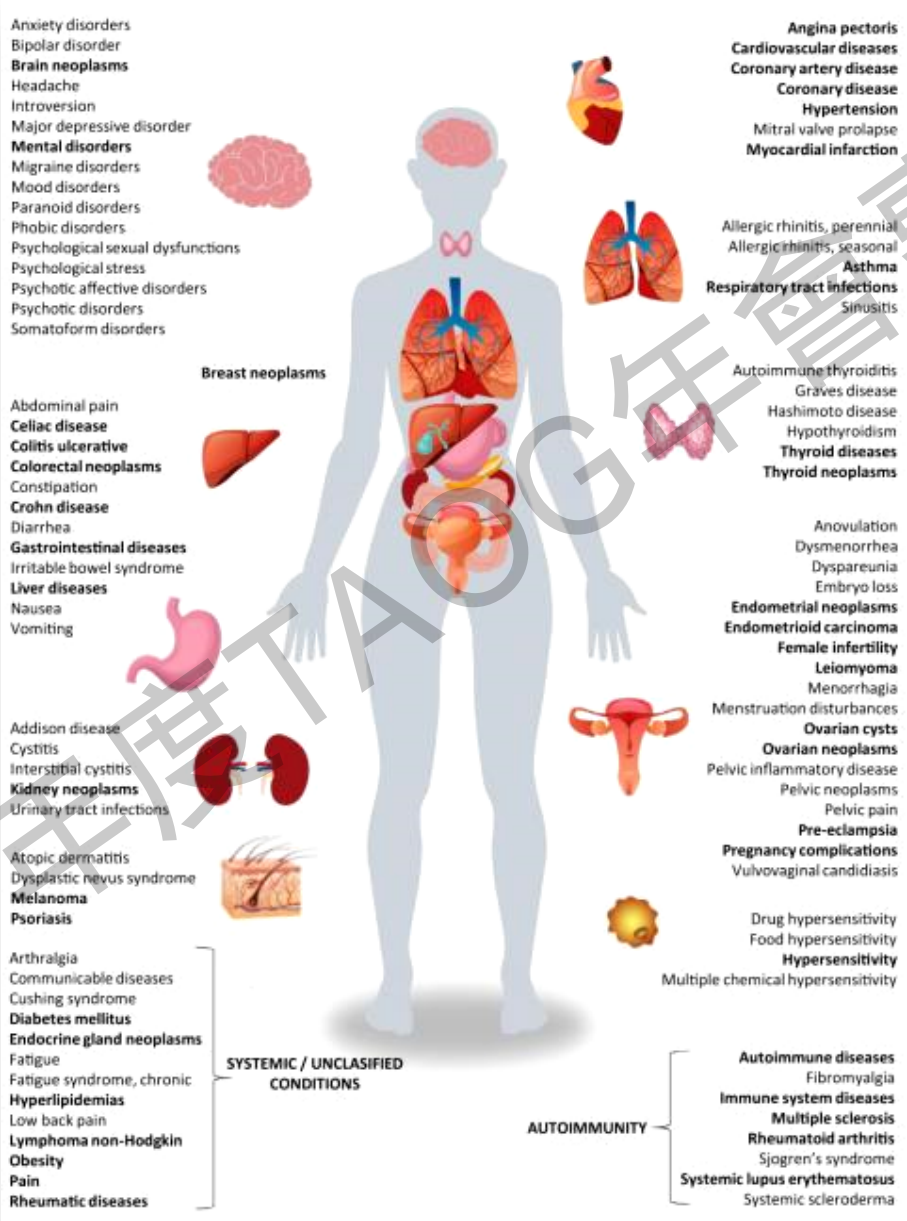
**Psychological
comorbidity**



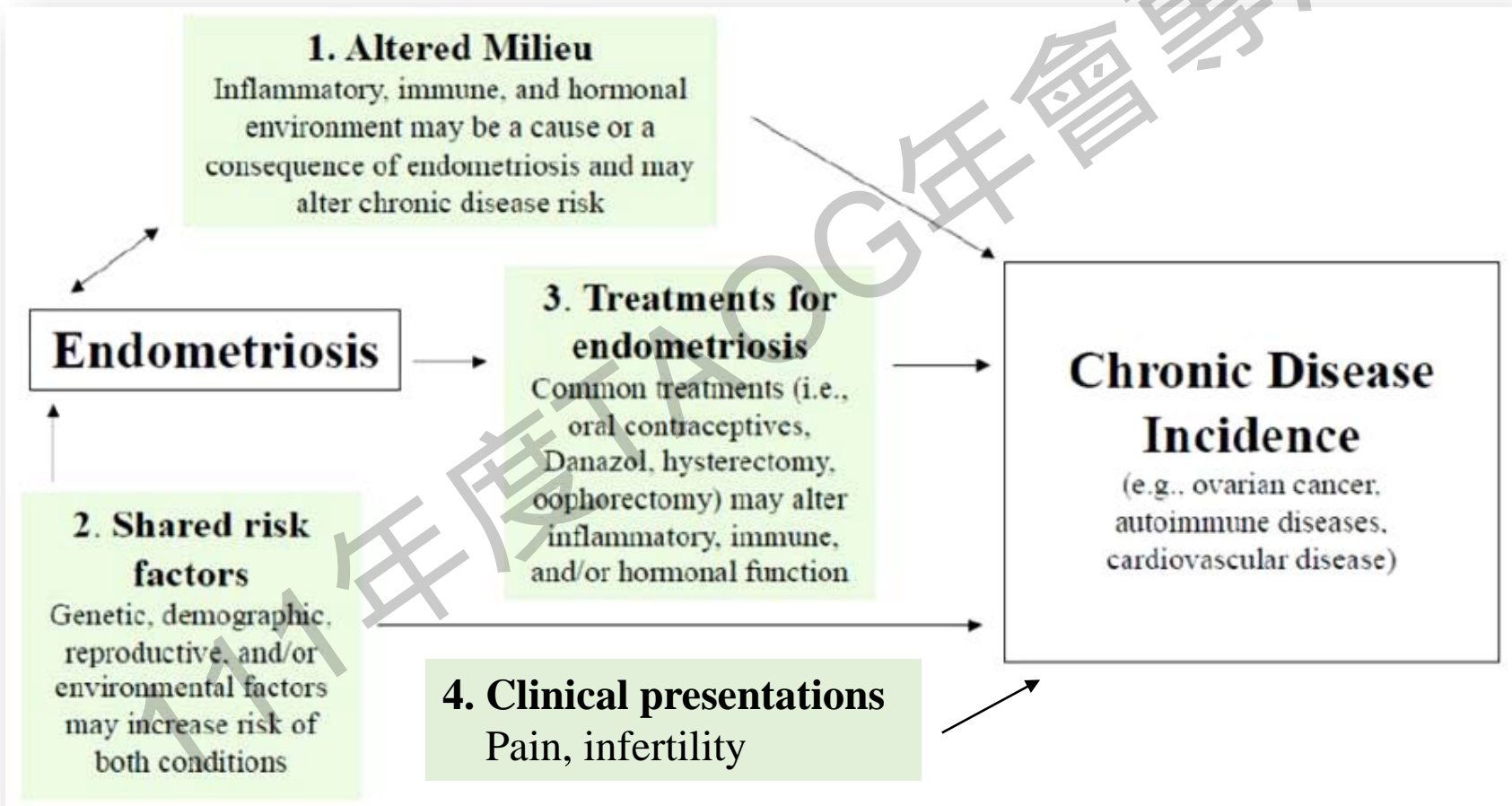
4

Conclusions

Possible comorbidities of endometriosis



Reasons for comorbidity of endometriosis



Article

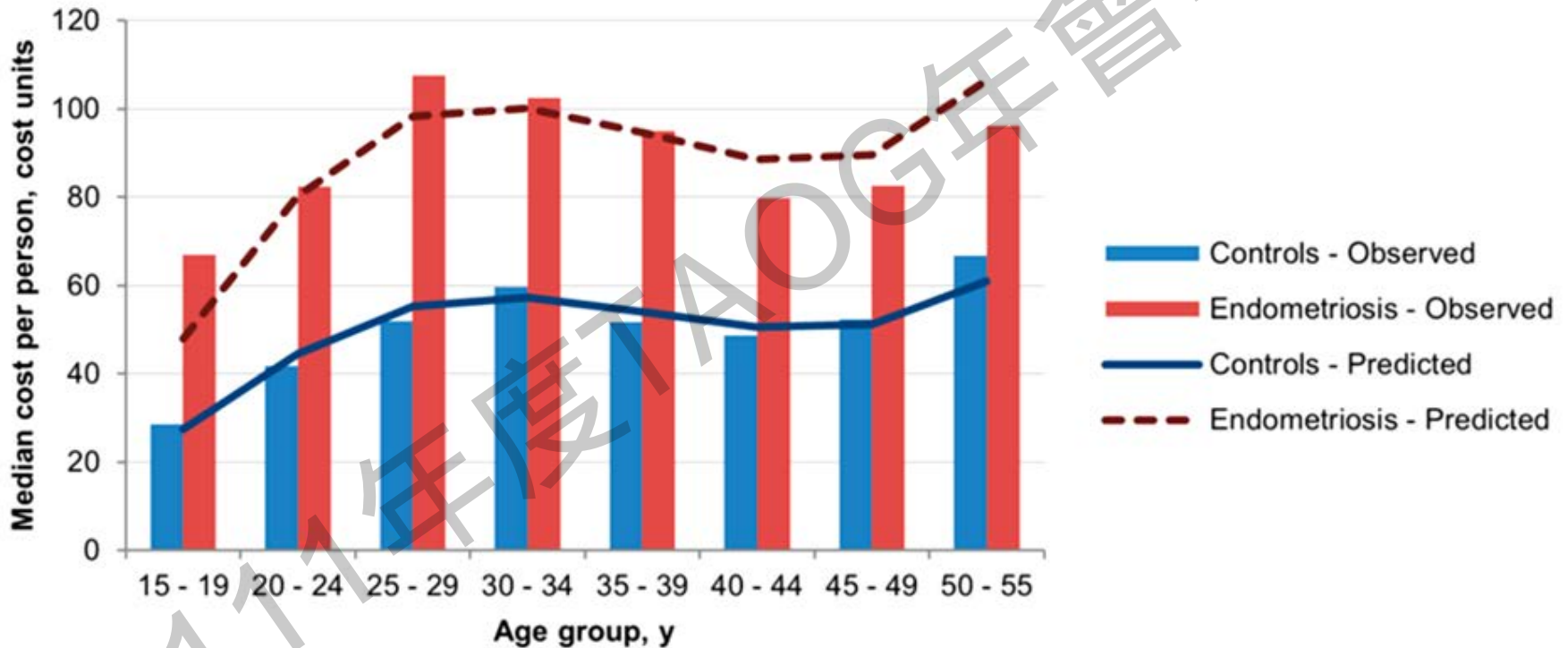
Burden of Endometriosis: Infertility, Comorbidities, and Healthcare Resource Utilization

Vered H. Eisenberg ^{1,*}, Dean H. Decter ¹, Gabriel Chodick ², Varda Shalev ² and Clara Weil ²

Eisenberg et al. J. Clin. Med. 2022

A retrospective case–control study
Israel databases of a 2.1 million-member
nationwide healthcare plan

Endometriosis vs. **Controls**



Medical cost

Endometriosis > Ctrl

Outlines of endometriosis comorbidity



1

Introduction



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Physical
comorbidity



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Psychological
comorbidity



4

Conclusions

Physical comorbidity of endometriosis

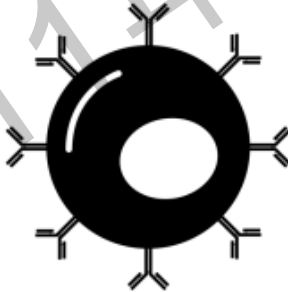
Cancer



CVD



Immune disorders



GI & others



Physical comorbidity of endometriosis

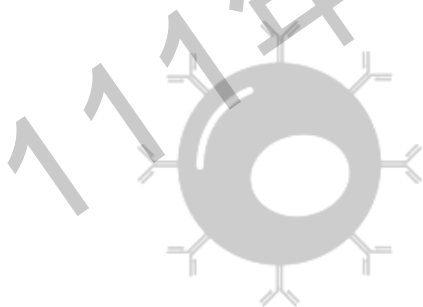
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CVD



Immune disorders

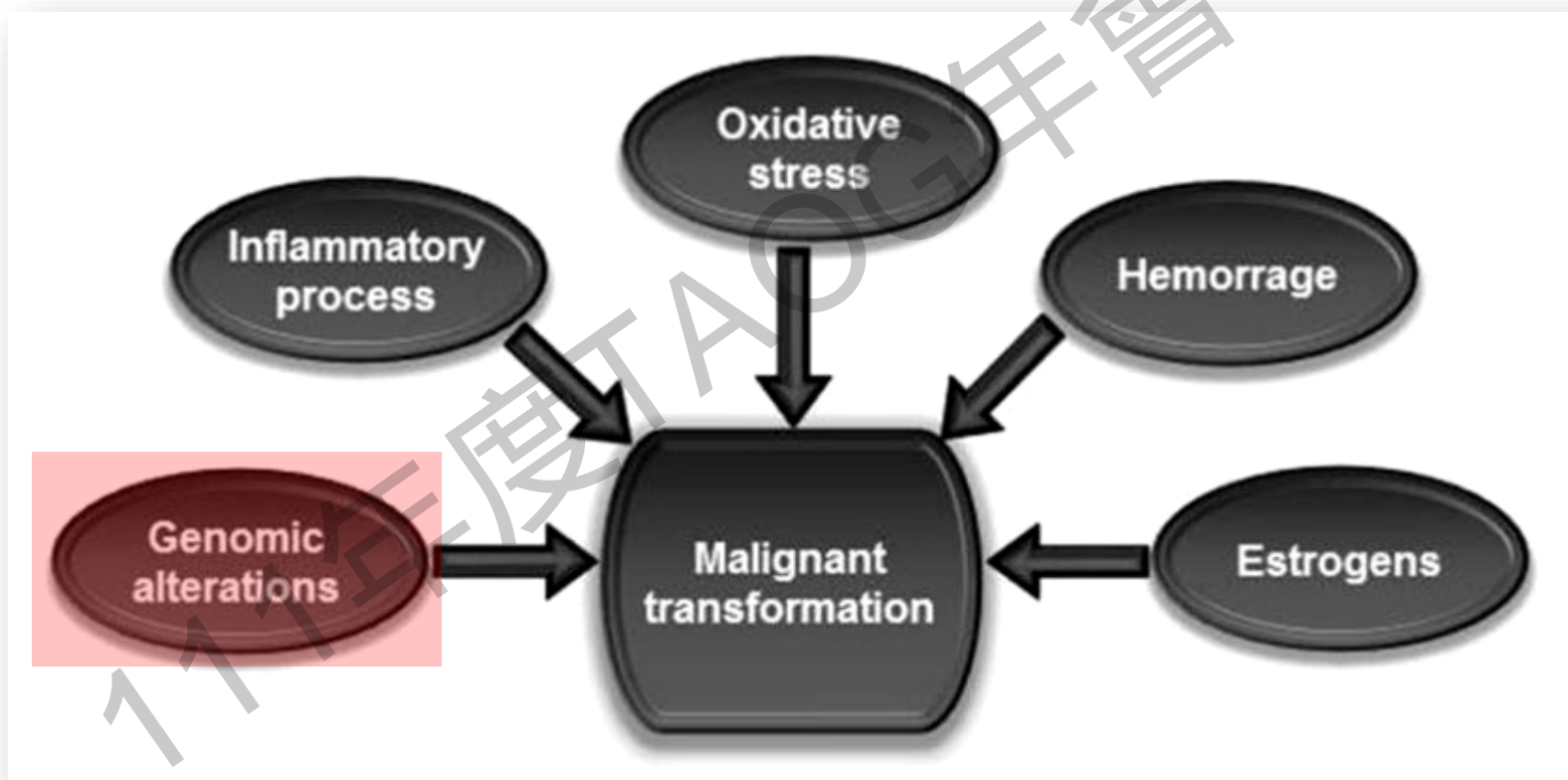


GI & others



Possible mechanisms for the malignant transformation of an endometriosis

Králíčková et al. Archives of Gynecology and Obstetrics 2020



Altered milieu + shared **genetic alterations**

Article

Genetic Contribution of Endometriosis to the Risk of Developing Hormone-Related Cancers

Aintzane Rueda-Martínez ¹, Aiarra Garitazelaia ¹, Ariadna Cilleros-Portet ¹, Sergi Mari ¹, Rebeca Arauzo ¹, Jokin de Miguel ¹, Bárbara E. González-García ¹, Nora Fernández-Jiménez ¹, Jose Ramon Bilbao ^{1,2} and Iraia García-Santisteban ^{1,*}

Rueda-Martínez et al. Int. J. Mol. Sci. 2021

A two-sample mendelian randomization (2SMR) analysis from public genome-wide association studies (GWAS)

Global 2SMR estimates between **endometriosis** and **cancers**

Outcome and Method	Beta	SE	p-Value
Endometrial cancer			
IVW	0.100	0.118	0.400
WM	0.028	0.093	0.767
MRE	1.786	0.420	0.004
Breast cancer			
IVW	0.001	0.045	0.987
WM	0.007	0.038	0.849
MRE	-0.068	0.294	0.824
Ovarian cancer			
IVW	0.251	0.051	9.34×10^{-7}
WM	0.258	0.068	1.37×10^{-4}
MRE	0.840	0.311	3.09×10^{-2}

Methods: inverse variance weighted (IVW), weighted median (WM), MR-Egger (MRE)

**Genetic association
with endometriosis**

Ovarian > EM > Breast cancer

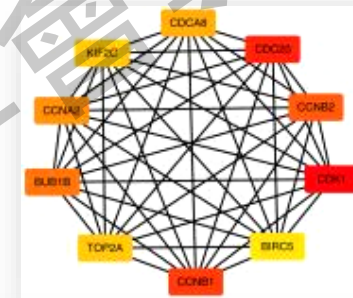
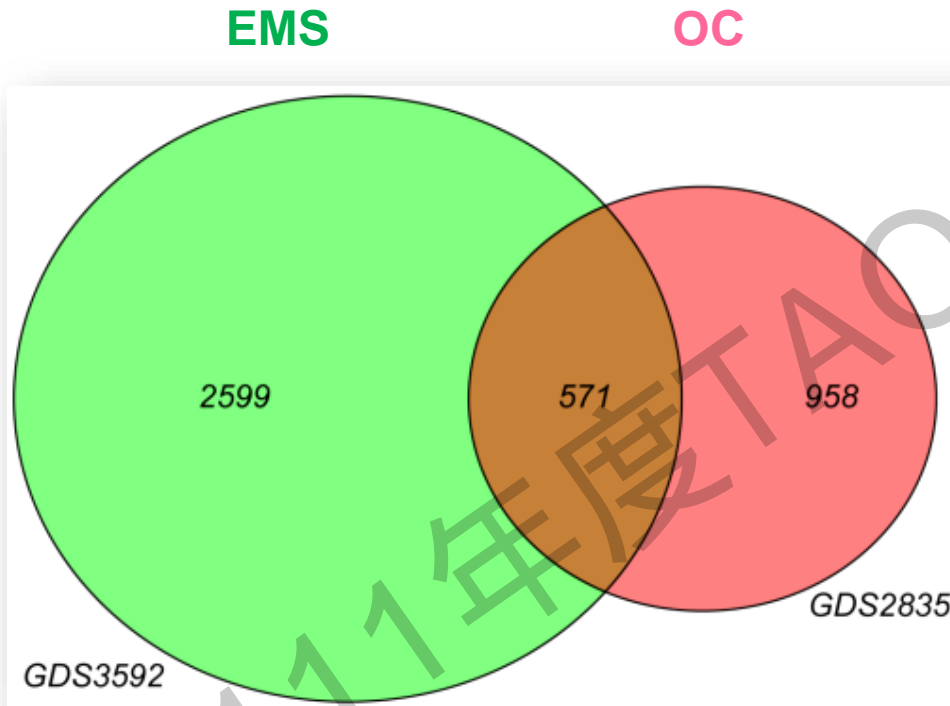
Bioinformatic analysis of key pathways and genes shared between endometriosis and ovarian cancer

Leyi Ni¹ · Yumei Chen¹ · Jie Yang¹ · Cong Chen¹

Ni et al. Archives of Gynecology and Obstetrics 2022

Two datasets from the Gene Expression Omnibus database and the limma package

EMS: endometriosis; OC: ovarian cancer; DEG: differentially expressed genes



Gene name	Protein name	Score
<i>CDK1</i>	Cyclin dependent kinase 1	65
<i>CDC20</i>	Cell division cycle 20	59
<i>CCNB1</i>	Cyclin B1	56
<i>CCNB2</i>	Cyclin B2	55
<i>BUB1B</i>	Budding uninhibited by benzimidazoles 1	50
<i>CCNA2</i>	Cyclin A2	49
<i>CDCA8</i>	Cell division cycle associated 8	47
<i>KIF20C</i>	Kinesin family member 2C	45
<i>TOP2A</i>	Topoisomerase II alpha	45
<i>BIRC5</i>	Baculoviral IAP repeat containing 5	44

571 shared DEGs between EMS and OC

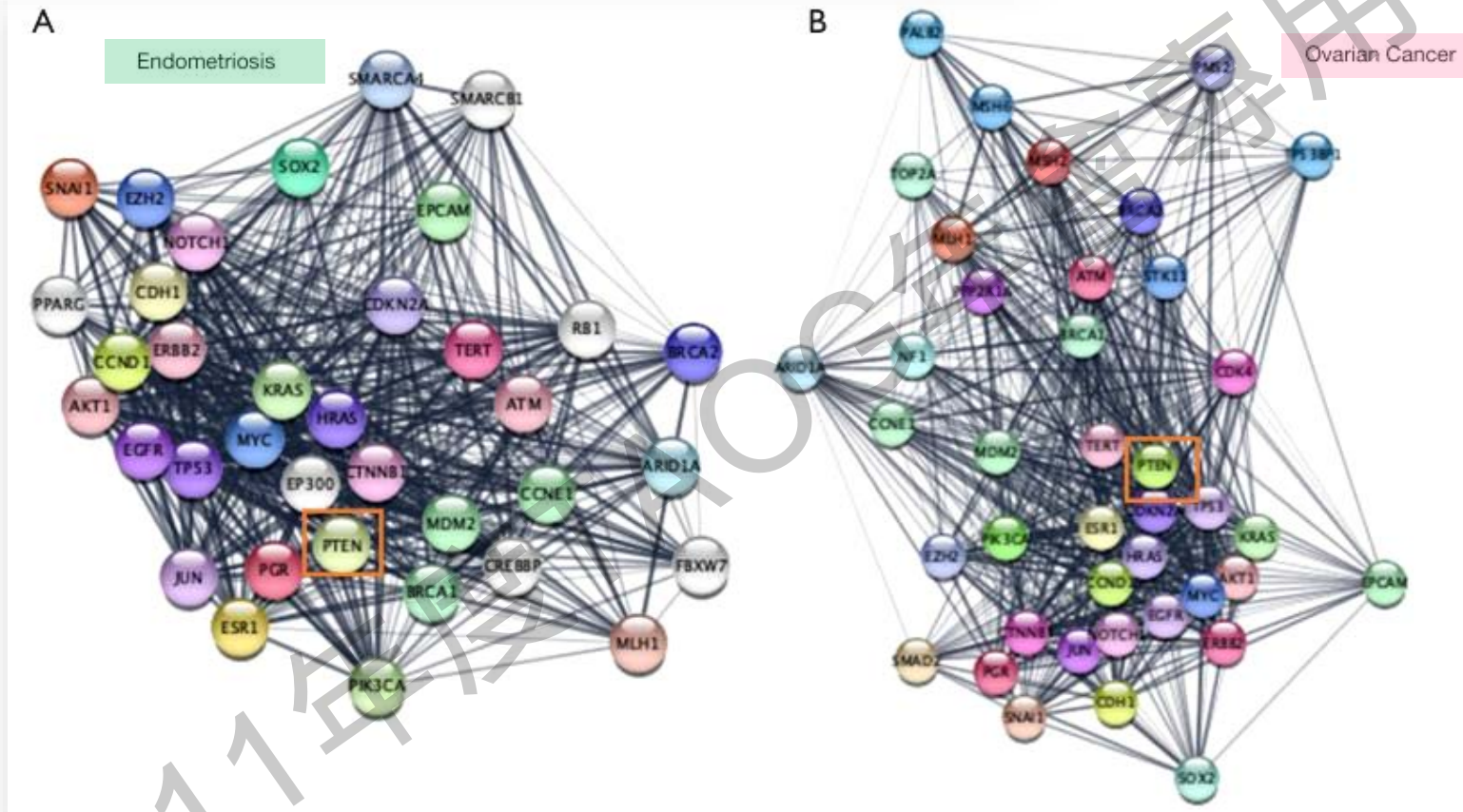
Top 10 hub genes between EMS and OC

Endometriosis and ovarian cancer risk, an epigenetic connection

Brunty et al. Ann Transl Med 2020

Sarah Brunty¹, Brenda Mitchell², Nadim Bou-Zgheib², Nalini Santanam^{1^}

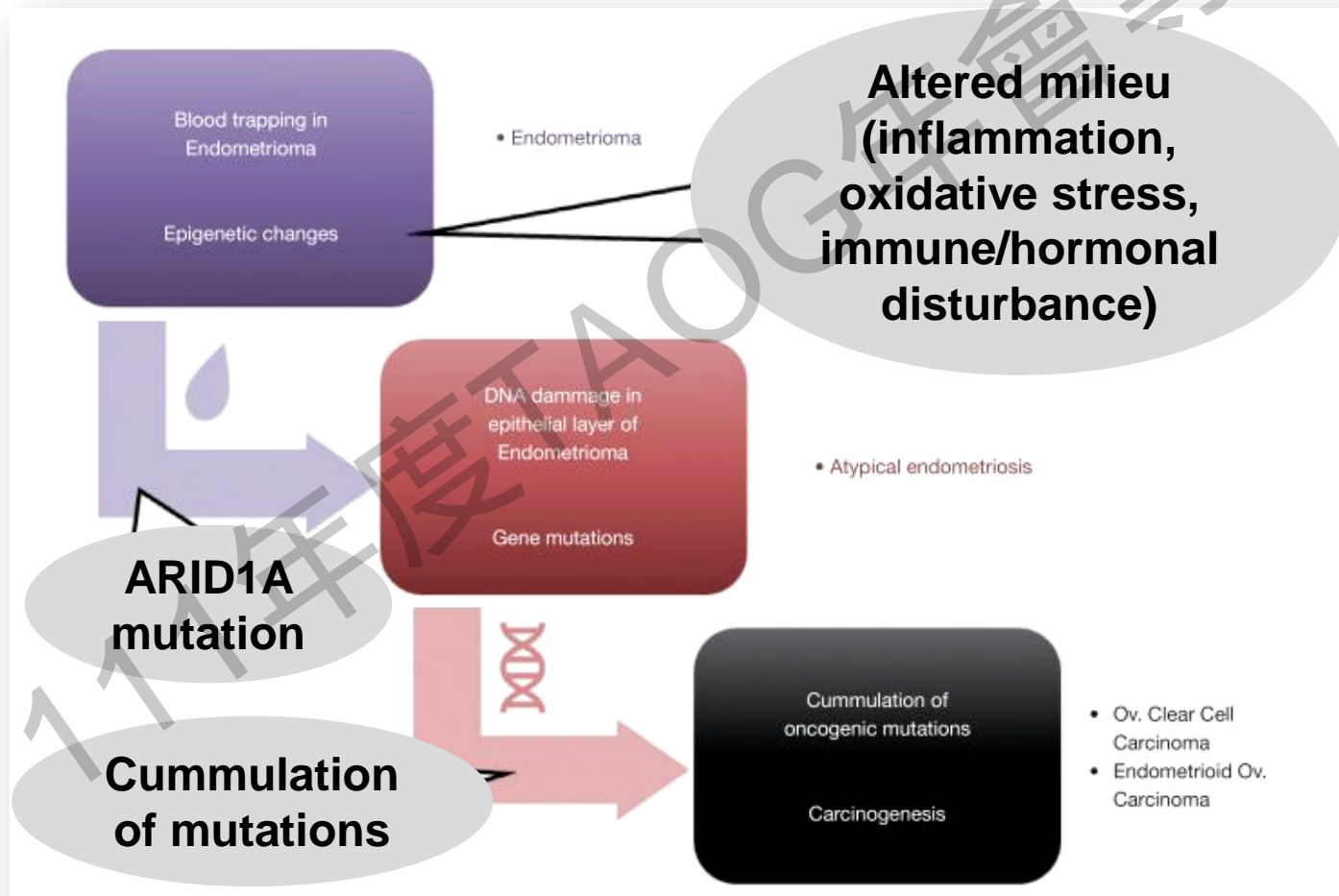
A review



Shared gene alteration between **endometriosis** and **ovarian cancer**:
ARID1A, PTEN, KRAS, PIK3CA, EZH2, CTNNB1...

Hypothetic model of pathogenesis of endometriosis-associated ovarian carcinoma

Samartzis et al. Ann Transl Med 2020

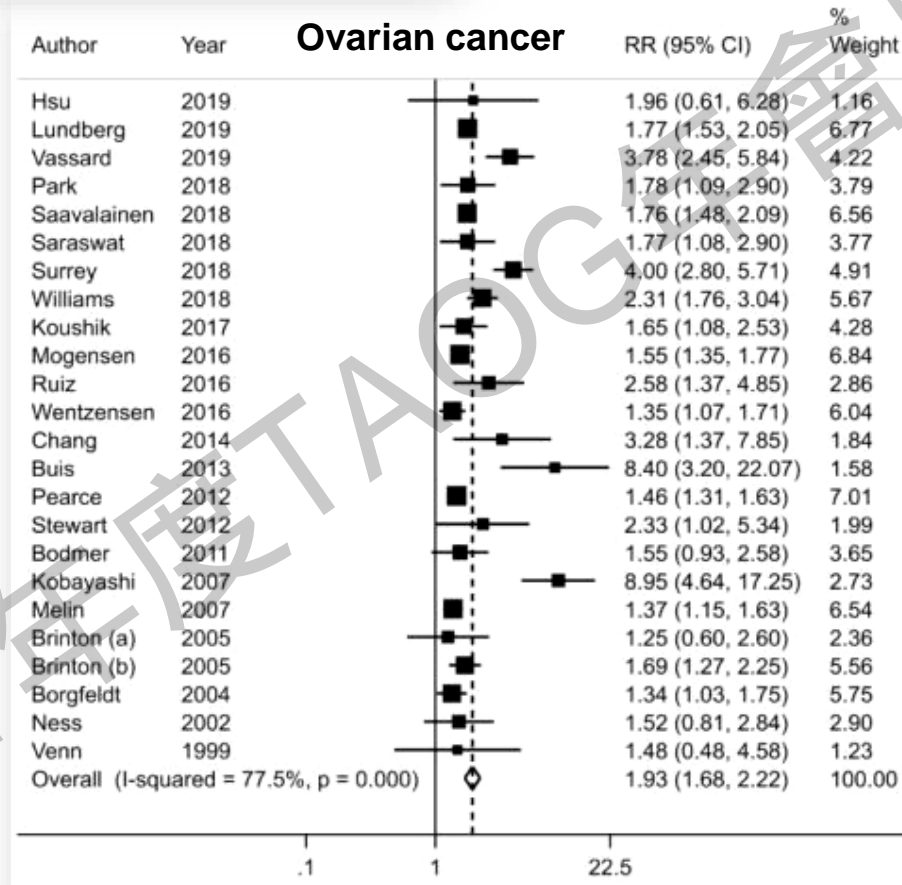


Endometriosis and cancer: a systematic review and meta-analysis

Marina Kvaskoff^{1,2,*}, Yahya Mahamat-Saleh^{1,2}, Leslie V. Farland³, Nina Shigesi⁴, Kathryn L. Terry^{5,6}, Holly R. Harris^{7,8}, Horace Roman^{9,10}, Christian M. Becker⁴, Sawsan As-Sanie¹¹, Krina T. Zondervan^{4,12}, Andrew W. Horne¹³, and Stacey A. Missmer^{6,14,*}

Kvaskoff et al. Human Reproduction Update 2021

24 studies



Ovarian cancer **Endometriosis** > **Ctrl** (RR=1.93)

Risk of Gynecologic Cancer According to the Type of Endometriosis

Liisu Saavalainen, MD, Heini Lassus, MD, PhD, Anna But, MS, Aila Tiitinen, MD, PhD, Päivi Härkki, MD, PhD, Mika Gissler, PhD, Erro Pukkala, PhD, and Oskari Heikinheimo, MD, PhD

Saavalainen et al. Obstet Gynecol 2018

49,933 surgically verified endometriosis

Cancer Type or Site	Observed No.	Expected No.	Ratio of Observed to Expected	95% CI
Cervix uteri*	28	37.1	0.76	0.50–1.09
Adenocarcinoma	11	10.4	1.06	0.53–1.88
Squamous cell carcinoma	8	17.2	0.46	0.20–0.91
Other	9	9.43	0.95	0.44–1.81
Corpus uteri*	65	62.4	1.04	0.80–1.32
Endometrioid	54	50.8	1.06	0.80–1.38
Other	11	11.6	0.95	0.47–1.70
Ovary [†]	129	73.2	1.76	1.47–2.08
Serous	50	36.5	1.37	1.02–1.80
Mucinous	10	11.3	0.88	0.42–1.62
Endometrioid	33	10.6	3.12	2.15–4.38
Clear cell	21	4.06	5.17	3.20–7.89
Other	15	10.8	1.40	0.78–2.30
Other female genital organs [‡]	37	38.0	0.97	0.69–1.34
Vulva	12	16.1	0.75	0.39–1.30
Vagina	6	4.2	1.43	0.52–3.10
Others	19	17.7	1.07	0.65–1.68
Not included above [§]				
Cervix uteri, noninvasive neoplasms ^{*§}	221	271.4	0.81	0.71–0.92
Borderline tumor of the ovary ^{†§}	46	35.5	1.29	0.95–1.72

Ovarian ca. (clear cell)

Endometriosis > Ctrl (RR=5.17)

Ovarian ca. (endometrioid)

Endometriosis > Ctrl (RR=3.12)

Ovarian ca. (serous)

Endometriosis > Ctrl (RR=1.37)



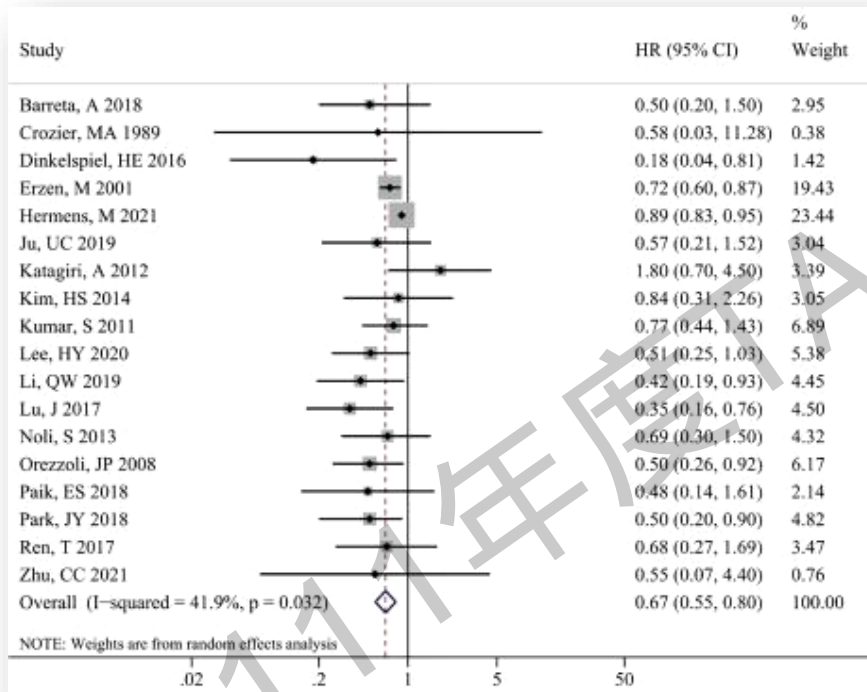
Association Between Endometriosis and Prognosis of Ovarian Cancer: An Updated Meta-Analysis

Peng Chen and Chi-Yuan Zhang*

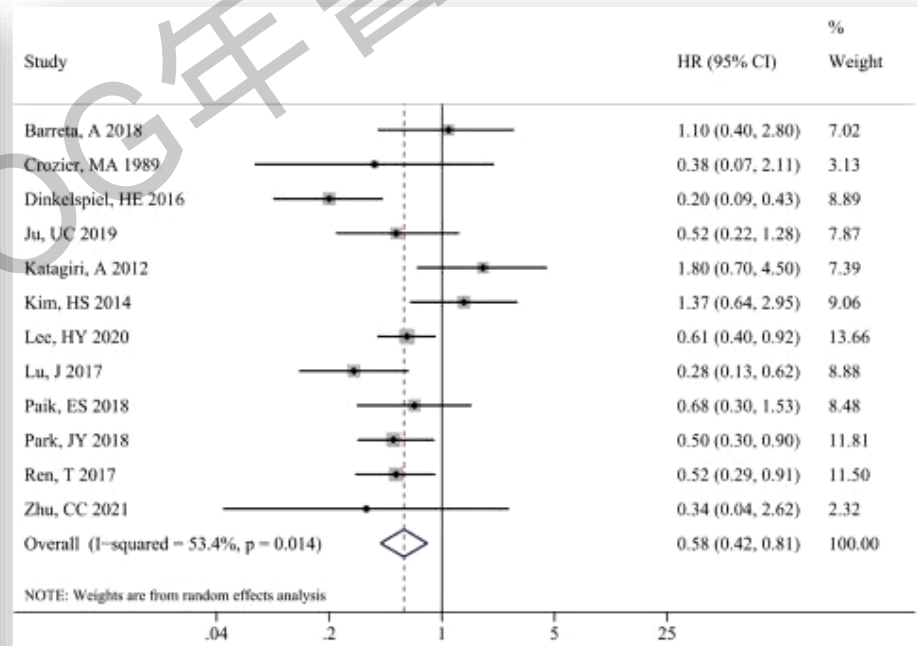
Chen et al. Front. Oncol 2022

21 studies (n=38,641)
Endometriosis-associated ovarian cancer
(**EAOC**) vs. **non-EAOC**

Overall survival (OS)



Progression-free survival (PFS)



OS & PFS

EAOC > non-EAOC

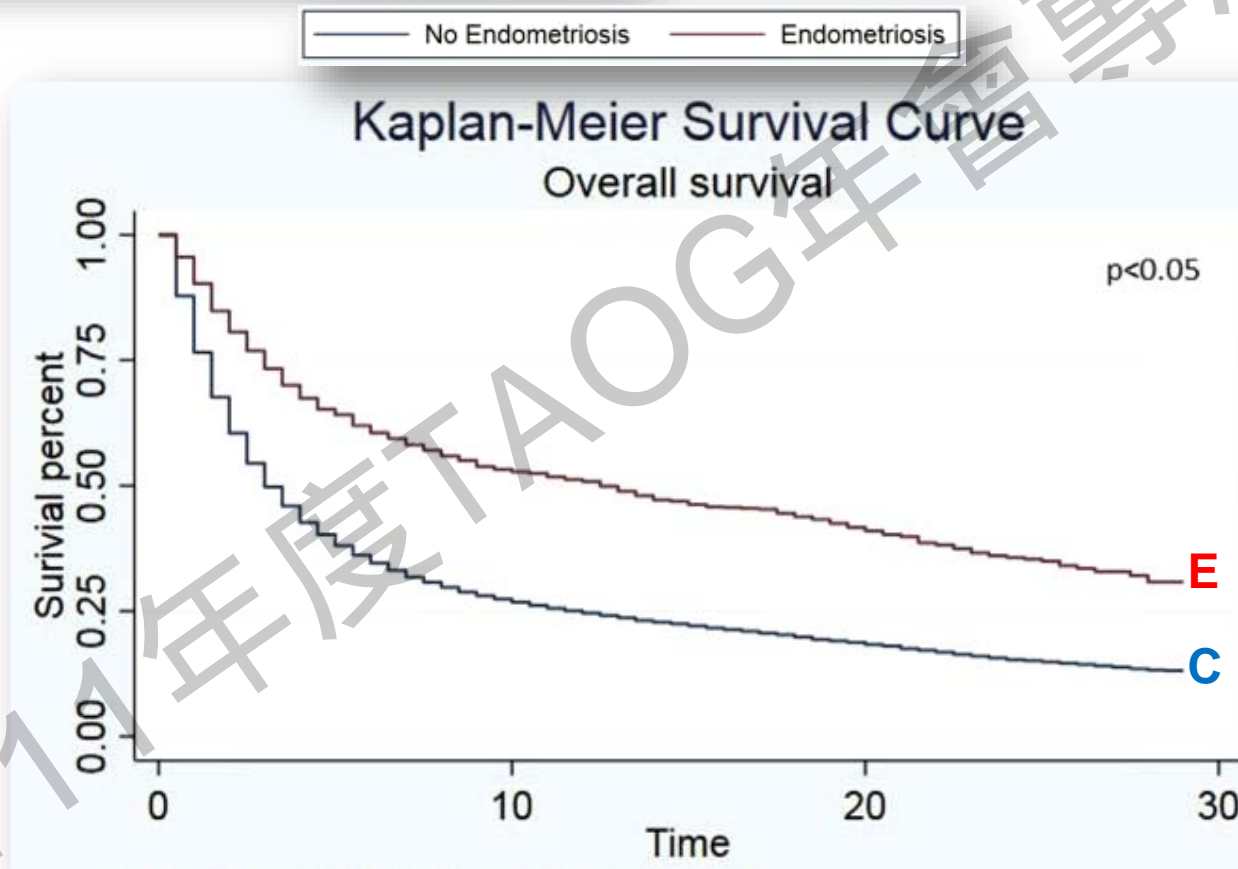
GYNECOLOGY

**Ovarian cancer prognosis in women with endometriosis:
a retrospective nationwide cohort study of 32,419
women**

Marjolein Hermens, MD; Anne M. van Altena, MD, PhD; Maaïke van der Aa, PhD; Johan Bulten, MD, PhD;
Huib A. A. M. van Vliet, MD, PhD; Albert G. Siebers, PhD; Ruud L. M. Bekkers, MD, PhD

Hermens et al. Am J Obstet Gynecol 2021

A retrospective nationwide cohort study
32,419 pts with **ovarian cancer**, of whom
1979 (6.1%) had proven endometriosis



Overall survival

Endometriosis > **Ctrl**

GYNECOLOGY

Ovarian cancer prognosis in women with endometriosis: a retrospective nationwide cohort study of 32,419 women



Marjolain Hermens, MD; Anne M. van Altena, MD, PhD; Maaïke van der Aa, PhD; Johan Bulten, MD, PhD; Huib A. A. M. van Vliet, MD, PhD; Albert G. Siebers, PhD; Ruud L. M. Bekkers, MD, PhD

Baseline characteristics of all patients with ovarian cancer 1990 to 2015

Variables	Endometriosis (n=2008)	No endometriosis (n=33,522)
Age, y ^a	56 (IQR, 49–63)	66 (IQR, 56–75)
Y of diagnosis ^b	2003 (IQR, 1997–2009)	2003 (IQR, 1996–2009)
Surgical treatment for ovarian cancer ^c		
Yes	1936 (97.8)	22,386 (73.6)
No	43 (2.2)	8042 (26.4)
Debulking surgery ^d		
Yes	730 (36.9)	10,989 (36.1)
No	1249 (63.1)	19,451 (63.9)
Residual disease ^e		
Complete resection, no macroscopic residual	241 (12.2)	2988 (9.8)
Optimal, residual <1 cm	388 (19.6)	5611 (18.4)
Incomplete, residual >1 cm	83 (4.2)	2122 (7.0)
Unknown or not applicable	1267 (64.1)	19,719 (64.8)
Chemotherapy ^f		
Yes	1313 (66.3)	20,724 (68.1)
No	666 (33.7)	9716 (31.9)
Ovarian cancer stage ^g		
Stage 1	1020 (52.5)	5617 (18.5)
Stage 2	247 (12.5)	2262 (7.4)
Stage 3	513 (25.9)	13,069 (45.6)
Stage 4	150 (7.6)	5606 (18.4)
Unknown	49 (2.5)	3086 (10.1)
Histologic subtype ^h		
Clear-cell ovarian cancer	338 (17.1)	1187 (3.9)
Endometrioid ovarian cancer	533 (26.9)	2483 (8.2)
Serous ovarian cancer	694 (35.1)	13,832 (45.4)
Mucinous ovarian cancer	228 (11.5)	2958 (9.7)
Adenocarcinoma NOS	186 (9.4)	9980 (32.8)
Histologic grading ⁱ		
Low grade	393 (19.9)	2756 (9.1)
Intermediary	464 (23.4)	4901 (16.1)
High grade	585 (29.6)	11,131 (36.8)
Unknown	537 (27.1)	11,652 (38.3)
Vital status as of Jan. 31, 2019 ^j		
Alive	912 (46.1)	5728 (18.8)
Passed away	1067 (53.9)	24,712 (81.2)

Hermens et al. Am J Obstet Gynecol 2021

A retrospective nationwide cohort study of 32,419 pts with **ovarian cancer**, of whom 1979 (6.1%) had proven endometriosis

Young age
Early stage
Complete resection
Low grade

Endometriosis > Ctrl

REVIEW

Impact of endometriosis on risk of ovarian, endometrial and cervical cancers: a meta-analysis

Jia Ji¹, Ruijuan Liu², Shifeng Tang², Fubin Feng², Cun Liu², Lu Wang³, Wenge Zhao¹, Tingting Zhang¹, Yan Yao¹, Xue Wang¹, Changgang Sun¹

Content first available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

The risk of extra-ovarian malignancies among women with endometriosis: A systematic literature review and meta-analysis

S. Gandini^a, M. Lazzeroni^a, F.A. Peccatori^a, B. Bendinelli^a, C. Saieva^a, D. Palli^a, G. Masala^a, S. Caini^{a,*}

human reproduction update

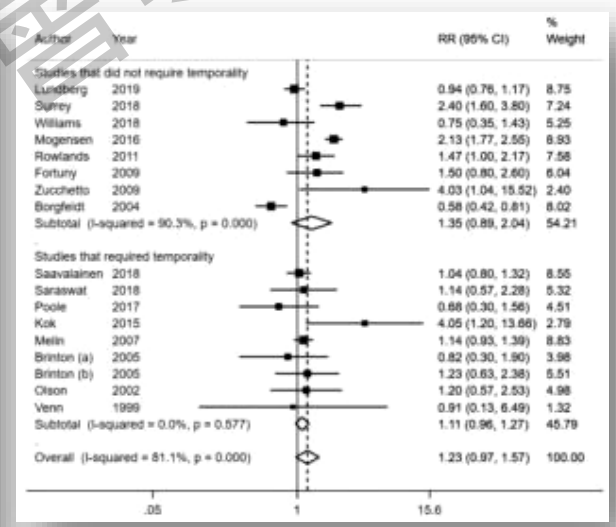
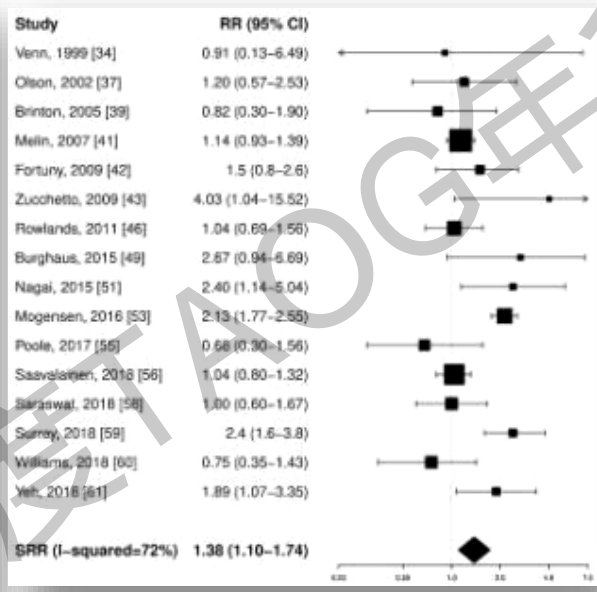
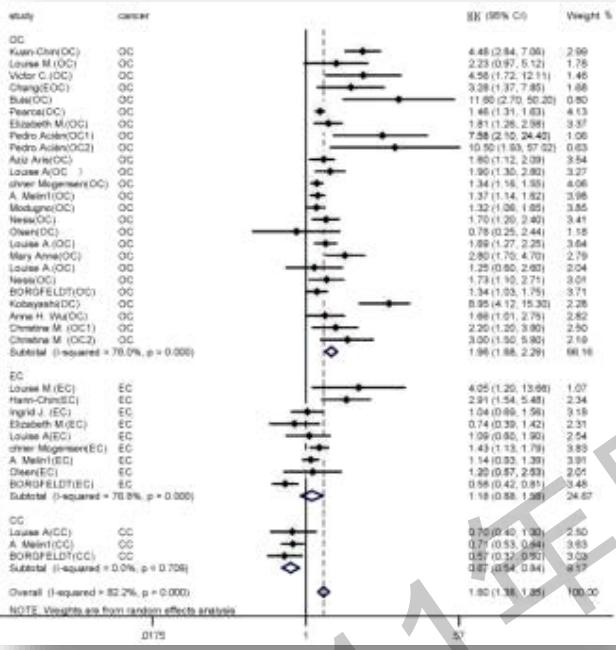
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Jia et al. Archives of Gynecology and Obstetrics 2019

Gandini et al. Critical Reviews in Oncology / Hematology 2019

Kvaskoff et al. Human Reproduction Update 2021



EM cancer

Endometriosis = Ctrl

Endometriosis > Ctrl

Endometriosis = Ctrl



Endometriosis and risks for ovarian, endometrial and breast cancers: A nationwide cohort study



Julie Brøchner Mogensen ^a, Susanne K. Kjær ^{a,b}, Lene Mellekjær ^a, Allan Jensen ^{a,*}

Mogensen et al. Gynecologic Oncology 2016

A retrospective population-based cohort study
Danish National Patient Register
45,790 women with endometriosis

Histotype of cancer	O	E	SIR (95% CI)
Ovarian			
Serous	70	66.80	1.05 (0.82–1.32)
Mucinous	10	13.41	0.75 (0.36–1.37)
Endometrioid	28	17.09	1.64 (1.09–2.37)
Clear-cell	25	6.87	3.64 (2.36–5.38)
Endometrial			
Type 1	67	43.41	1.54 (1.20–1.96)
Type 2	4	3.78	1.06 (0.28–2.71)
Breast			
Ductal	1034	997.28	1.04 (0.97–1.10)
Lobular	176	153.82	1.14 (0.98–1.33)

Type 1 EM cancer

Endometriosis > Ctrl

Type 2 EM cancer

Endometriosis = Ctrl

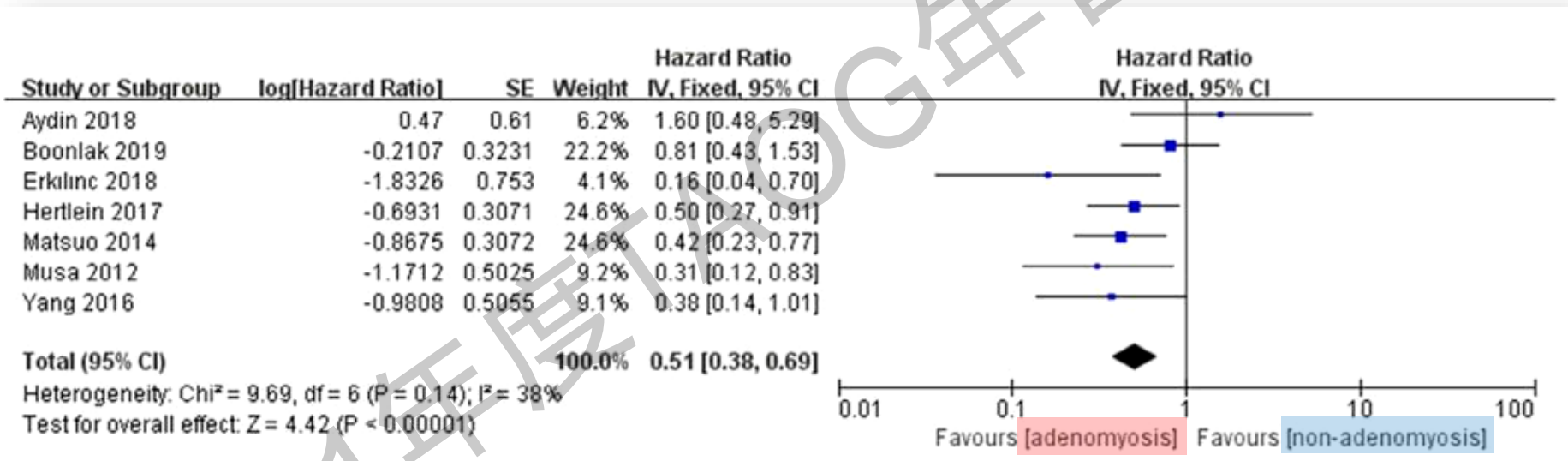
Prognostic significance of co-existent adenomyosis on outcomes and tumor characteristics of endometrial cancer: A meta-analysis

Min An, Hua Duan and Ying Zhang

An et al. J. Obstet. Gynaecol. Res. 2020

7 retrospective studies comprising
1308 **EM cancer pts with adenomyosis** and
3734 pts **without adenomyosis**

Overall survival rate



Overall survival

Adenomyosis > Ctrl

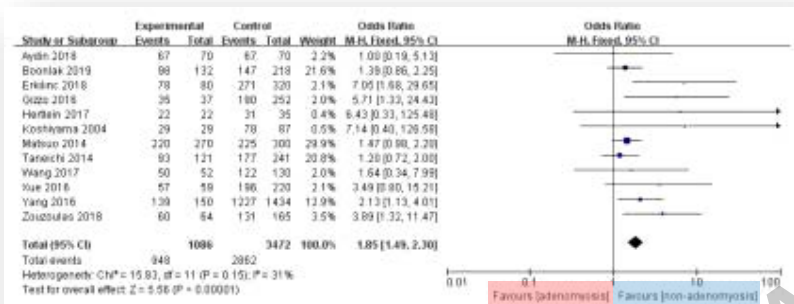
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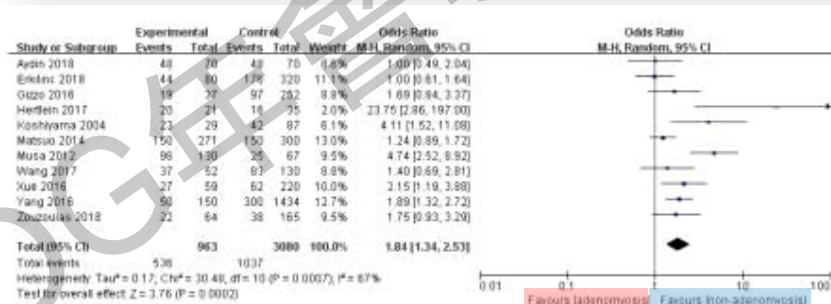
An et al. J. Obstet. Gynaecol. Res. 2020

14 retrospective studies comprising 1308 EM cancer pts with adenomyosis and 3734 pts without adenomyosis

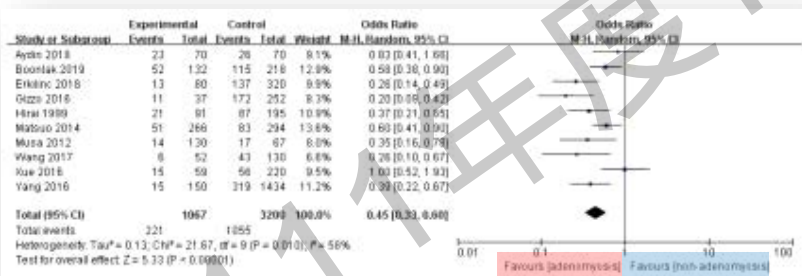
FIGO I-II



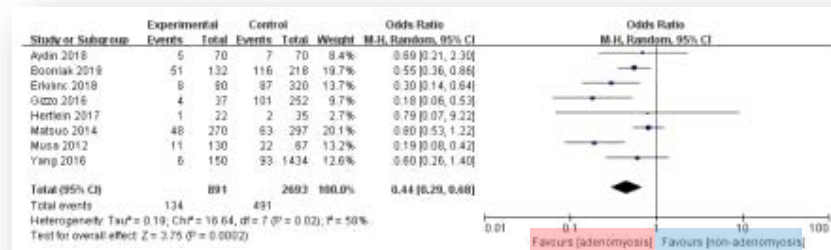
Grade I



Deep myometrial invasion (DMI)



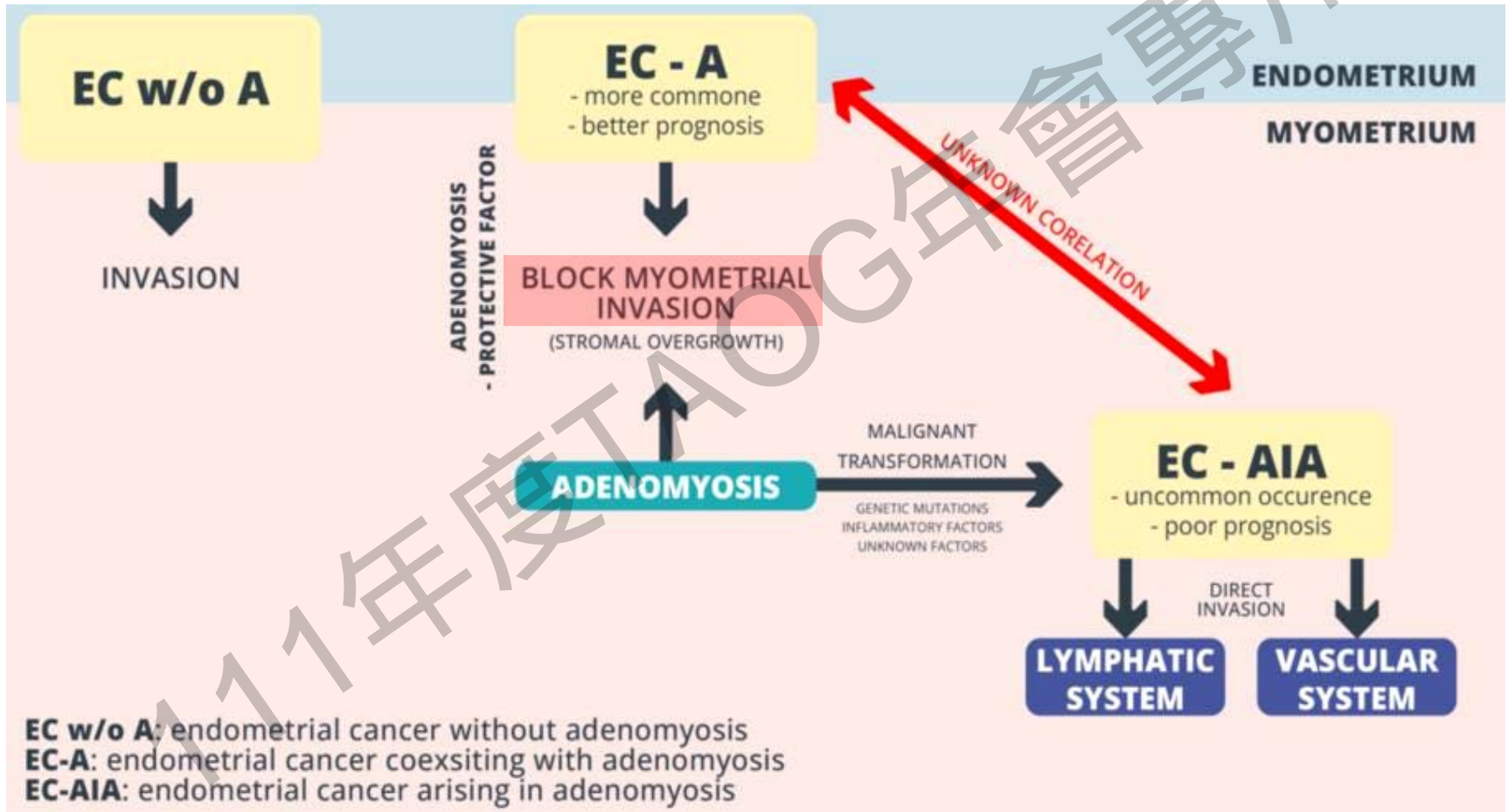
LVSI



Early stage/Good grade
DMI/LVSI

Adenomyosis > Ctrl
Adenomyosis < Ctrl

Adenomyosis may **block** myometrial invasion of EM cancer



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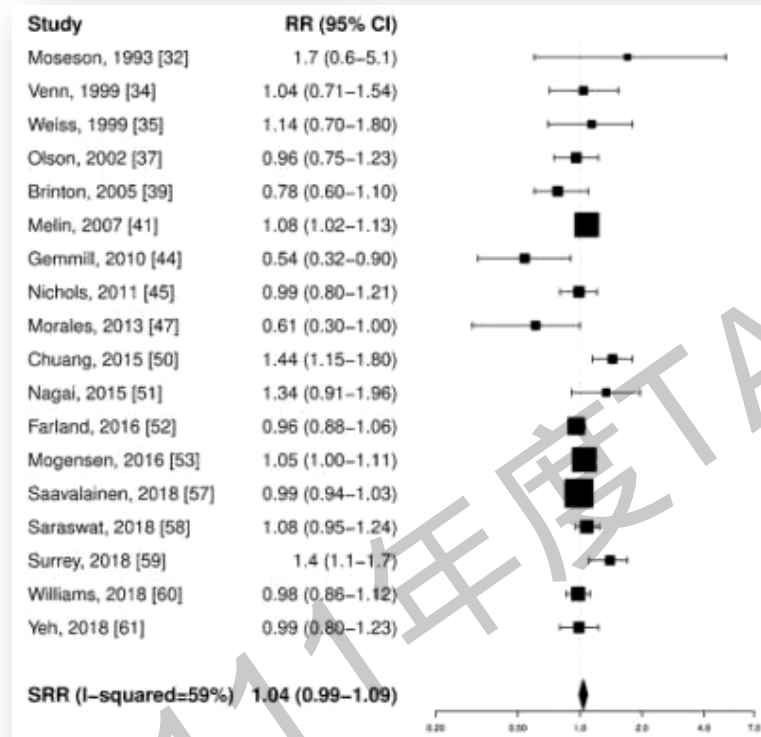
Critical Reviews in Oncology / Hematology

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Gandini et al. Critical Reviews in Oncology / Hematology 2019

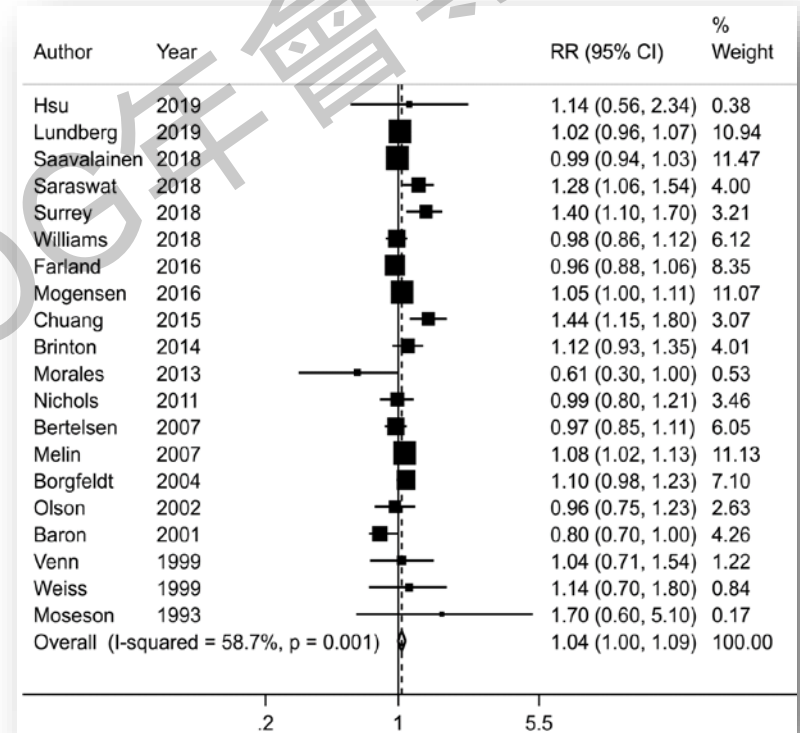


human reproduction update

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Kvaskoff et al. Human Reproduction Update 2021



Breast cancer

Endometriosis = Ctrl

Endometriosis > Ctrl

Laparoscopically Confirmed Endometriosis and Breast Cancer in the Nurses' Health Study II

Leslie V. Farland, ScD, Rulla M. Tamimi, ScD, A. Heather Eliassen, ScD, Donna Spiegelman, ScD, Susan E. Hankinson, ScD, Wendy Y. Chen, MD, MPH, and Stacey A. Missmer, ScD

Farland et al. Obstet Gynecol 2016

A prospective cohort study
 Nurses' Health Study II cohort (**NHS II**)
 5,389 women **with endometriosis**
 (laparoscopically confirmed) vs.
 109,936 women **without endometriosis**

Endometriosis	Cases Per Person-Year	Age and Calendar Time-Adjusted Model [HR (95% CI)]*	Multivariable-Adjusted Model [HR (95% CI)]*
Breast cancer overall			
No	4,479/2,329,489	1.0 (referent)	1.0 (referent)
Yes	500/215,434	1.07 (0.97-1.17)	0.96 (0.88-1.06)

Breast cancer (overall)

Endometriosis = Ctrl

Tumor Hormone Receptor Status	Patients Without Endometriosis	Patients With Endometriosis	Age and Calendar Time-Adjusted Model [HR (95% CI)]*†	Multivariable-Adjusted Model [HR (95% CI)]*†
ER+/PR+	2,333	246	1.14 (1.00-1.30)	1.00 (0.87-1.14)
ER+/PR-	309	62	2.17 (1.65-2.85)	1.90 (1.44-2.50)
ER-/PR-	528	49	1.00 (0.75-1.34)	0.90 (0.67-1.21)

Breast cancer (ER+/PR+)

Endometriosis = Ctrl

Breast cancer (ER-/PR-)

Endometriosis = Ctrl

Breast cancer (ER+/PR-)

Endometriosis > Ctrl

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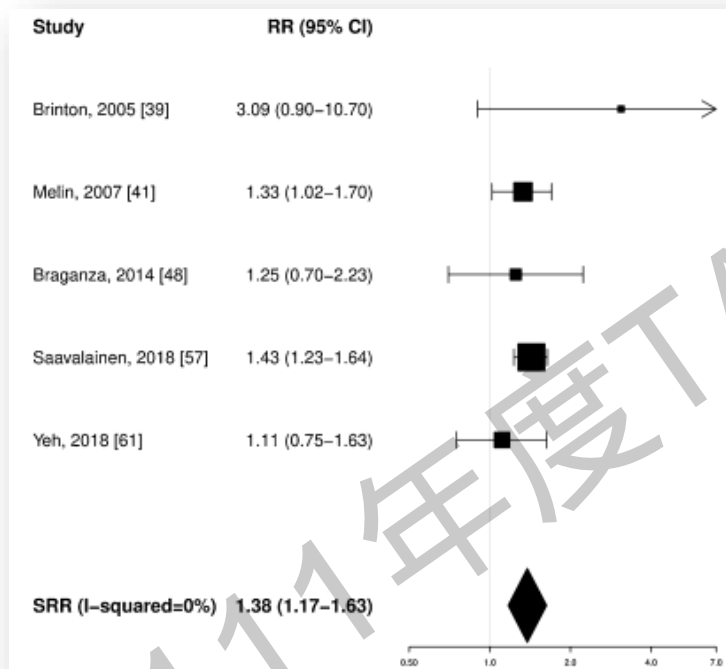
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Gandini et al. Critical Reviews in Oncology / Hematology 2019

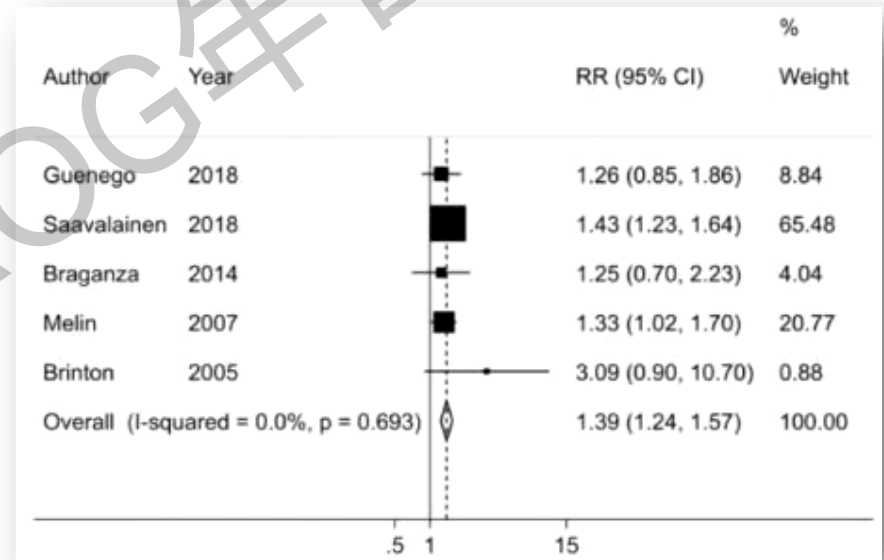


human reproduction update

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Kvaskoff et al. Human Reproduction Update 2021



Thyroid cancer

Endometriosis > Ctrl

Endometriosis > Ctrl

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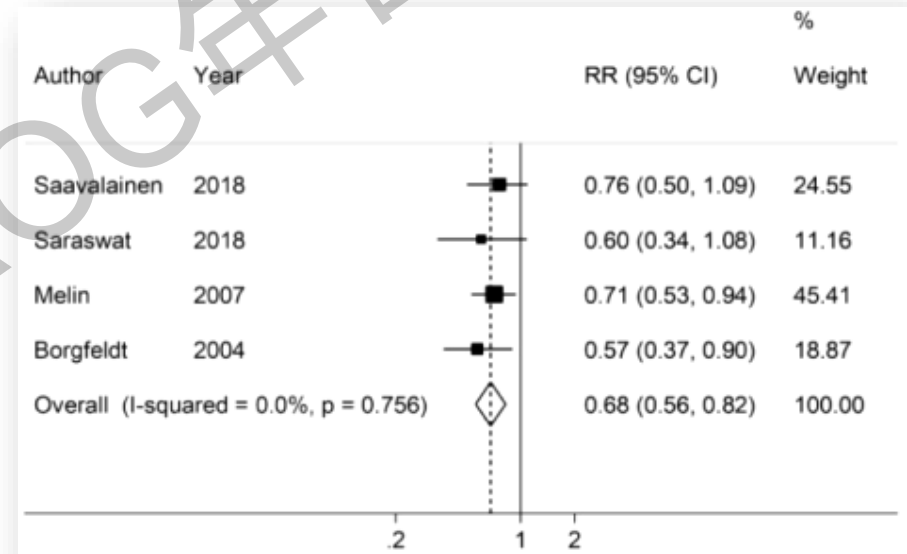
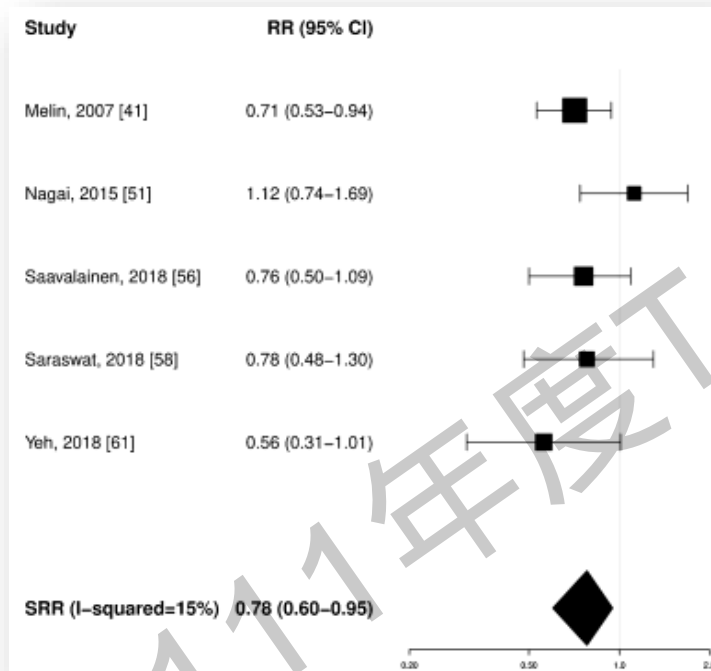
Gandini et al. Critical Reviews in Oncology / Hematology 2019

human reproduction update

Endometriosis and cancer: a systematic review and meta-analysis

Marina Kvaskoff^{1,2,*}, Yahya Mahamat-Saleh^{1,2}, Leslie V. Farland³, Nina Shigesaki⁴, Kathryn L. Terry^{5,6}, Holly R. Harris^{7,8}, Horace Roman^{9,10}, Christian M. Becker⁴, Sawsan As-Sanie¹¹, Krina T. Zondervan^{4,12}, Andrew W. Horne¹³, and Stacey A. Missmer^{6,14,*}

Kvaskoff et al. Human Reproduction Update 2021



Cervical cancer

Endometriosis < Ctrl

Endometriosis < Ctrl

Content lists available at ScienceDirect

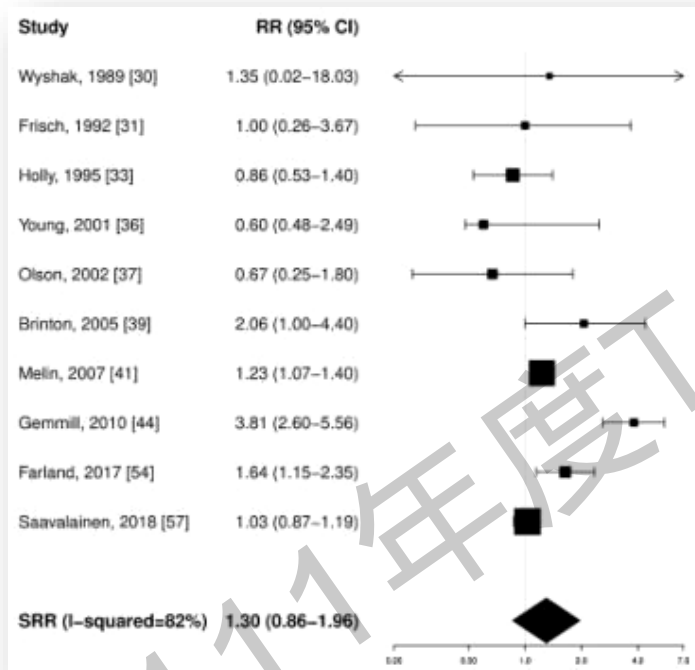
Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

The risk of extra-ovarian malignancies among women with endometriosis: A systematic literature review and meta-analysis

S. Gandini^a, M. Lazzeroni^a, F.A. Peccatori^a, B. Bendinelli^a, C. Saieva^d, D. Palli^d, G. Masala^d, S. Caini^e

Gandini et al. Critical Reviews in Oncology / Hematology 2019

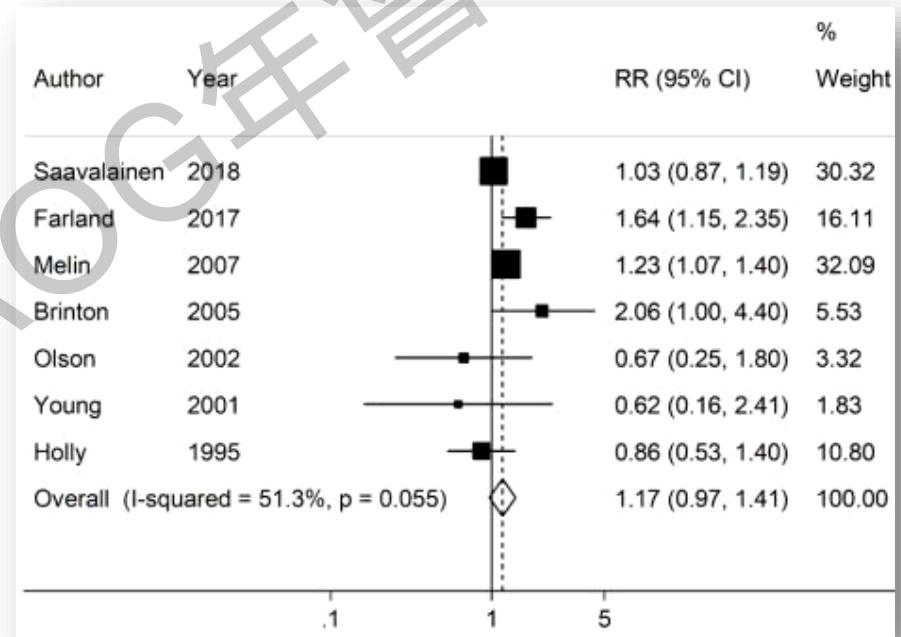


human reproduction update

Endometriosis and cancer: a systematic review and meta-analysis

Marina Kvaskoff^{1,2,*}, Yahya Mahamat-Saleh^{1,2}, Leslie V. Farland³, Nina Shigesi⁴, Kathryn L. Terry^{5,6}, Holly R. Harris^{7,8}, Horace Roman^{9,10}, Christian M. Becker⁴, Sawsan As-Sanie¹¹, Krina T. Zondervan^{4,12}, Andrew W. Horne¹³, and Stacey A. Missmer^{6,14,*}

Kvaskoff et al. Human Reproduction Update 2021



Melanoma

Endometriosis = Ctrl

Endometriosis = Ctrl

Physical comorbidity of endometriosis

Cancer



CVD



Immune disorders



GI & others



GYNECOLOGY

Endometriosis and atherosclerosis: what we already know and what we have yet to discover

Luca Santoro, MD, PhD; Ferruccio D'Onofrio, MD; Roberto Flore, MD;
Antonio Gasbarrini, MD; Angelo Santoliquido, MD

Santoro et al. AJOG 2015

A review

Studies evaluating markers of atherosclerosis in women affected by endometriosis

Study authors, country	Population	Parameter	Main results
Pretta et al, ⁷ Italy	66 patients, 66 centers	ccIMT, DC, SIP	Women with endometriosis do not have more subclinical atherosclerosis than the general population.
Kinugasa et al, ⁸ Japan	41 patients, 28 centers	FMD, ADMA, SIP	Increased plasma ADMA levels and enhanced inflammation are associated with inhibited function in women with endometriosis.
Santoro et al, ⁹ Italy	37 patients, 31 centers	ccIMT, FMD, SIP, EAP	Women with endometriosis have more subclinical atherosclerosis with respect to controls, as documented by endothelial function impairment and inflammation, in absence of structural atherosclerotic changes.
Santoro et al, ¹⁰ Italy	22 patients, 10 centers	ccIMT, FMD, SIP, EAP	Surgical treatment of endometriosis is associated with a regression of endothelial dysfunction in these patients.
Tani et al, ¹¹ Japan	28 patients, 21 centers	PWV, SIP, EAP	Women with endometriosis show significantly increased arterial stiffness with respect to general population.

ADMA, plasma asymmetric dimethylarginine; ccIMT, carotid intima-media thickness; DC, distensibility coefficient; EAP, endothelial activation parameters; FMD, flow-mediated dilation; PWV, pulse wave velocity; SIP, serological inflammatory parameters.

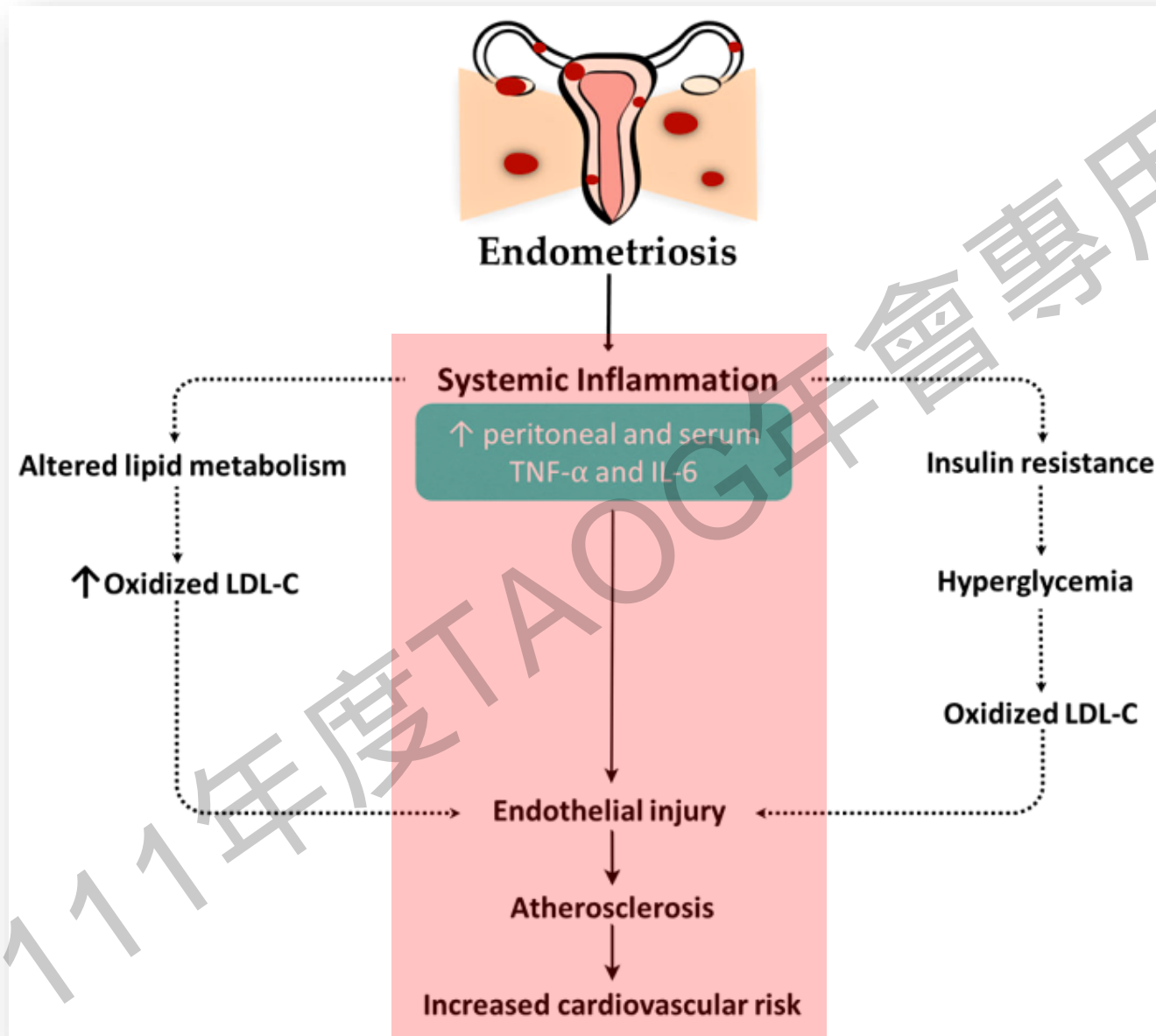
Endometriosis

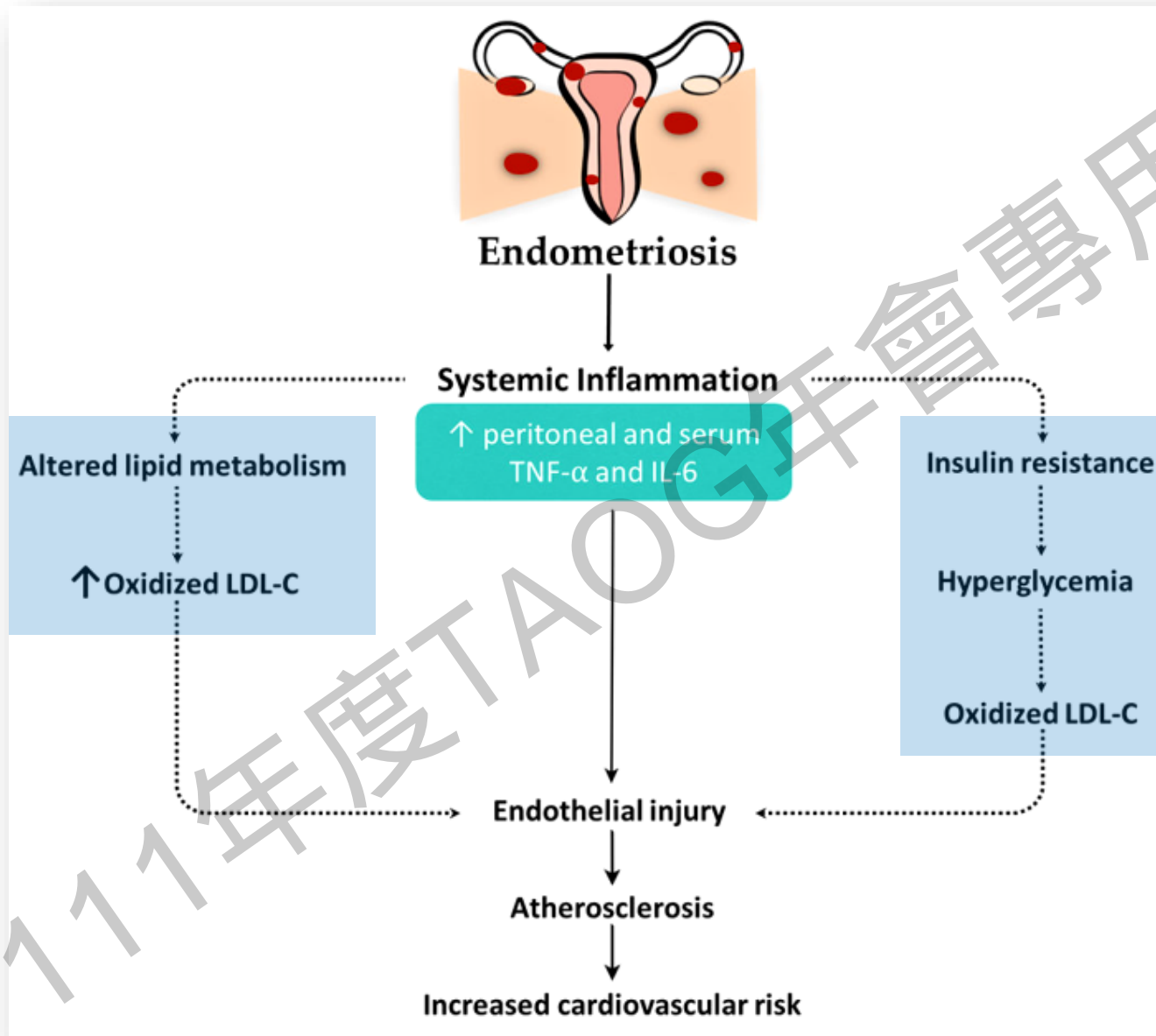


Endothelial dysfunction



Subclinical atherosclerosis





Epidemiology/Population

Association Between Endometriosis and Hypercholesterolemia or Hypertension

Fan Mu, Janet Rich-Edwards, Eric B. Rimm, Donna Spiegelman, John P. Forman, Stacey A. Missmer

Mu et al. Hypertension 2017

Outcome	Exposure	
	Endometriosis	
	No	Yes
Hypercholesterolemia		
No. of cases	34626	3708
Person-years	1 373 691	105 236
Age- and calendar time-adjusted model	1.00	1.31 (1.27–1.36)
Multivariable adjusted	1.00	1.25 (1.21–1.30)
Hypertension		
No. of cases	26 034	2871
Person-years	1 582 120	132 355
Age- and calendar time-adjusted model	1.00	1.16 (1.11–1.20)
Multivariable adjusted	1.00	1.14 (1.09–1.18)

Diabetologia (2021) 64:552–560
<https://doi.org/10.1007/s00125-020-05347-6>

ARTICLE



A prospective study of endometriosis and risk of type 2 diabetes

Leslie V. Farland¹ · William J. Degnan² · Holly R. Harris^{3,4} · Deirdre K. Tobias^{5,6} · Stacey A. Missmer^{7,8}

Farland et al. Diabetologia 2021

Endometriosis	Cases/person-years	HR for incident type 2 diabetes (95% CI)		p value ^c
		Model 1 ^a	Model 2 ^b	
Stratified by age				
<50 years old				
No	3261/1,575,674	1.0 (referent)	1.0 (referent)	
Yes	352/133,918	1.08 (0.97, 1.21)	1.09 (0.97, 1.22)	0.59
≥50 years old				
No	4282/872,611	1.0 (referent)	1.0 (referent)	
Yes	601/109,199	1.13 (1.04, 1.23)	1.06 (0.97, 1.15)	
Stratified by menopausal status				
Premenopausal				
No	3330/1,607,710	1.0 (referent)	1.0 (referent)	
Yes	204/100,320	0.93 (0.81, 1.07)	1.07 (0.92, 1.23)	0.42
Postmenopausal				
No	3602/730,315	1.0 (referent)	1.0 (referent)	
Yes	677/128,436	1.11 (1.02, 1.21)	1.08 (0.99, 1.18)	
Stratified by BMI				
<30 kg/m²				
No	1635/1,702,054	1.0 (referent)	1.0 (referent)	
Yes	245/168,105	1.31 (1.14, 1.50)	1.17 (1.02, 1.35)	0.01
≥30 kg/m²				
No	4940/452,048	1.0 (referent)	1.0 (referent)	
Yes	579/48,084	1.02 (0.93, 1.11)	1.00 (0.91, 1.09)	

Hypertension

Endometriosis > Ctrl (aRR=1.14)

Hypercholesterolemia

Endometriosis > Ctrl (aRR=1.25)

Type 2 DM

Endometriosis > Ctrl (aHR=1.17)

Further Evidence for Hypercoagulability in Women With Ovarian Endometriomas

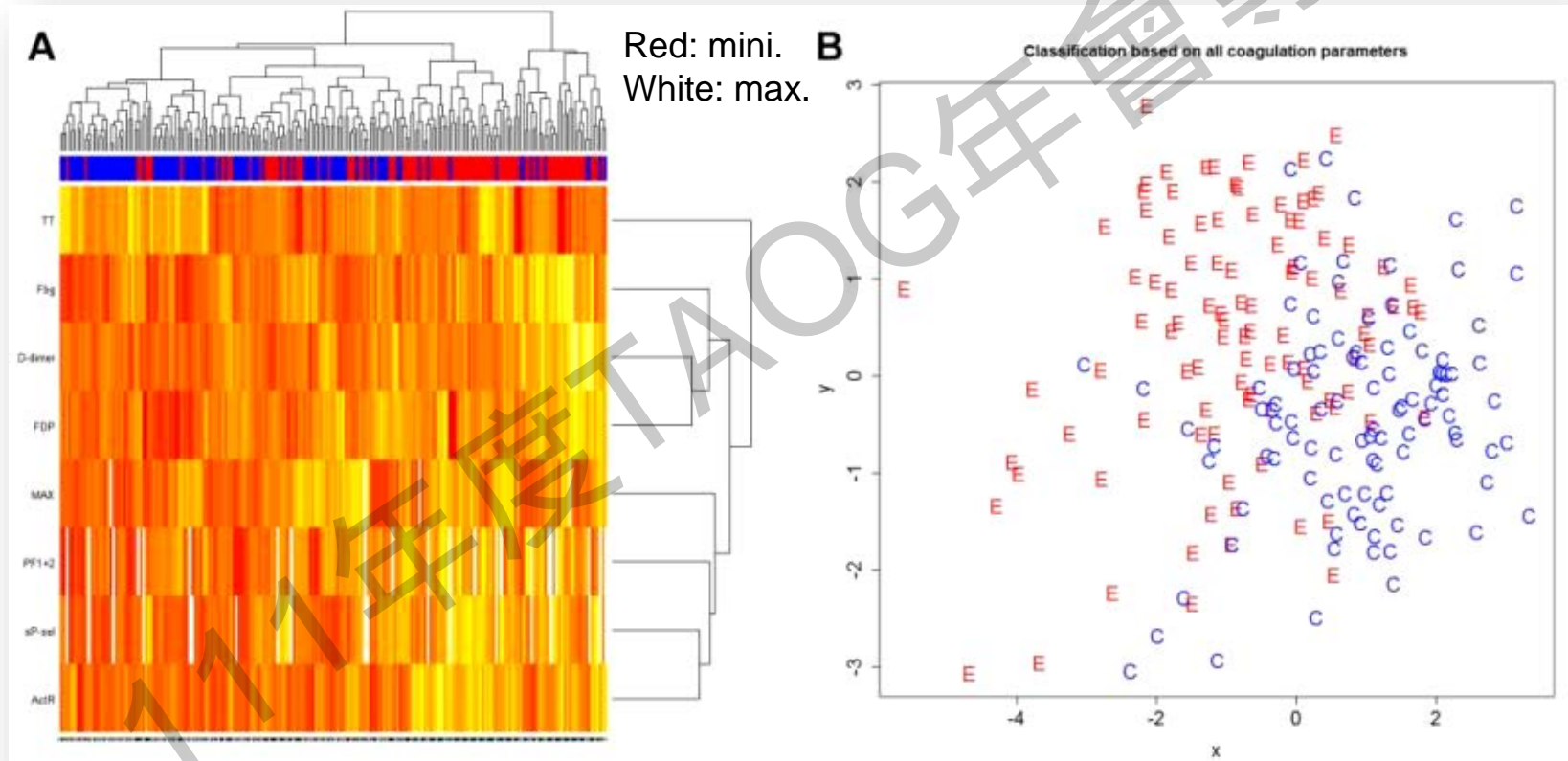
Ding Ding, MD, PhD¹, Xishi Liu, MD, PhD^{1,2}, and Sun-Wei Guo, PhD^{1,2}

Reproductive Sciences
2018, Vol. 25(11) 1540-1548
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DOI: 10.1177/1933719118799195
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Ding et al. Reproductive Sciences 2018

A cross-sectional study
E (endometriosis) and **C (control)**

Hierarchical clustering heatmap of coagulation parameters



Endometriosis presented a **hypercoagulable status** compared to **control**

Association Between Laparoscopically Confirmed Endometriosis and Risk of Early Natural Menopause

Madhavi Thombre Kulkarni, MS, PhD; Amy Shafir, ScD; Leslie V. Farland, ScD; Kathryn L. Terry, ScD; Brian W. Whitcomb, PhD; A. Heather Eliassen, ScD; Elizabeth R. Bertone-Johnson, ScD; Stacey A. Missmer, ScD

Kulkarni et al. JAMA Network Open. 2022

A prospective cohort study
 106,633 women in the **NHS II**
 6640 **with endometriosis**
 99,993 **without endometriosis**

Table 2. Multivariable-Adjusted Associations of Laparoscopically Confirmed Endometriosis With Early Natural Menopause^a

Laparoscopically confirmed endometriosis	Early natural menopause cases/person-years	Hazard ratio (95% CI)		
		Model 1	Model 2	Model 3
Without	2345/1 508 462	1 [Reference]	1 [Reference]	1 [Reference]
With	197/79 290	1.51 (1.30-1.74)	1.46 (1.26-1.69)	1.28 (1.10-1.48)

Early natural menopause

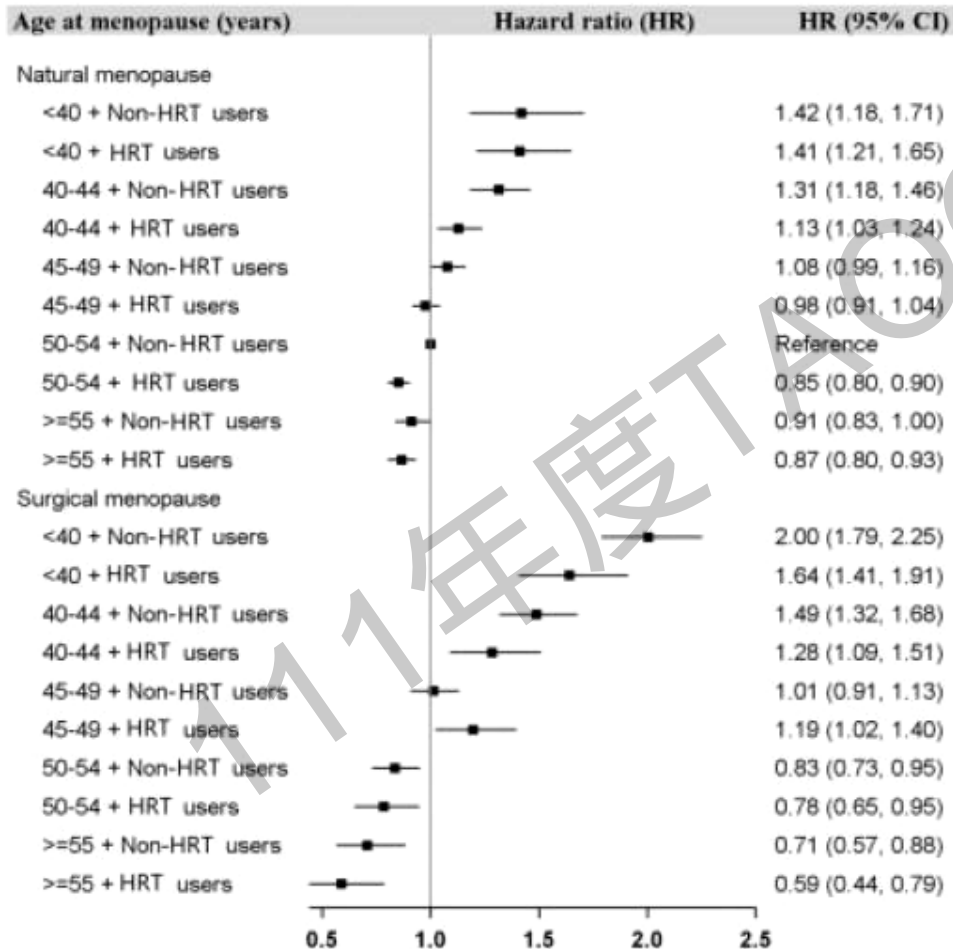
**With endometriosis > without endometriosis
 (HR=1.51)**

Type of menopause, age of menopause and variations in the risk of incident cardiovascular disease: pooled analysis of individual data from 10 international studies

Zhu et al. Human Reproduction 2020

Pooled individual-level data from 10 observational studies
203,767 postmenopausal women

CVD



Natural or surgical menopause



Age at menopause



CVD risk

Endometriosis and Risk of Coronary Heart Disease

Fan Mu, ScD; Janet Rich-Edwards, ScD; Eric B. Rimm, ScD;
Donna Spiegelman, ScD; Stacey A. Missmer, ScD

A prospective cohort study
116,430 women in the **Nurses' Health Study II**

5,296 women with laparoscopically confirmed **endometriosis** and
109,161 women **without endometriosis**

	Myocardial Infarction		Angina		Coronary Bypass/Angioplasty/Stent		Combined Coronary Heart Disease	
	Endometriosis Confirmed by Laparoscopy (No/Yes)							
	No	Yes	No	Yes	No	Yes	No	Yes
No. of CHD cases	429	69	742	149	599	91	1231	207
Person-years	1 822 783	154 696	1 820 499	153 892	1 821 888	154 555	1 818 018	153 556
Age and calendar year adjusted	1.00	1.63 (1.27–2.11)	1.00	2.07 (1.73–2.47)	1.00	1.49 (1.19–1.86)	1.00	1.73 (1.49–2.00)
Multivariable-adjusted*	1.00	1.52 (1.17–1.98)	1.00	1.91 (1.59–2.29)	1.00	1.35 (1.08–1.69)	1.00	1.62 (1.39–1.89)

MI

Endometriosis > Ctrl (aRR=1.52)

Angina

Endometriosis > Ctrl (aRR=1.91)

CABG

Endometriosis > Ctrl (aRR=1.35)

CHD

Endometriosis > Ctrl (aRR=1.62)

Article

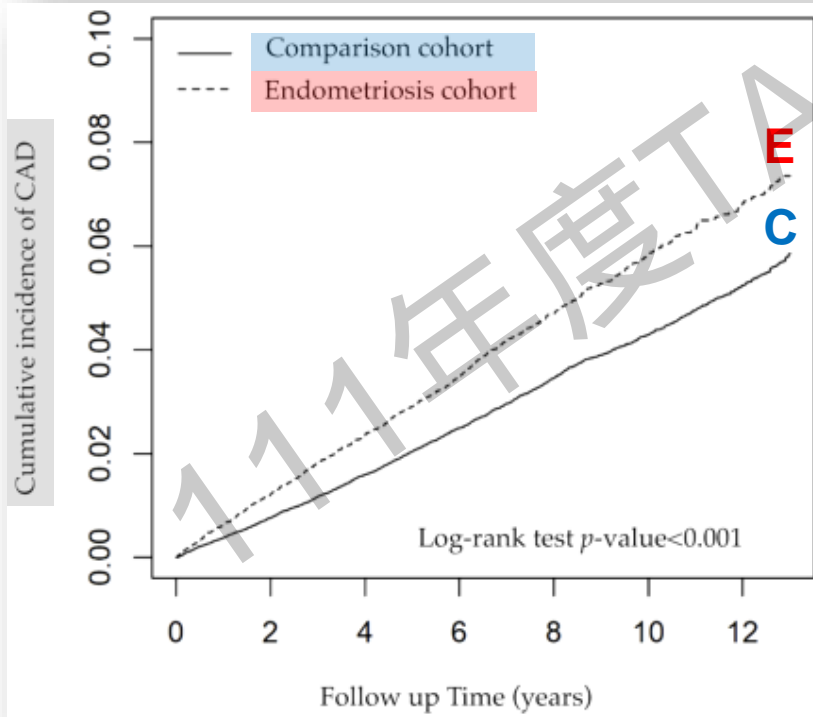
Endometriosis Is Associated with an Increased Risk of
Coronary Artery Disease in Asian WomenPei-Chen Li ¹, Yu-Cih Yang ^{2,3}, Jen-Hung Wang ⁴, Shinn-Zong Lin ⁵ and Dah-Ching Ding ^{1,6,*}

Li et al. J. Clin. Med. 2021

A retrospective population-based cohort study (NHIRD)
19,454 **Endometriosis (EM)** vs. 77,816 **without EM**

Endometriosis	N	CAD Event	Person-Years	IR	HR (95% CI)	
					Crude	Adjusted [†]
No	77,816	2392	546,412	4.38	1.00 (reference)	1.00 (reference)
Yes	19,454	853	143,169	5.96	1.36 (1.26, 1.47) ***	1.34 (1.22, 1.47) ***

N: number of patients; CAD: coronary artery disease; IR: incidence rates per 1000 person-years; HR: hazard ratio; CI: confidence interval;

[†] Model was adjusted for age, comorbidities, and medication listed in Table 1. *** $p < 0.001$.

CAD

Endometriosis > Ctrl
(aHR=1.34)



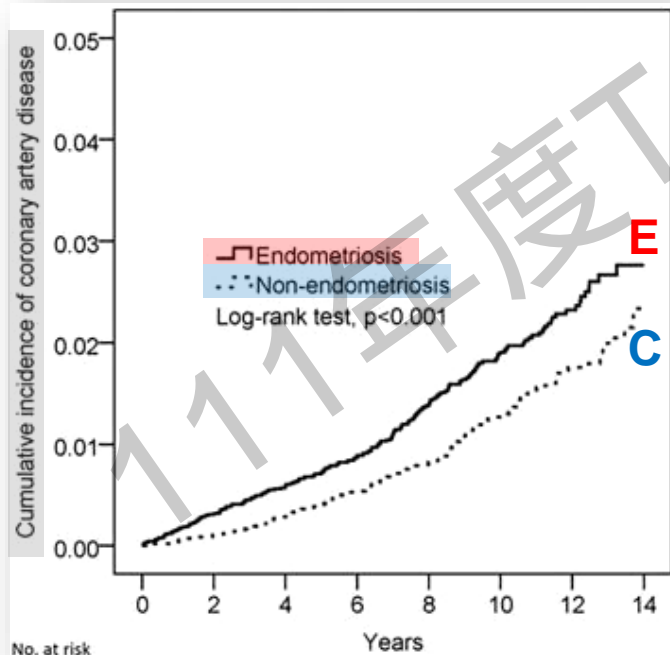
Endometriosis and New-Onset Coronary Artery Disease in Taiwan: A Nationwide Population-Based Study

Chun-Hui Wei^{1†}, Renin Chang^{2†}, Yu Hsun Wan³, Yao-Min Hung^{4,5,6*} and James Cheng-Chung Wei^{7,8,9*}

Wei et al. Front. Med. 2021

A retrospective population-based cohort study (NHIRD)
13,988 **Endometriosis (EM)** vs. 13,988 **without EM**

	No. of CAD	Observed Person-Years	Incidence Density (Per 1,000 Person-Years)	Crude HR	95% C.I.	p-value	Adjusted HR [†]	95% C.I.	p-value
Endometriosis									
No	159	122,678	1.3	1			1		
Yes	199	108,346	1.8	1.46	1.19–1.80	<0.001	1.52	1.23–1.87	<0.001



CAD

Endometriosis > Ctrl
(aHR=1.52)

A retrospective population-based cohort study (NHIRD)
 17,543 **Endometriosis (EM)** vs. 70,172 **without EM**

MACCE: major adverse cardiovascular and cerebrovascular events

	MACCE			Major CVD			CVA		
	aHR	95% CI	P-value	aHR	95% CI	P-value	aHR	95% CI	P-value
EM									
No	1.00			1.00			1.00		
Yes	1.17	1.05–1.29	0.0053	1.19	1.01–1.40	0.0385	1.16	1.02–1.31	0.0285
Age (year)									
18-34	1.00			1.00			1.00		
35-50	3.39	2.94–3.91	<0.0001	3.06	2.45–3.83	<0.0001	3.74	3.12–4.49	<0.0001
Level of urbanization									
1 (rural)	1.00			1.00			1.00		
2	1.03	0.85–1.26	0.7533	0.98	0.72–1.33	0.8773	1.12	0.88–1.43	0.3671
3	0.86	0.73–1.02	0.0868	0.83	0.64–1.08	0.1616	0.91	0.73–1.13	0.3901
4 (urban)	0.84	0.70–1.00	0.0463	0.89	0.68–1.17	0.3977	0.83	0.66–1.04	0.1015
Level of income									
1 (lowest)	1.00			1.00			1.00		
2	0.83	0.71–0.97	0.0197	0.81	0.64–1.04	0.0928	0.82	0.67–1.00	0.0445
3	0.99	0.87–1.12	0.8288	0.95	0.78–1.15	0.5963	0.99	0.85–1.16	0.9075
4 (highest)	0.74	0.63–0.86	<0.0001	0.59	0.46–0.76	<0.0001	0.79	0.65–0.95	0.0125
Comorbidity									
Hypertension	3.70	3.35–4.10	<0.0001	4.80	4.08–5.65	<0.0001	3.20	2.82–3.63	<0.0001
Diabetes mellitus	1.42	1.25–1.60	<0.0001	1.66	1.39–1.99	<0.0001	1.32	1.13–1.55	0.0004
Dyslipidemia	1.01	0.90–1.13	0.9261	0.96	0.81–1.14	0.6439	1.03	0.90–1.19	0.6443
Gout	1.12	0.93–1.35	0.2468	1.35	1.04–1.76	0.0251	1.01	0.79–1.30	0.9099
Amenorrhea	0.99	0.89–1.10	0.8861	0.86	0.72–1.02	0.0761	1.06	0.93–1.21	0.3742

MACCE

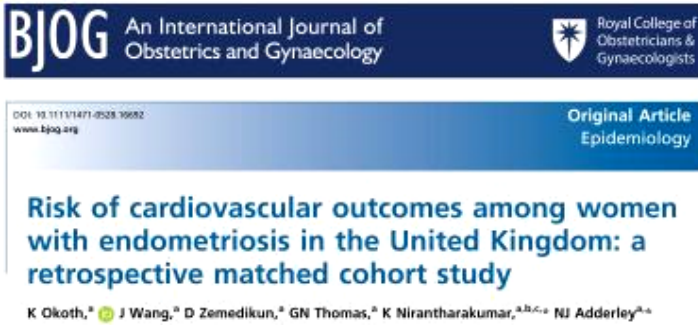
Endometriosis > Ctrl (aHR=1.17)

CVD

Endometriosis > Ctrl (aHR=1.19)

CVA

Endometriosis > Ctrl (aHR=1.16)



Okoth et al. BJOG 2021

A retrospective population-based cohort study (UK)
56,090 **Endometriosis (EM)** vs. 223,669 **without EM**

CVD, Cardiovascular disease; IHD, ischemic heart disease

	Composite CVD		IHD		Cerebrovascular disease	
	Endometriosis	Unexposed	Endometriosis	Unexposed	Endometriosis	Unexposed
Population	55 832	222 556	55 999	223 237	55 930	223 050
Events, <i>n</i> (%)	574 (1.03)	1676 (0.75)	279 (0.5)	753 (0.33)	294 (0.53)	881 (0.39)
Person-years	357 959.8	1 233 555	360 270.9	1 241 282	360 076.3	1 240 657
Crude incidence rate/ 1000 person-years	1.60	1.36	0.77	0.61	0.82	0.71
Age at outcome (years), median (IQR)	42.6 (37.5–46.8)	43.4 (39.1–47.1)	43.2 (39.4–47.1)	43.5 (40.0–46.8)	41.3 (36.3–46.6)	43.0 (38.3–47.0)
Crude HR (95% CI)	1.16 (1.06–1.28)		1.26 (1.09–1.44)		1.13 (0.99–1.29)	
<i>P</i> value	0.002		0.001		0.067	
Adjusted HR (95% CI)	1.24 (1.14–1.37)		1.40 (1.22–1.61)		1.19 (1.04–1.36)	
<i>P</i> value	<0.001		<0.001		0.010	

CVD

Endometriosis > Ctrl (aHR=1.24)

IHD

Endometriosis > Ctrl (aHR=1.40)

CVA

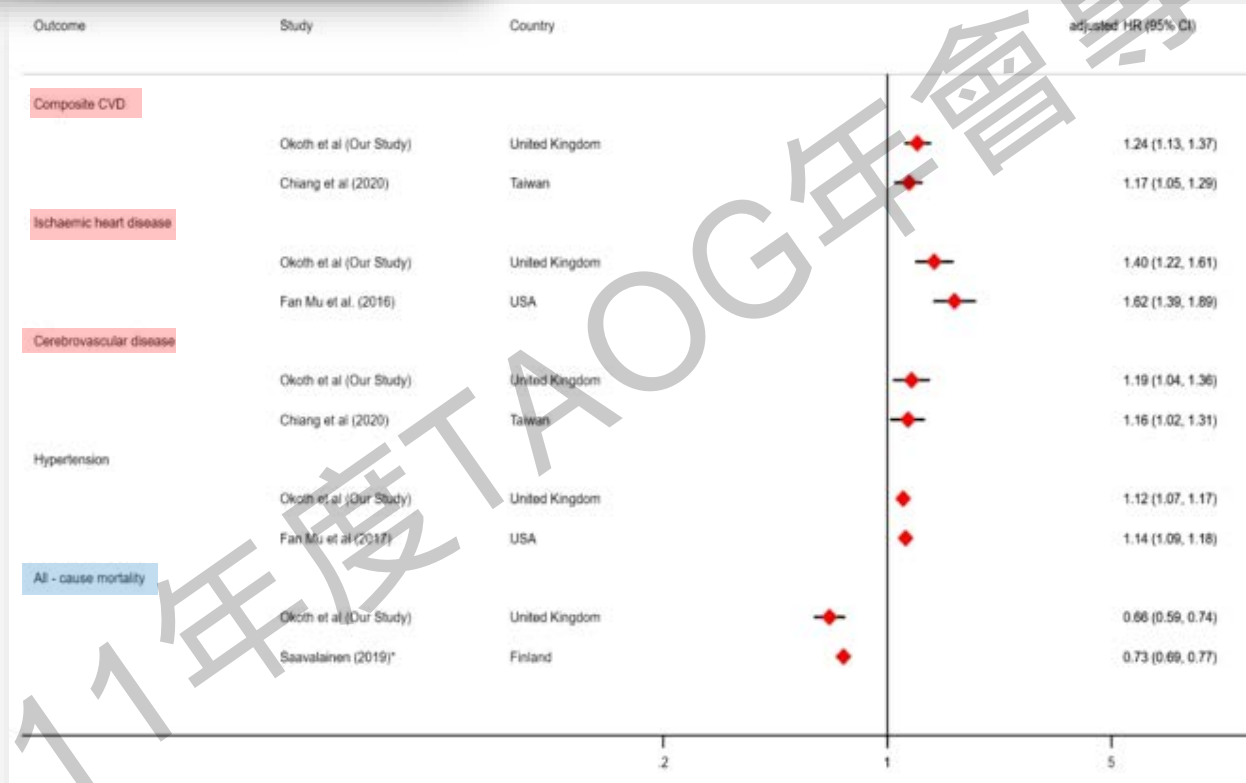
Endometriosis > Ctrl (aHR=1.19)

Risk of cardiovascular outcomes among women with endometriosis in the United Kingdom: a retrospective matched cohort study

K Okoth,^a J Wang,^a D Zemedikun,^a GN Thomas,^a K Nirantharakumar,^{a,b,c,d} NJ Adderley^{a,e}

Okoth et al. BJOG 2021

A retrospective population-based cohort study (UK)
56,090 **Endometriosis (EM)** vs. 223,669 **without EM**



Endometriosis



CVD
IHD
CVA



Mortality

Mortality of midlife women with surgically verified endometriosis—a cohort study including 2.5 million person-years of observation

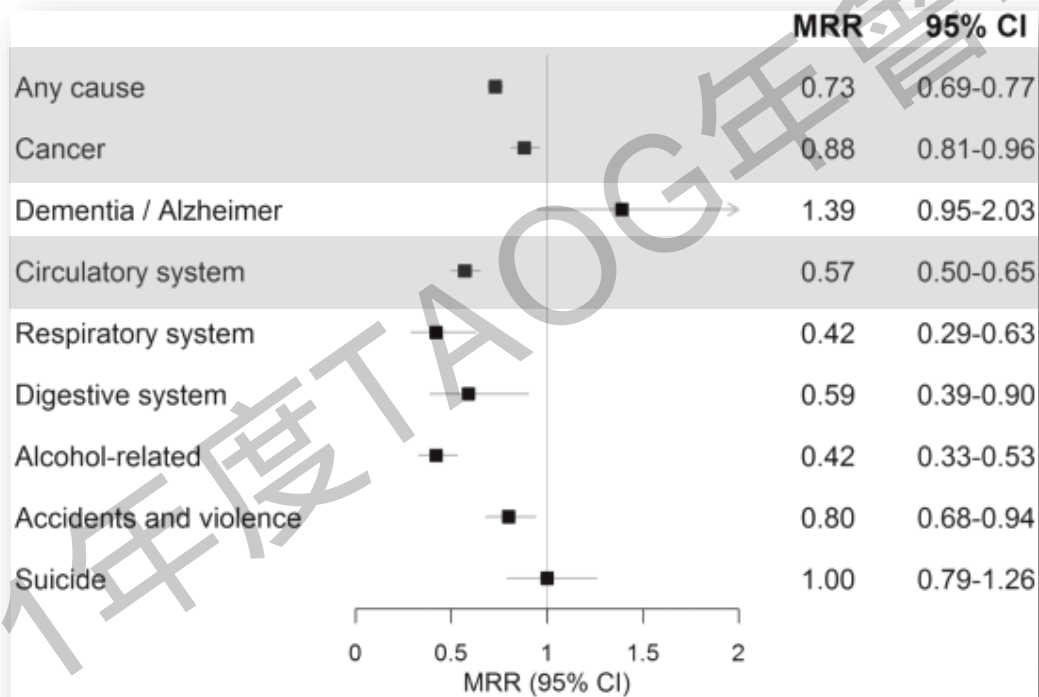
L. Saavalainen¹, A. But², A. Tiitinen¹, P. Härkki¹, M. Gissler^{3,4}, J. Haukka^{2,3}, and O. Heikinheimo^{1,4}

Saavalainen et al. Human Reproduction 2019

A nationwide retrospective cohort study (Finland)
Median follow-up of 17 years

49,956 women with surgically verified diagnosis of **endometriosis** vs.
98,824 age- and municipality-matched women **without endometriosis**

Mortality



MRR, mortality rate ratios

Any cause **Endometriosis** < **Ctrl** (aHR=0.73)

Cancer **Endometriosis** < **Ctrl** (aHR=0.88)

CVD **Endometriosis** < **Ctrl** (aHR=0.57)

Physical comorbidity of endometriosis

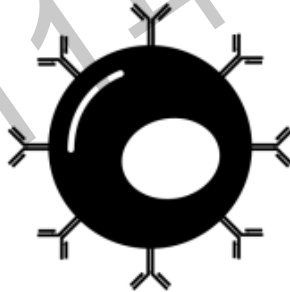
Cancer



CVD



Immune disorders

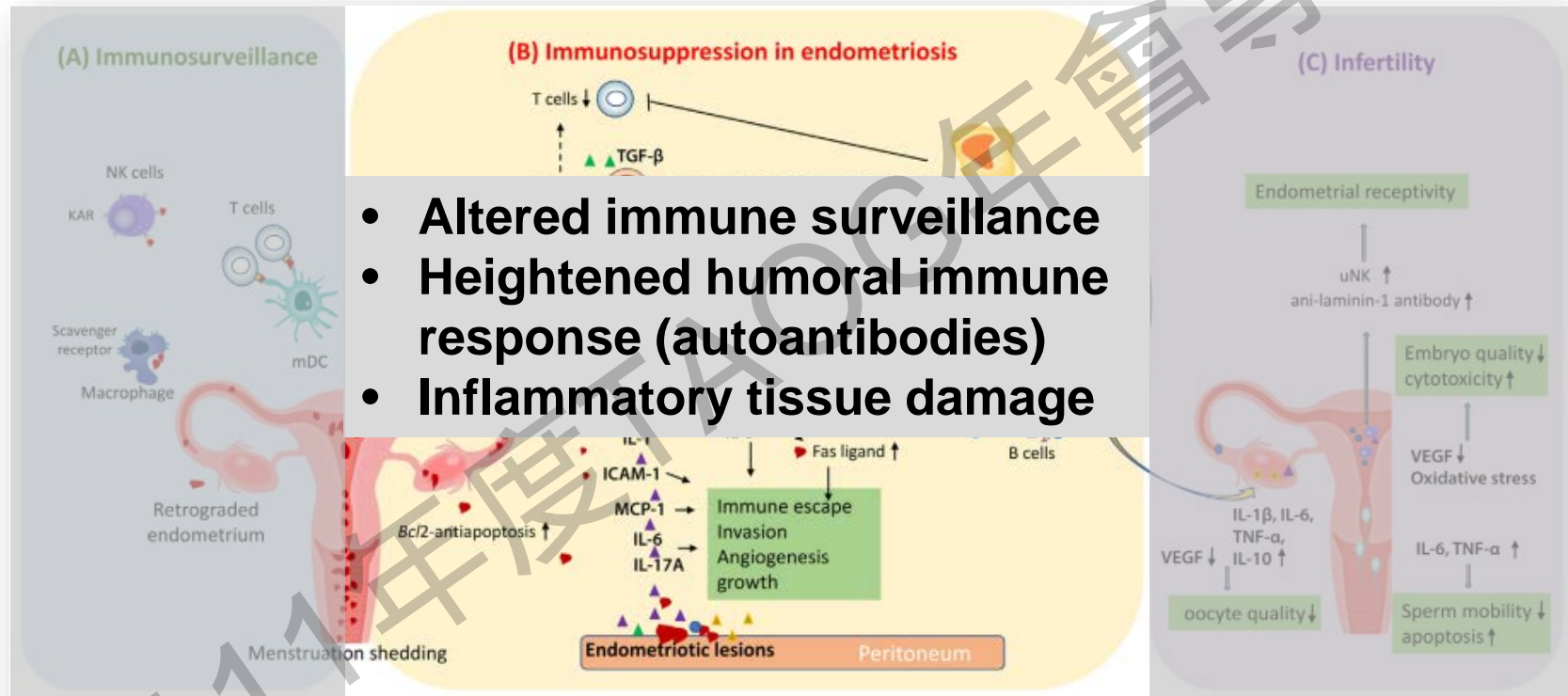


GI & others



The pathophysiology of endometriosis with immunity

Zhang et al. Autoimmunity Reviews 2018



Similar immune alternation between **endometriosis** and **autoimmunity**



A review

Endometriosis related autoantibodies

Anti-thyroid peroxidase
Anti-cardiolipin
ANA

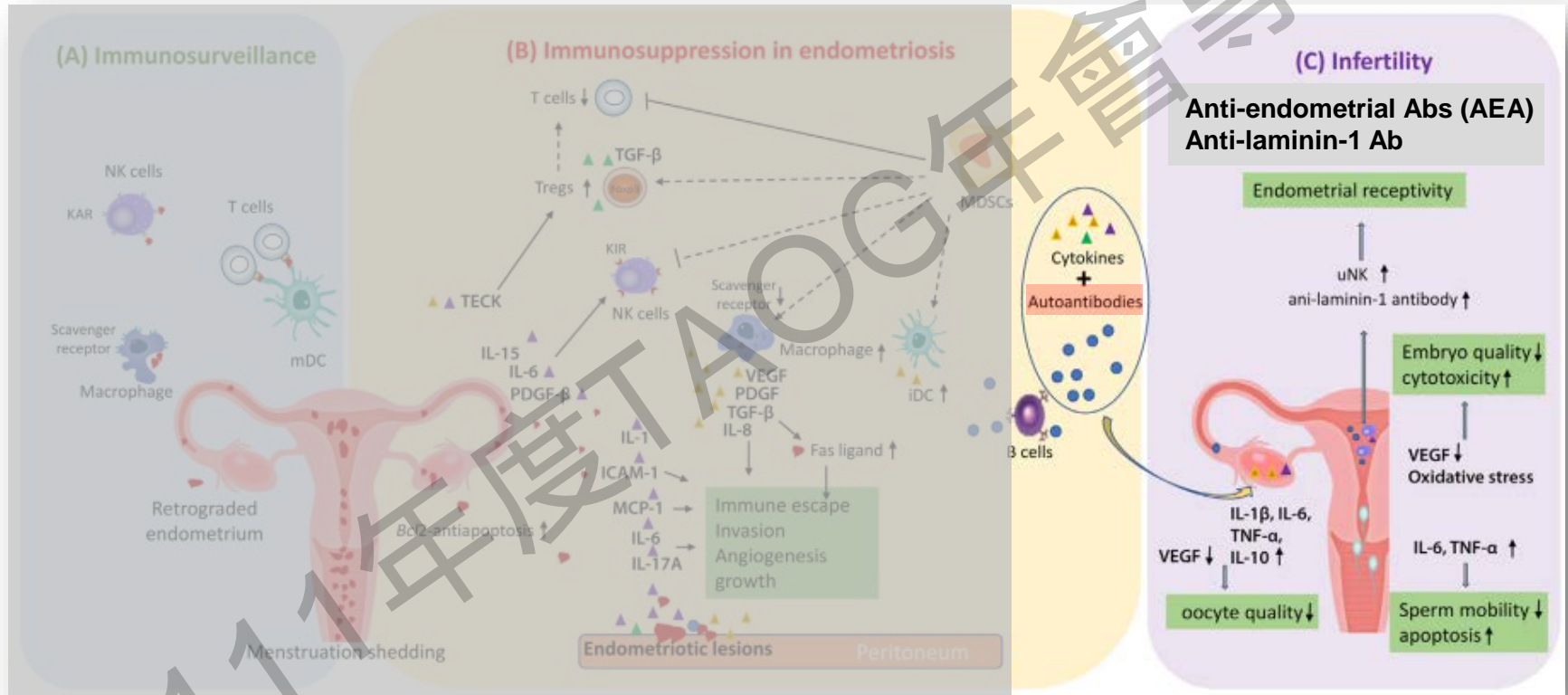
Anti-endometrial Abs (AEA)

Marker	Clinical relevance	References
Anti-alpha2-HS	- Significantly higher in endometriosis patients - Low sensitivity and lack of specificity	[99-100]
Anti-SLP2, anti-TMOD3, anti-TPM3	May be useful in early disease stages	[101-2]
Anti-alpha-enolase	- Specificity and sensitivity comparable to CA125 - Elevated from stages I to III	[109]
Anti-PDIK1L	- Better sensitivity and specificity compared to CA125 - Does not increase in later stages of disease	[111]
Anti-survivin	Levels are not significantly elevated in endometriosis	[123]
Anti-PEP	- Anti-PEP was not found in serum or peritoneal samples - PEP levels were increased during secretory phase of moderate to severe disease	[125]
Anti-laminin-1	Levels are associated with infertility due to endometriosis	[130-1]
Anti-thyroid peroxidase	Levels are associated with endometriosis and polycystic ovarian syndrome	[141]
Anti-IMP1 and cyclin B	- May be a candidate marker for ovarian endometrioma - High sensitivity and reasonable specificity	[146]
Anti-carbonic anhydrase	- Increased IgG levels in endometriosis - Possibly just the CA-II isozyme	[148-50]
Oxidative stress markers	Anti-malondialdehyde-modified LDL, oxidized LDL and lipid peroxide-modified rabbit serum albumin are elevated in endometriosis	[155]
Anti-cardiolipin	- Elevated sera levels in endometriosis - IgM may be elevated during all stages of disease - Elevated, but statistically insignificant, levels in endometriosis	[156-9,161]
ANA	- Statistically elevated in endometriosis - May be a secondary immunological effect of pelvic endometriosis	[80,160,162]
Anti-Syntaxin 5	- Statistically elevated in endometriosis - May offer superior specificity to CA125	[164]

Anti-SLP2, anti-TMOD3, anti-TPM3, and anti-PDIK1L are useful for early diagnosis

Autoantibodies may lead to infertility

Zhang et al. Autoimmunity Reviews 2018



Autoantibodies may impair **oocyte/embryo quality**, **sperm motility** and **EM receptivity**

Co-occurrence of immune-mediated conditions and endometriosis among adolescents and adult women

Amy L Shafir^{1,2} | Marissa C. Palmor^{2,3,4} | Jessica Fourquet^{5,6} | Amy D. DiVasta^{1,2,7} |
 Leslie V. Farland⁸ | Allison F. Vitonis^{2,3} | Holly R Harris^{9,10} | Marc R. Laufer^{2,3,7} |
 Daniel W. Cramer³ | Kathryn L. Terry^{2,3,11} | Stacey A. Missmer^{1,2,11,12}

Shafir et al. Am J Reprod Immunol. 2021

A cross-sectional analysis in the
 Women's Health Study

551 pts with **endometriosis (surgical Dx)**
 652 controls **without endometriosis**

Risk factors for **surgically diagnosed endometriosis**

Physician diagnosis of immune dysfunction diseases	Cases N	Controls N	Age-adjusted OR (95% CI)	Multivariable-adjusted ¹ OR (95% CI)
Autoimmune and inflammatory^{2,5}				
No	526	630	1.00 (Ref)	1.00 (Ref)
Yes	25	22	1.72 (0.91–3.22)	1.87 (0.92–3.80)
Endocrine^{3,5}				
No	529	606	1.00 (Ref)	1.00 (Ref)
Yes	22	46	0.76 (0.44–1.32)	0.85 (0.46–1.58)
Chronic pain and fatigue states^{4,5}				
No	533	645	1.00 (Ref)	1.00 (Ref)
Yes	18	7	5.32 (1.94–14.6)	5.81 (1.89–17.9)
Allergies				
No	326	480	1.00 (Ref)	1.00 (Ref)
Yes	225	172	2.09 (1.61–2.71)	1.76 (1.32–2.36)
Asthma				
No	399	537	1.00 (Ref)	1.00 (Ref)
Yes	152	115	1.79 (1.34–2.40)	1.35 (0.97–1.88)
Eczema				
No	497	565	1.00 (Ref)	1.00 (Ref)
Yes	54	87	0.69 (0.47–1.00)	0.68 (0.44–1.04)
Mononucleosis				
No	473	591	1.00 (Ref)	1.00 (Ref)
Yes	78	61	2.28 (1.55–3.35)	1.75 (1.14–2.68)

Autoimmune is a risk factor for **endometriosis**



The possible role of genetic variants in autoimmune-related genes in the development of endometriosis

Bianca Bianco*, Gustavo M. André, Fábila L. Vilarino, Carla Peluso, Fernanda Abani Mafra, Denise M. Christofolini, Caio P. Barbosa

A review

Candidate gene	Chromosome	Rs	Function	Studies with endometriosis (Ref)
FOXP3	Xp11.23	3761548 3761549 2232366 2232368 2280883 2476601	It encodes FOXP3 protein which regulates the activation of T cell and functions as a transcriptional repressor and downregulates cytokine production in T cells.	André et al. (2011) [90]
PTPN22	1p13.3-13.1	2476601	The mechanism of action of PTPN22 in autoimmunity still needs to be clarified. However, increased inhibition of T-cell-receptor signaling caused by the PTPN22 C1858T polymorphism could predispose to autoimmunity either by affecting thymic deletion of autoreactive T cells or by affecting the development or function of peripheral T cells.	Amma et al. (2011) [91] Ploski et al. (2011) [92] Gomes et al. (2011) [93]
FCRL3			FCRL3 gene: B cell differentiation	
FCGR2B	11p11.2	—	FCGR2B encodes a low-affinity Fc receptor for IgG2 antibodies, maintaining immune homeostasis.	—
STAT4	2q32.2-q32.3	—	An important player in directing helper T cells toward the proinflammatory T helper type 1 and T helper type 17 lineages.	—
CTLA4	2q33	231775 3087241	CTLA4 is a member of the immunoglobulin superfamily that is expressed on the surface of activated T cells and downregulates T cell function, besides being a critical mediator of peripheral tolerance.	Vigano et al. (2005) [90] Lerner et al. (2011) [91]
NF-κB1	4q24	28368591	NF-κB1 regulates the immune and inflammatory response and stimulates cell proliferation, apoptosis, adhesion, motility, and angiogenesis in many cell types.	Zhou et al. (2010) [95]
HLA-DQB1	6p21.3	rs606059	HLA-DQB1 belongs to the HLA class II beta chain paralogs and it plays a central role in the immune system by presenting peptides derived from extracellular proteins.	Wang et al. (2002) [99] Whang et al. (2006) [101] Sandqvist et al. (2011) [100]
TNFAIP3	10q25.3	—	A central regulator of inflammatory responses.	—
IRF5	10q25.3	—	This gene encodes a member of the IRF family, a group of transcription factors with diverse roles, including virus restriction.	—
TRAFs			TRAFs gene: B cell differentiation	
VDR	12q13.1	11188271 73323 10755810 1544410	Vitamin D is a hormone that has essential roles as endocrine functions, regulating cell replication and has also been shown to play an important role in other metabolic pathways, such as those involved in immune response. Vitamin D suppresses lymphocyte proliferation and immunoglobulin synthesis, besides inhibit the action pro-	Vilarino et al. (2011) [71]
BLYS			BLYS gene: B cell differentiation	
TYK2	19p13.2	—	This gene encodes a member of the tyrosine kinase and, more specifically, the Janus kinases (JAKs) protein families. This protein associates with the cytoplasmic domain of type I and type II cytokine receptors and promiscue cytokine signals by phosphorylating receptor subunits. It is also component of both the type I and type III interferon signaling pathways. As such, it may play a role in antiviral immunity.	—

Shared genes of **endometriosis** and **autoimmunity**

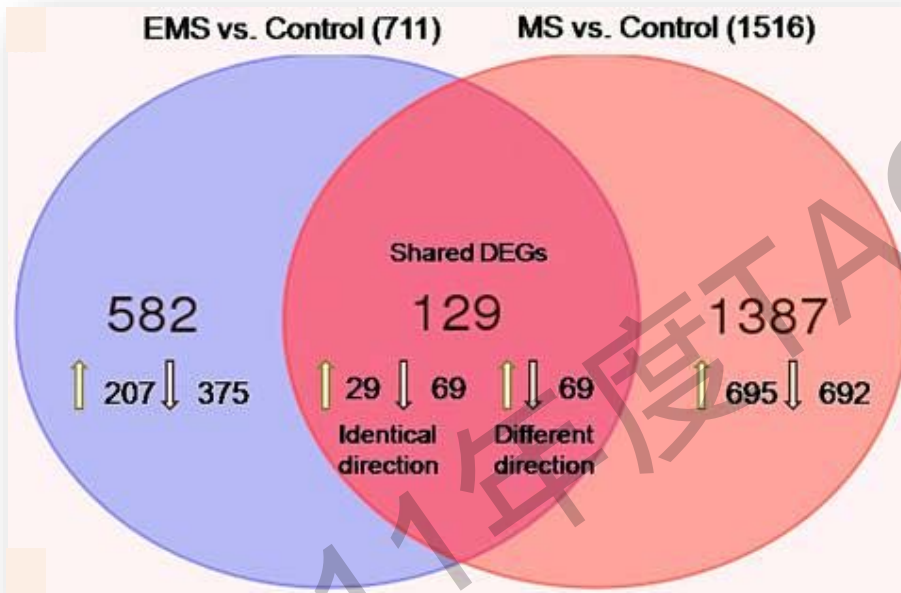
Identification of Shared Molecular Signatures Indicate the Susceptibility of Endometriosis to Multiple Sclerosis

Amit Katiyar, Sujata Sharma, Tej P. Singh and Punit Kaur*

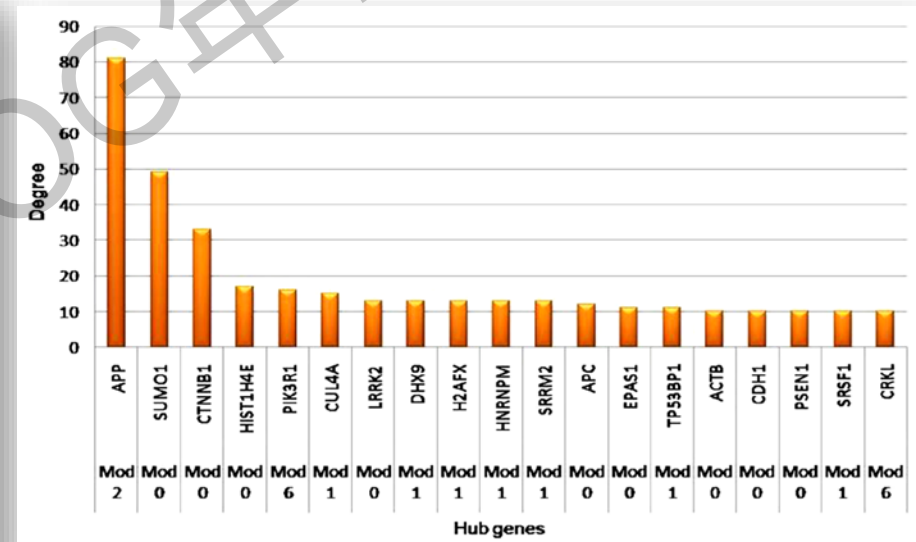
Katiyar et al. Front. Genet. 2018

Gene Expression Omnibus (GEO) database
GEO2R web tool

EMS: endometriosis; MS: multiple sclerosis; DEG: differentially expressed genes



Hub genes



129 shared DEGs between **EMS** and **MS**

Identification of Shared Molecular Signatures Indicate the Susceptibility of Endometriosis to Multiple Sclerosis

Amit Katiyar, Sujata Sharma, Tej P. Singh and Punit Kaur*

Katiyar et al. Front. Genet. 2018

Gene Expression Omnibus (GEO) database
GEO2R web tool

EMS: endometriosis; MS: multiple sclerosis

KEGG -ID	Dysregulated pathways	Classification	*KEGG	#GO	sPPI		& Hits
					Genes	Edges	
hsa04012	ErbB signaling pathway	Signal transduction	2	16	2	0	20
hsa04020	Calcium signaling pathway	Signal transduction	4	16	0	0	20
hsa04514	Cell adhesion molecules	Signaling molecules and interaction	7	13	0	0	20
hsa04670	Leukocyte transendothelial migration	Immune system	0	12	0	5	17
hsa04512	ECM-receptor interaction	Signaling molecules and interaction	0	17	0	0	17
hsa04310	Wnt signaling pathway	Signal transduction	1	0	0	13	14
hsa04110	Cell cycle	Cell growth and death	0	0	1	6	7
hsa04114	Oocyte meiosis	Cell growth and death	0	0	1	4	5
hsa04666	Fc gamma R-mediated phagocytosis	Immune system	0	0	0	3	3
hsa04062	Chemokine signaling pathway	Immune system	0	2	1	0	3
hsa04060	Cytokine-cytokine receptor interaction	Signaling molecules and interaction	0	3	0	0	3
hsa04080	Neuroactive ligand-receptor interaction	Signaling molecules and interaction	0	3	0	0	3
hsa04350	TGF-beta signaling pathway	Signal transduction	0	2	0	0	2
hsa04115	p53 signaling pathway	Cell growth and death	0	0	1	0	1

Shared dysregulated pathways of EMS and MS

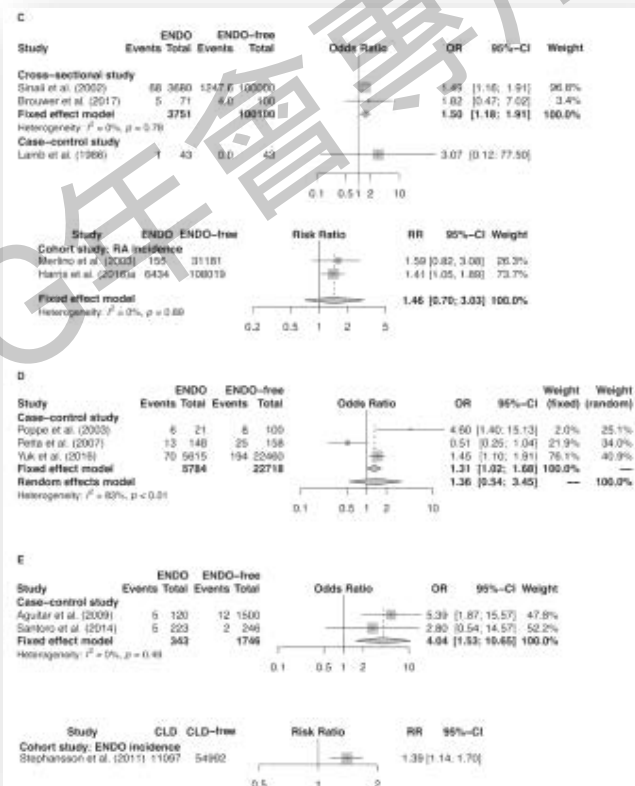
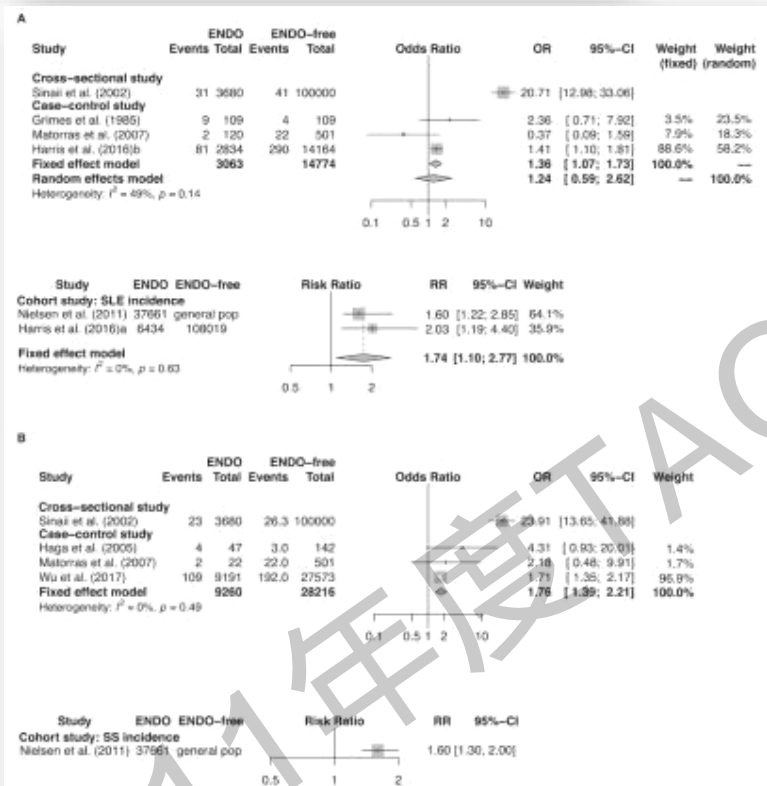
The association between endometriosis and autoimmune diseases: a systematic review and meta-analysis

Nina Shigeski^{1,2,*}, Marina Kvaskoff^{3,4}, Shona Kirtley⁵, Qian Feng¹, Hai Fang^{6,7}, Julian C. Knight², Stacey A. Missmer^{1,8,9}, Nilufer Rahmioglu^{1,2}, Krina T. Zondervan^{1,2,8,10}, and Christian M. Becker^{1,11}

Shigeski et al. Human Reproduction Update 2019

26 studies

Low or very low quality of evidence



- SLE, RA, Sjogren's syndrome
- Autoimmune thyroid disorder
- Celiac disease, multiple sclerosis (MS)
- Inflammatory bowel disease (IBD)

Endometriosis > Ctrl

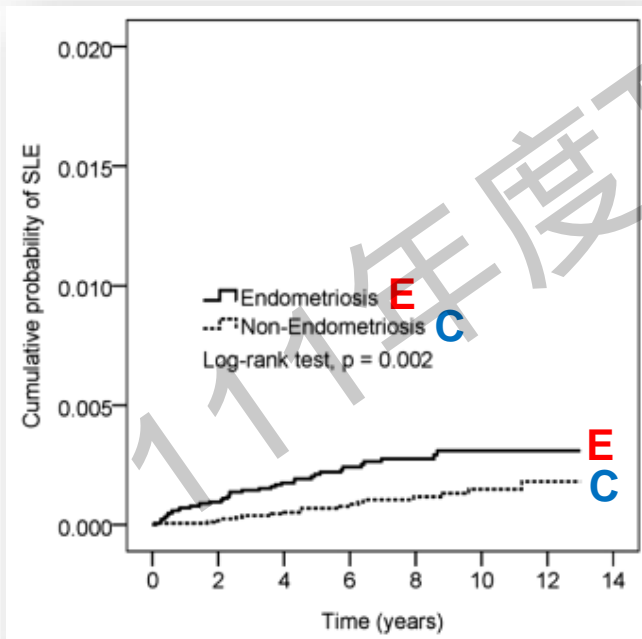
OPEN Association between endometriosis and risk of systemic lupus erythematosus

Yu-Hsi Fan^{1,6}, Pul-Ying Leong^{2,3,8}, Jeng-Yuan Chiou⁴, Yu-Hsun Wang⁵, Ming-Hsiang Ku⁶ & James Cheng-Chung Wei^{1,3,7}

A population-based retrospective cohort study Taiwan's NHIRD

Endometriosis (n=16,758) and **Non-endometriosis** (n=16,758)

Characteristics	Number of SLE cases	Person-years	Incidence density rate	Crude HR	95% CI	Adjusted HR	95% CI
Endometriosis							
No	18	126,860	0.1	1		1	
Yes	39	113,985	0.3	2.36	1.35–4.13	2.37	1.35–4.14



SLE

Endometriosis > Ctrl
(aHR=2.37)

Risk of systemic lupus erythematosus in patients with endometriosis: A nationwide population-based cohort study

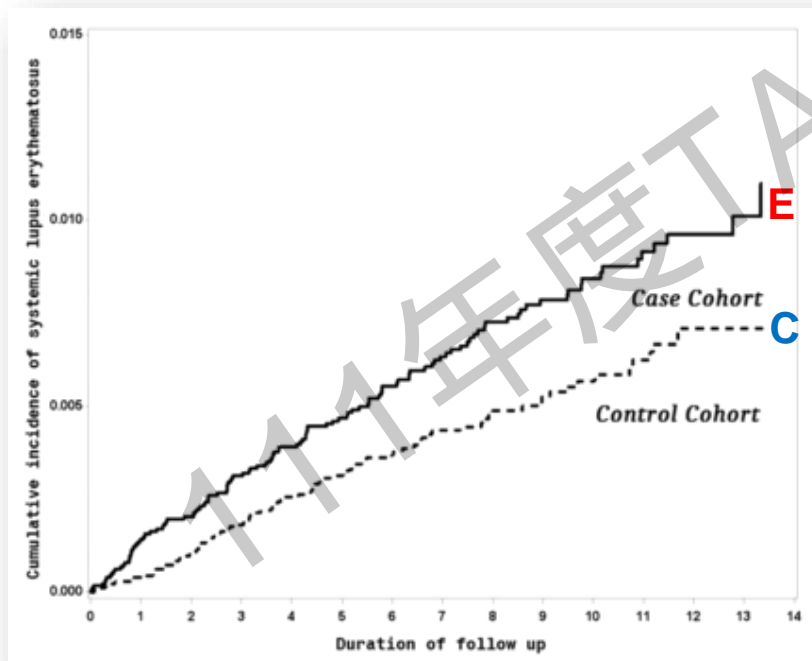
Ya-Hui Lin¹ · Yu-Cih Yang² · Shih-Fen Chen³ · Chung-Y Hsu⁴ · Yu-Chih Shen^{1,5} 

Lin et al. Archives of Gynecology and Obstetrics 2020

A population-based retrospective cohort study
Taiwan's NHIRD

Endometriosis (n=17,779) and
Non-endometriosis (n=17,779)

Variable	Patients with endometriosis			Patients without endometriosis			Crude ^b HR (95% CI)	Adjusted ^c HR (95% CI)
	SLE	Person years	IR ^a	SLE	Person years	IR ^a		
Total	124	144,277	0.85	83	143,678	0.57	1.48 (1.12–1.96)**	1.86 (1.36–2.53)***



SLE

Endometriosis > Ctrl
(aHR=1.86)

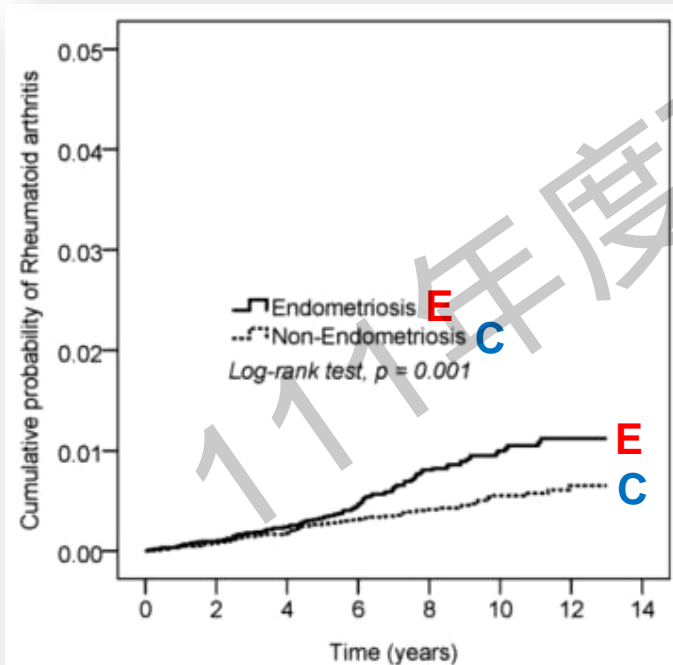
Original article

Increased risk of rheumatoid arthritis among patients with endometriosis: a nationwide population-based cohort studyYu-Hao Xue^{1,*}, Liang-Tian You¹, Hsin-Fu Ting¹, Yu-Wen Chen¹, Zi-Yun Sheng¹, Yi-Dong Xie¹, Yu-Hsun Wang², Jeng-Yuan Chiou^{3,*} and James Cheng-Chung Wei^{4,5,6}

Xue et al. Rheumatology 2021

A population-based retrospective cohort study
Taiwan's NHIRD**Endometriosis** (n=14,463) and
Non-endometriosis (n=14,463)

	No. of RA	Person-years	Incidence density (per 1000 person-years)	Crude HR	95% CI	Adjusted HR ^a	95% CI
Endometriosis							
No	62	118 863	0.5	1		1	
Yes	95	105 888	0.9	1.75	1.27, 2.41	1.75	1.27, 2.41



RA

Endometriosis > Ctrl
(aHR=1.75)

Risk of Rheumatoid Arthritis in Patients with Endometriosis:
 A Nationwide Population-Based Cohort Study

Shih-Fen Chen, PhD,¹ Yu-Cih Yang, MS,² Chung-Y Hsu, MD, PhD,³ and Yu-Chih Shen, MD, PhD⁴

Chen et al. JOURNAL OF WOMEN'S HEALTH 2021

A population-based retrospective cohort study
 Taiwan's NHIRD

Endometriosis (n=17,913) and
Non-endometriosis (n=17,913)

Variable	Patients with endometriosis			Patients without endometriosis			Crude ^b HR (95%CI)	Adjusted ^c HR (95%CI)	P-value for interaction
	RA	Person years	IR ^a	RA	Person years	IR ^a			
Total	52	145,775	3.56	19	145,058	1.30	2.73 (1.61–4.63)*	3.71 (2.91–5.73)*	0.77
Age									
<40	17	80,909	2.10	7	80,309	0.87	2.40 (0.99–5.78)	2.75 (0.84–4.73)	
≥40	35	64,866	5.39	12	64,749	1.85	2.95 (1.53–5.69)*	2.07 (1.69–5.97)*	
CCI score									0.68
0	47	139,704	3.36	18	139,075	1.29	2.60 (1.51–4.47)*	2.71 (1.47–4.53)*	
≥ 1	5	6071	8.23	1	5,983	1.67	5.31 (0.61–45.7)	6.70 (0.83–37.2)	

RA

Endometriosis > Ctrl
(aHR=3.71)



Association Between Endometriosis and Subsequent Risk of Sjögren's Syndrome: A Nationwide Population-Based Cohort Study

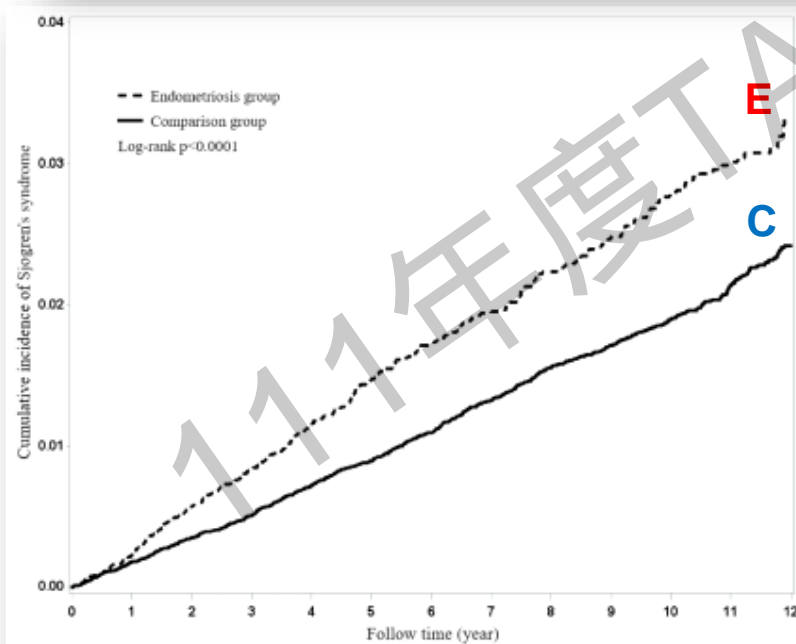
Yung-Hsiang Chao¹, Chin-Hsiu Liu^{2,3}, Yu-An Pan⁴, Fu-Shun Yen⁵, Jeng-Yuan Chlou⁶ and James Cheng-Chung Wei^{1,2,7,8*}

Chao et al. Front. Immunol. 2022

A population-based retrospective cohort study
Taiwan's NHIRD

Endometriosis (n=14,733) and
Non-endometriosis (n=58,932)

Variable	Sjögren's syndrome			Crude HR (95%CI)	Adjusted HR† (95%CI)
	Event	PY	IR		
Endometriosis					
No	826	427775	1.93	1	1
Yes	305	107253	2.84	1.47 (1.29-1.68)***	1.45 (1.27-1.65)***



Sjogren's syndrome

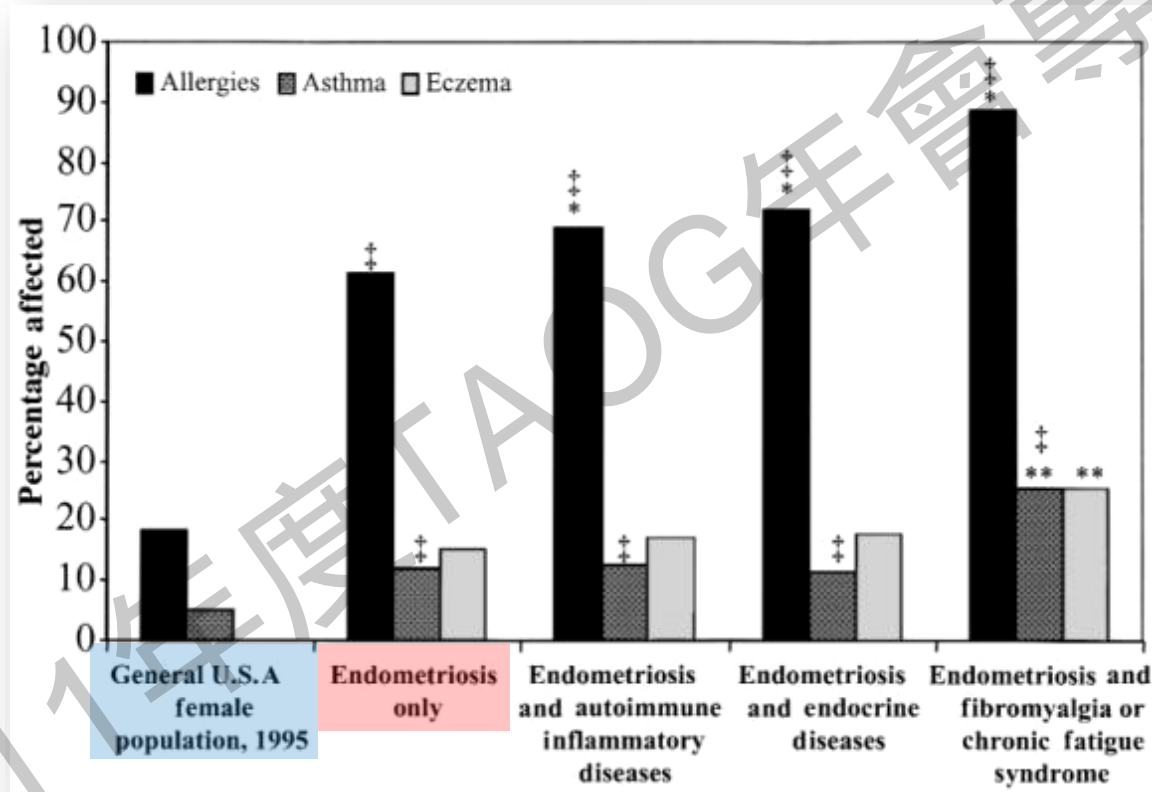
Endometriosis > Ctrl
(aHR=1.45)

High rates of autoimmune and endocrine disorders, fibromyalgia, chronic fatigue syndrome and atopic diseases among women with endometriosis: a survey analysis

N.Sinaii¹, S.D.Cleary², M.L.Ballweg³, L.K.Nieman¹ and P.Stratton¹

Sinaii et al. Human Reproduction 2002

A cross-sectional study
3,680 **surgically diagnosed endometriosis**



Allergies
Asthma

Endometriosis > Ctrl



Review

Endometriosis and type 1 allergies/immediate type hypersensitivity: a systematic review



Helle Folge Bungum^a, Christian Vestergaard^b, Ulla Breth Knudsen^{a,*}

Bungum et al. European Journal of Obstetrics & Gynecology and Reproductive Biology 2014

A review (5 studies)

Study	Year	Study population	n	Outcome measures	Evidence level	Results	NOS score	Risk of allergic manifestations
Lamb et al. [9]	1986	Case-control study. Cases (n = 43) women with endometriosis (The US Endometriosis Association) and with family members with endometriosis. Controls: (n = 43) female friends	86	Diagnose of asthma, eczema or hay fever. Family/self history of food sensitivities.	III	Significantly higher frequency of eczema, hay fever, and food sensitivities among cases. All conditions occurred significantly more frequent among family members of cases, except for asthma.	1	Increased risk of allergic disease.
Nichols et al. 1987 [11]	1987	Case-control study. Cases (n = 88) women endometriosis. Controls (n = 88) female friends.	176	Symptoms of food sensitivities, eczema, asthma, hay fever.	III	Overall relative risk (RR) of 1.95 for allergic manifestations for cases compared to controls.	1	Increased risk of allergic disease.
Sinaii et al. [12]	2002	Cross-sectional survey. All women were members of the United States (US) Endometriosis Association. Cases (n = 467)	3680	Rates on allergies, asthma and eczema compared to the general female population of USA.	III	Asthma and allergy rates were significantly higher among women with endometriosis than the US female population.	NA	Increased risk of allergic disease.
Ferrero et al. [21]	2005	Women with surgically and histologically confirmed endometriosis. Controls (n = 412) in surgery for benign gynaecological disorders.	879	Asthma prevalence and severity.	III	Asthma prevalence and severity similar in cases and controls.	6	No increased risk of asthma.
Matalliotakis et al. [10]	2012	Cases (n = 501) with surgically confirmed endometriosis. Controls (n = 188) with tubal or male factor infertility, but without endometriosis.	689	Allergy on medications, complaints of sinus or perennial allergic rhinitis, asthma, family history of allergic disease, and correlation with stages of endometriosis.	III	Significantly higher prevalence of allergies on medications, allergic rhinitis, asthma and a positive family history of allergies among cases. No significant difference detected between allergic disease and stages of endometriosis.	5	Increased risk of allergic disease.

Endometriosis



Allergic disease

Co-occurrence of immune-mediated conditions and endometriosis among adolescents and adult women

Amy L Shafir^{1,2} | Marissa C. Palmor^{2,3,4} | Jessica Fourquet^{5,6} | Amy D. DiVasta^{1,2,7} |
 Leslie V. Farland⁸ | Allison F. Vitonis^{2,3} | Holly R Harris^{9,10} | Marc R. Laufer^{2,3,7} |
 Daniel W. Cramer³ | Kathryn L. Terry^{2,3,11} | Stacey A. Missmer^{1,2,11,12}

Shafir et al. Am J Reprod Immunol. 2021

A cross-sectional analysis in the
 Women's Health Study

551 pts with **endometriosis (surgical Dx)**
 652 controls **without endometriosis**

Risk factors for **surgically diagnosed endometriosis**

Physician diagnosis of immune dysfunction diseases	Cases N	Controls N	Age-adjusted OR (95% CI)	Multivariable-adjusted ¹ OR (95% CI)
Autoimmune and inflammatory^{2,5}				
No	526	630	1.00 (Ref)	1.00 (Ref)
Yes	25	22	1.72 (0.91-3.22)	1.87 (0.92-3.80)
Endocrine^{3,5}				
No	529	606	1.00 (Ref)	1.00 (Ref)
Yes	22	46	0.76 (0.44-1.32)	0.85 (0.46-1.58)
Chronic pain and fatigue states^{4,5}				
No	533	645	1.00 (Ref)	1.00 (Ref)
Yes	18	7	5.32 (1.94-14.6)	5.81 (1.89-17.9)
Allergies				
No	326	480	1.00 (Ref)	1.00 (Ref)
Yes	225	172	2.09 (1.61-2.71)	1.76 (1.32-2.36)
Asthma				
No	399	537	1.00 (Ref)	1.00 (Ref)
Yes	152	115	1.79 (1.34-2.40)	1.35 (0.97-1.88)
Eczema				
No	497	565	1.00 (Ref)	1.00 (Ref)
Yes	54	87	0.69 (0.47-1.00)	0.68 (0.44-1.04)
Mononucleosis				
No	473	591	1.00 (Ref)	1.00 (Ref)
Yes	78	61	2.28 (1.55-3.35)	1.75 (1.14-2.68)

Allergies and asthma are risk factors for **endometriosis**

Contents lists available at ScienceDirect
Respiratory Medicine
 journal homepage: www.elsevier.com/locate/rmed

Asthma is associated with endometriosis: A retrospective population-based cohort study

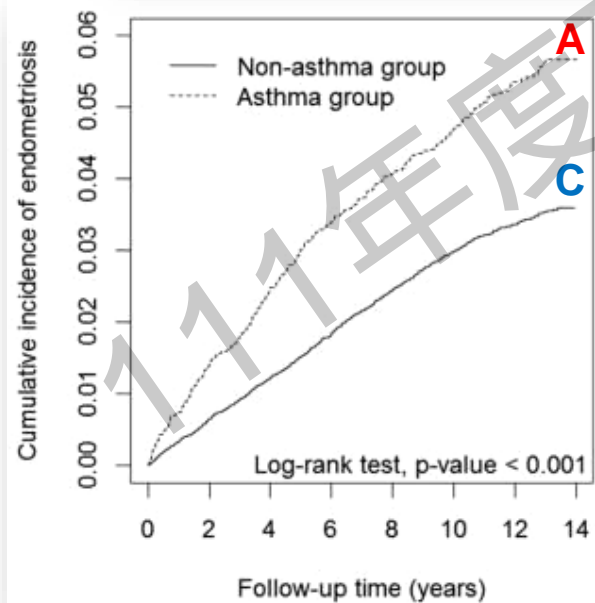
Yi-Hao Peng^{a,b,c}, Shan-Yu Su^{d,e}, Wei-Chih Liao^{f,g}, Chien-Wen Huang^{h,i,j}, Chung Y. Hsu^{k,l}, Hsuan-Ju Chen^{m,n}, Trong-Neng Wu^o, Wen-Chao Ho^{p,q}, Chin-Ching Wu^{r,s,t}

Peng et al. Respiratory Medicine 2017

A population-based retrospective cohort study
 Taiwan's NHIRD

Asthma (n=7,337) and **Non-asthma** (n=29,348)

Characteristics	Event no	Person-years	IR	HR (95% CI)	
				Univariate	Multivariate ^a
Asthma					
No	926	321083	2.88	1.00	1.00
Yes	371	80141	4.63	1.61 (1.42–1.81)***	1.50 (1.33–1.70)***



Endometriosis

Asthma > Ctrl
(aHR=1.50)

Genetic overlap analysis of endometriosis and asthma identifies shared loci implicating sex hormones and thyroid signalling pathways

E.O. Adewuyi^{1,2,*}, D. Mehta¹, International Endogene Consortium (IEC)¹, 23andMe Research Team^{3,4}, and D.R. Nyholt^{1,4}

Adewuyi et al. Human Reproduction 2022

Genome-wide association study (GWAS) data Endometriosis vs. asthma

Genome-wide significant **genes** associated with **endometriosis** and **asthma**

Summary of **pathways** associated with **endometriosis** and **asthma**

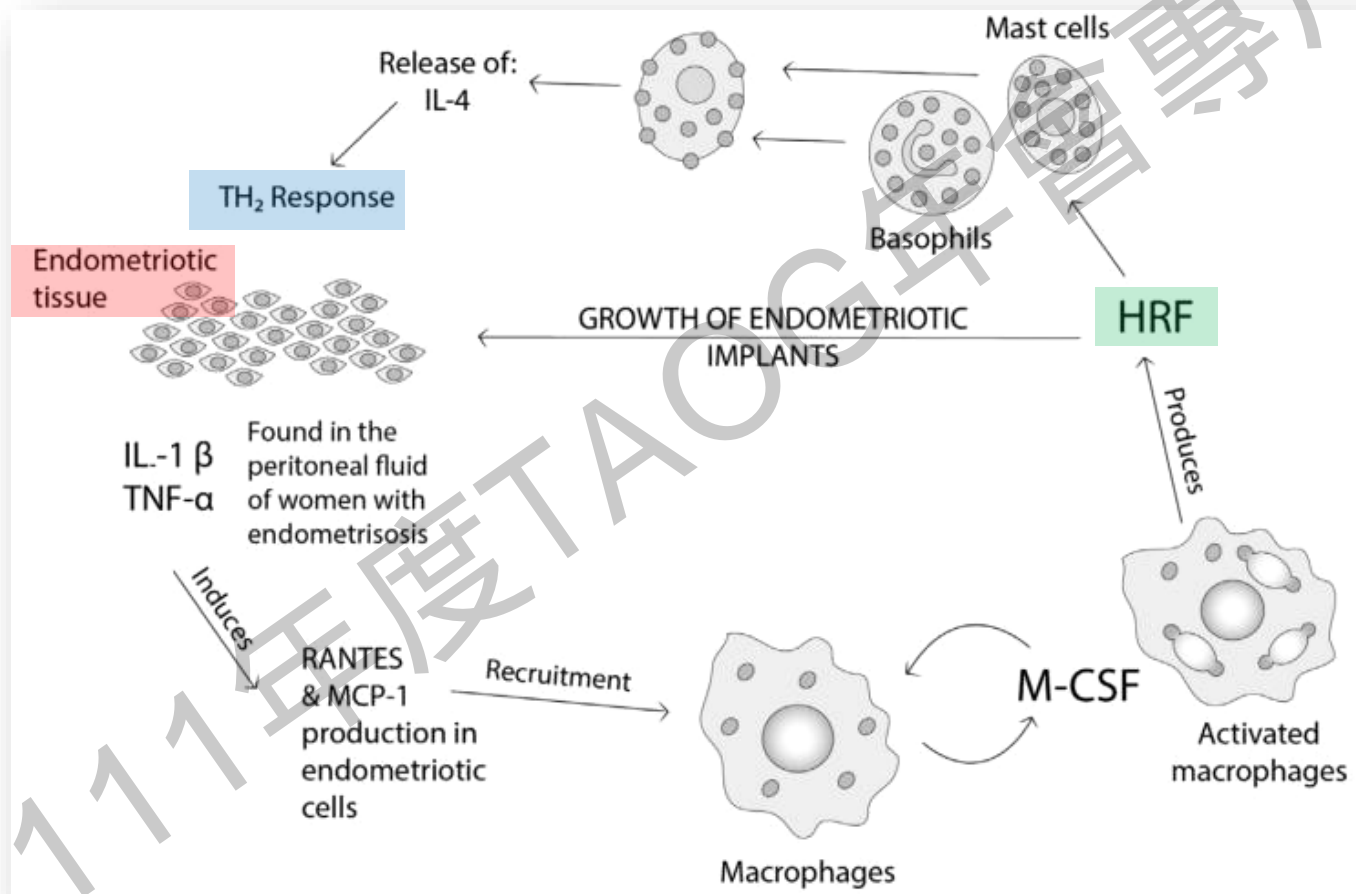
Chr	Start position	Stop position	Gene	P_{gene} endometriosis	P_{gene} asthma	FCP
IEC endometriosis and UKB asthma GWAS						
15	67356101	67487533	SMAD3	8.49×10^{-8}	1.91×10^{-16}	6.80×10^{-17}
6	31105313	31107127	PSORS1C2	1.11×10^{-2}	5.04×10^{-11}	1.63×10^{-11}
14	92980118	93155339	RIN3	1.65×10^{-4}	3.99×10^{-6}	1.76×10^{-10}
16	11038345	11276046	CLEC16A	3.13×10^{-2}	1.70×10^{-9}	1.31×10^{-9}
15	67493371	67547533	AAGAB	1.92×10^{-3}	5.36×10^{-6}	2.47×10^{-6}
10	21823094	22032559	MILLT10	5.65×10^{-5}	3.37×10^{-6}	4.46×10^{-6}
12	56390964	56400425	SUOX	3.87×10^{-2}	1.10×10^{-6}	9.61×10^{-7}
10	21781587	21786191	CASC10	2.65×10^{-4}	2.07×10^{-6}	1.22×10^{-6}
1	22443798	22470462	WNT4	8.30×10^{-8}	1.81×10^{-2}	3.21×10^{-1}
15	67547138	67794598	JQCH	2.61×10^{-4}	1.46×10^{-3}	7.78×10^{-6}
17	46210802	46507637	SKAP1	8.09×10^{-7}	1.87×10^{-1}	2.87×10^{-1}
1	174128548	174964445	RABGAP1L	6.09×10^{-5}	8.07×10^{-4}	8.76×10^{-7}
8	9413424	9639856	TNKS	3.51×10^{-4}	2.12×10^{-4}	1.30×10^{-6}
1	174979925	174992561	MPPS14	1.26×10^{-1}	6.25×10^{-4}	1.37×10^{-6}
17	38785049	38821393	KRT222	1.40×10^{-1}	5.76×10^{-3}	1.40×10^{-6}
8	8640864	8751155	MHAF1	3.89×10^{-2}	2.30×10^{-5}	1.54×10^{-6}
8	10753555	11058875	XKR6	2.97×10^{-1}	3.68×10^{-3}	1.86×10^{-6}
17	38810917	38821433	KRT222	1.33×10^{-3}	8.85×10^{-3}	2.00×10^{-6}
IEC endometriosis and TAGC asthma GWAS						
10	21823094	22032559	MILLT10	1.74×10^{-8}	3.66×10^{-4}	1.27×10^{-7}
12	102789465	102874423	JQCH	1.89×10^{-6}	9.54×10^{-3}	3.39×10^{-7}
19	46367247	46377055	FOXO3	2.69×10^{-4}	2.30×10^{-3}	1.23×10^{-7}
15	67356101	67487533	SMAD3	1.93×10^{-1}	3.08×10^{-9}	1.60×10^{-10}
1	22443798	22470462	WNT4	1.61×10^{-8}	3.63×10^{-1}	1.30×10^{-6}
16	11038345	11276046	CLEC16A	2.25×10^{-2}	4.55×10^{-8}	2.22×10^{-8}

Pathways	Term ID	Adjusted P-value	Genes
Male sex differentiation	GO:0046661	0.020	WNT4, GATA3, GATA4, FGF10, BCL2, NCOA1, HMOX1, CBL, MGST1, AGO4, CSDE1, STAT5B
Mammary gland development	GO:0030879	0.023	WNT4, MED1, GATA3, CREB1, ERBB4, FGF10, ARHGAP35, LATS1, NCOA1, DEAF1, STAT5B
Androgen biosynthetic process	GO:0006702	0.035	WNT4, MED1, HSD17B6, SCARB1
Thyroid hormone signalling pathway	KEGG:04919	0.026	WNT4, MED1, ATP2A3, GATA4, ATP1B1, NCOA1, NRAS, MED12L, TSC2
Brain derived neurotrophic factor (BDNF) signalling pathway	WP:WPP2380	0.036	VAV3, CREB1, MAP3K1, ALPL, MEF2A, RHOG, TSC2, NGK1, CDKSR1, STAT5B
Abnormal respiratory system morphology	HP:0012252	0.0042	SMAD3, WNT4, FIP1L1, TBK1, FOXPI1, GATA4, IRF5, FANCG, ERBB4, HPGD, MST1R, FGF10, BCL2, MLX, CD28, DNMT3B, IDUA, TRAP, CD3G, CBL, ALPL, NRAS, HPS6, LBR, CRELD1, CTC1, VCP, KMT2E, LMNB1, TSC2, MGP, HAAD, FS, ITGA3, VPS13B, PRRX1, FLJ1, IAMTOR2, DEAF1, STAT5B
Abnormal oral physiology	HP:0031815	0.0082	FIP1L1, C12ORF65, TBK1, FOXPI1, IRF5, ERBB4, FGF10, TH, CBL, ALS2, LBR, VCP, FS, DEAF1, STAT5B
Abnormality of immune system physiology	HP:0010978	0.013	SMAD3, WNT4, GATA3, FIP1L1, TBK1, FOXPI1, GATA4, IRF5, FANCG, HPGD, FGF10, BCL2, MLX, TNPO3, CD28, DNMT3B, CTSB, CD70, IDUA, TRAP, CD3G, CBL, ALPL, NRAS, HPS6, LBR, TOP3A, CRELD1, REV3L, CTC1, LMNB1, KDSR, TSC2, SHOC2, MGP, FS, ITGA3, WDR4, FLJ1, IAMTOR2, DEAF1, STAT5B, ATN1
Fatigue	HP:0012378	0.028	SMAD3, FIP1L1, TBK1, IYD, FOXPI1, GATA4, IRF5, ERBB4, BCL2, MLX, TNPO3, ABCG2, CBL, LBR, VCP, TSC2, AGK, STAT5B
Irregular hyperpigmentation	HP:0007400	0.048	IGF1, SPRED1, FANCG, CD28, CBL, NRAS, LBR, TOP3A, CDKN2B, REV3L, CTC1, KMT2E, KDSR, TSC2

Shared genes and pathways between **endometriosis** and **asthma**

The possible interaction between hypersensitivity reaction and endometriosis

Bungum et al. European Journal of Obstetrics & Gynecology and Reproductive Biology 2014



Shared factor of histamine releasing factor (HRF) between endometriosis and Th2 response

Physical comorbidity of endometriosis

Cancer



CVD



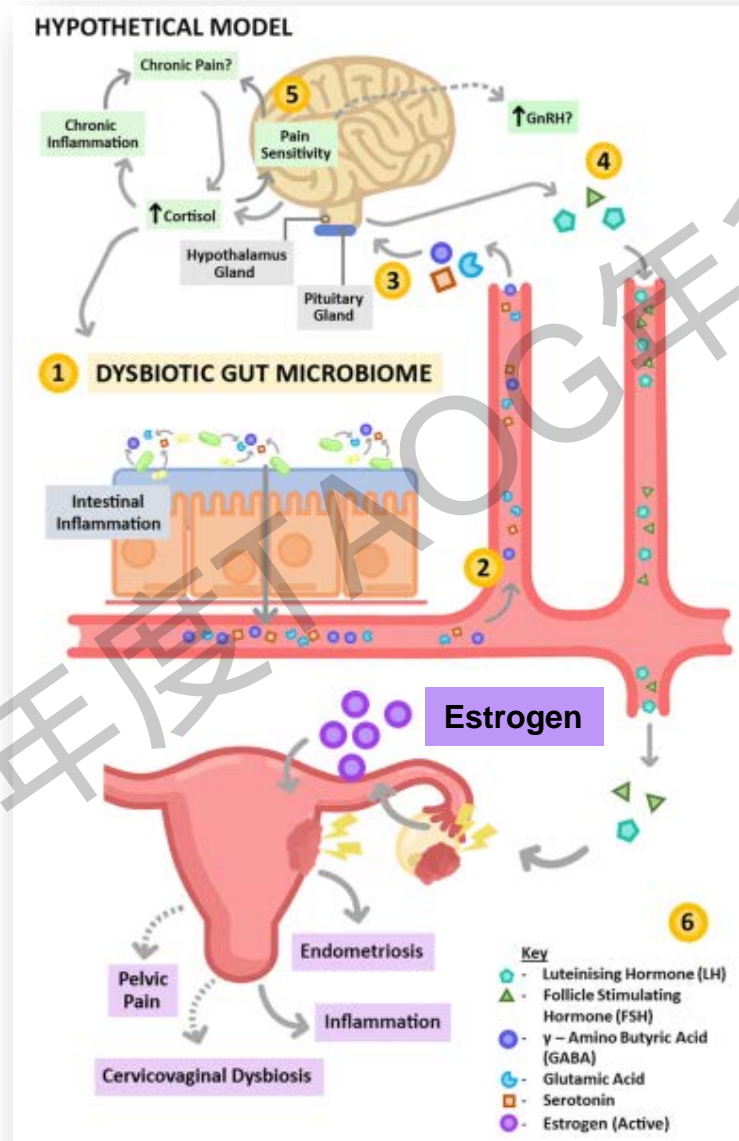
Immune disorders



GI & others



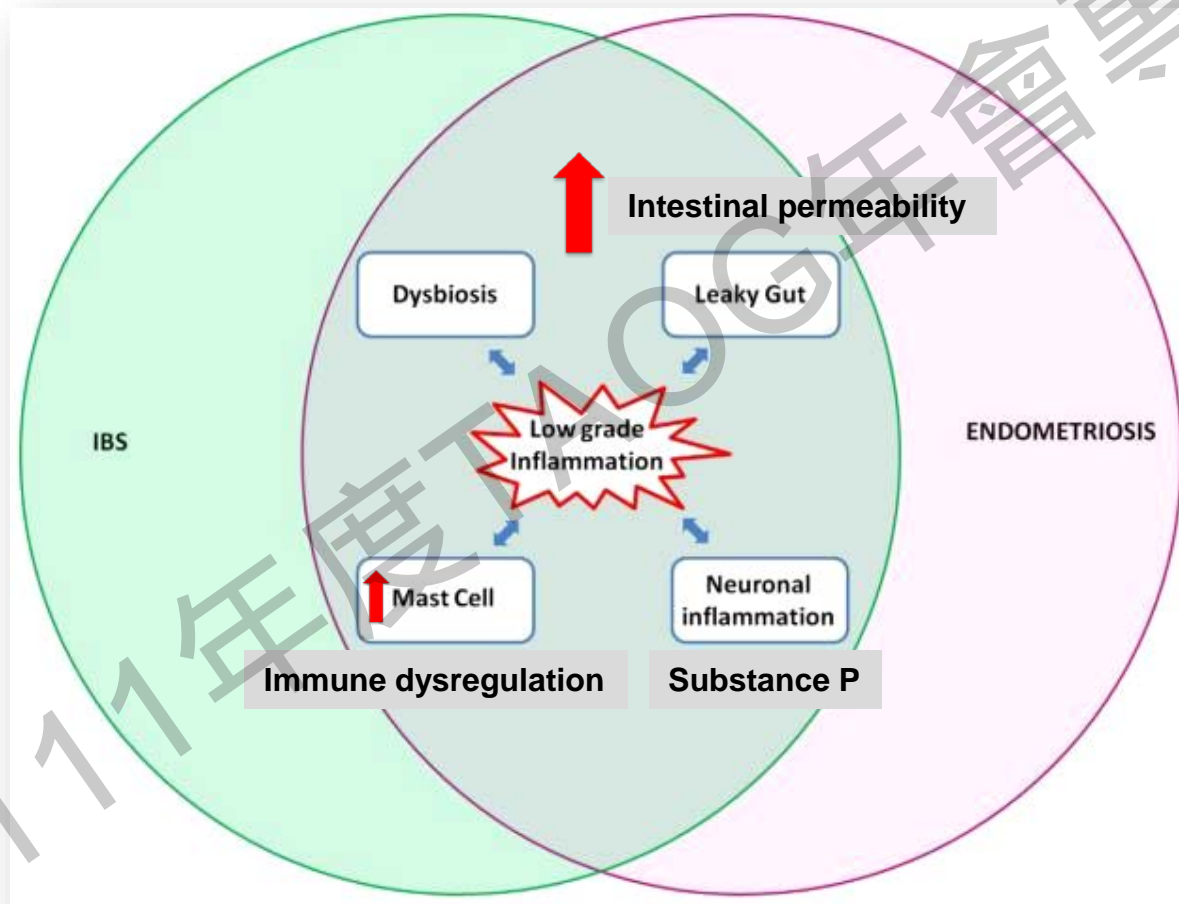
Gut dysbiosis is associated with endometriosis and its symptoms



Gut-brain axis

Salliss et al. Human
Reproduction Update 2022

Common pathophysiology between irritable bowel syndrome (IBS) and endometriosis



Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

Journal homepage: www.elsevier.com/locate/ejogrb

Review article

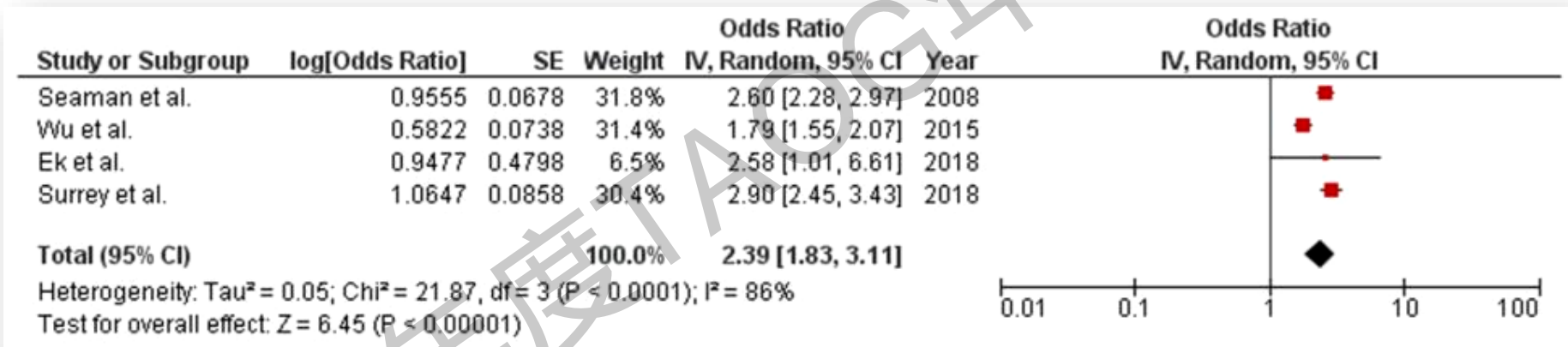
A systematic review and meta-analysis of the associations between endometriosis and irritable bowel syndrome

Khadija Saidi^a, Shantanu Sharma^a, Bodil Ohlsson^{b,*}

Saidi et al. European Journal of Obstetrics & Gynecology and Reproductive Biology 2020

4 studies

Irritable bowel syndrome



Irritable bowel syndrome

Endometriosis > Ctrl
(OR=2.39)

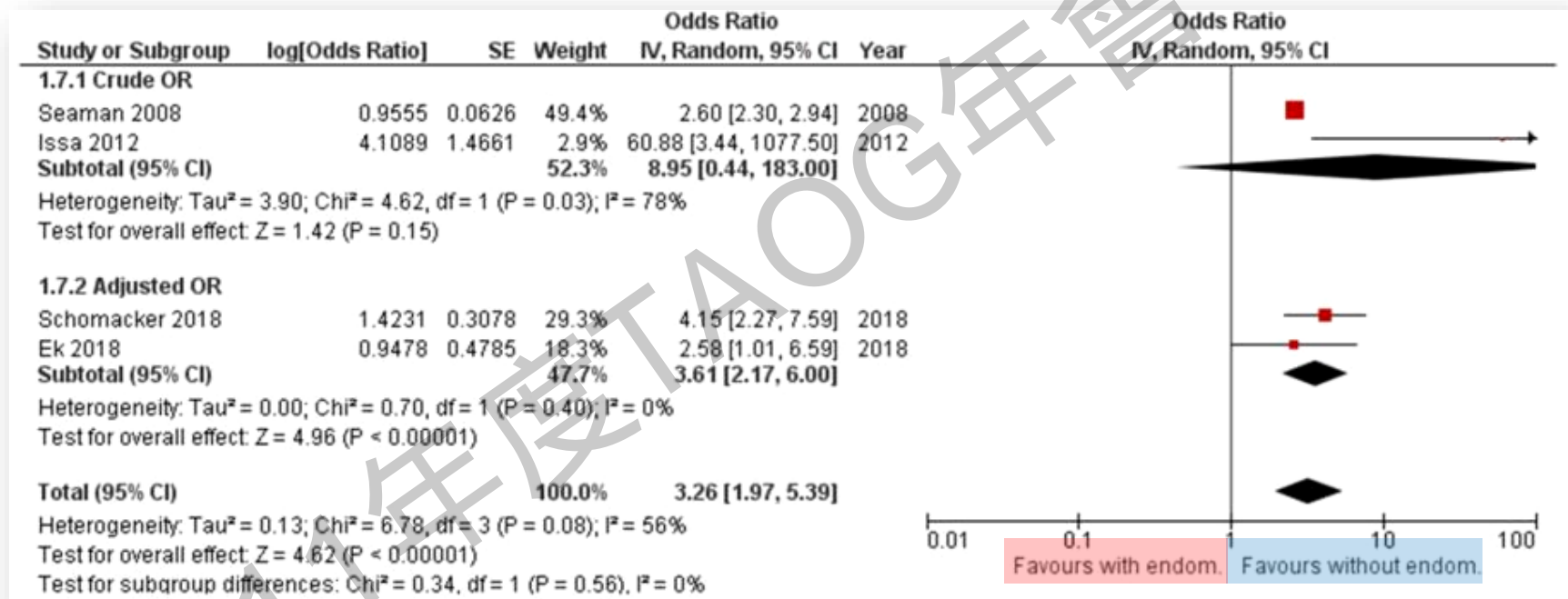
Endometriosis and irritable bowel syndrome: a systematic review and meta-analysis

Francesca Chiaffarino¹ · Sonia Cipriani¹ · Elena Ricci¹ · Paola Agnese Mauri^{1,2} · Giovanna Esposito² · Marta Barretta³ · Paolo Vercellini^{1,2} · Fabio Parazzini^{1,2}

Chiaffarino et al. Archives of Gynecology and Obstetrics 2021

4 studies

Irritable bowel syndrome



Irritable bowel syndrome

Endometriosis > Ctrl
(OR=3.26)

Association Between Bowel Obstruction or Intussusception and Endometriosis

Sarah Aldhaferi, MD, MSc;^{1,2} Eva Suarathana, MD, PhD;¹ Perrine Capmas, MD, PhD;^{1,3} Ahmed Badeghiesh, MD, MPH;^{1,2} Yaron Gil, MD;¹ Togas Tulandi, MD, MHCM¹

Aldhaferi et al. J Obstet Gynaecol Can 2021

A population-based study
18,427,520 women
96,539 women with bowel obstruction

	No bowel occlusion, no. (%); n = 18 327 156	Adhesive bowel obstruction; n = 32 830		Non-adhesive bowel obstruction; n = 63 709		All bowel obstruction; n = 96 539	
		No. (%)	Crude OR (95% CI); aOR ^a (95% CI)	No. (%)	Crude OR (95% CI); aOR ^a (95% CI)	No. (%)	Crude OR (95% CI); aOR ^a (95% CI)
Pelvic endometriosis							
Pelvic endometriosis present	132 076 (0.72)	510 (1.55)	2.2 (2.0–2.4); 3.2 (2.6–3.9)	909 (1.43)	2.0 (1.9–2.1); 2.4 (2.0–2.8)	1419 (1.47)	2.1 (2.0–2.2); 2.6 (2.3–3.0)
Location							
Ovarian	48 473 (0.26)	149 (0.45)	1.7 (1.5–2.0); 2.3 (1.5–3.5)	202 (0.32)	1.2 (1.0–1.4); 1.1 (0.7–1.6)	351 (0.36)	1.4 (1.2–1.5); 1.4 (1.1–1.9)
Tubal	9304 (0.05)	32 (0.10)	1.9 (1.4–2.7); 2.6 (1.1–6.3)	38 (0.06)	1.2 (0.9–1.6); 0.9 (0.3–2.3)	70 (0.07)	1.4 (1.1–1.8); 1.4 (0.7–2.7)
Intestine	5157 (0.03)	125 (0.38)	13.6 (11.4–16.2); 12.7 (7.9–20.3)	390 (0.61)	22.0 (19.7–24.3); 15.2 (11.4–20.2)	515 (0.53)	19.1 (17.4–20.9); 14.6 (11.4–18.8)
Pelvic peritoneum and rectovaginal septum	48 151 (0.26)	145 (0.44)	1.7 (1.4–2.0); 2.7 (1.8–4.0)	212 (0.33)	1.3 (1.1–1.5); 1.7 (1.2–2.3)	357 (0.37)	1.4 (1.3–1.6); 2.0 (1.5–2.6)
Other	42 963 (0.23)	181 (0.55)	2.4 (2.0–2.7); 3.9 (2.9–5.2)	318 (0.50)	2.1 (1.9–2.4); 2.9 (2.3–3.6)	499 (0.52)	2.2 (2.0–2.4); 3.2 (2.7–3.8)

^a Adjusted for age, obesity, quartile of income, race, urban vs. rural, insurance type, and tobacco use.

Bowel obstruction

Endometriosis > Ctrl
(aOR=2.6)

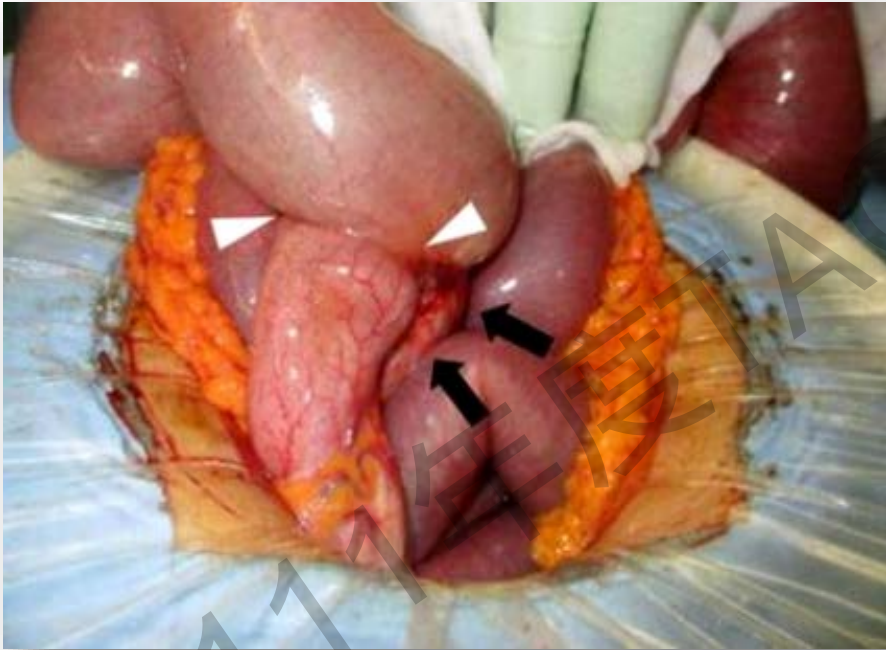
CASE REPORT

Small bowel obstruction caused by appendiceal and ileal endometriosis: a case report

Kazuki Kobayashi^{1*}, Masato Yamadera¹, Hiroaki Takeo² and Michinori Murayama¹

Kobayashi et al. Journal of Surgical Case Reports 2022

A case report



Appendiceal & ileal endometriosis



Contents lists available at ScienceDirect

International Journal of Surgery Case Reports

journal homepage: www.casereports.com



A case of endometriosis causing acute large bowel obstruction

Zexi Allan



Allan International Journal of Surgery Case Reports 2018

A case report



Rectosigmoid endometriosis

Physical comorbidity of endometriosis---others

High rates of autoimmune and endocrine disorders, fibromyalgia, chronic fatigue syndrome and atopic diseases among women with endometriosis: a survey analysis

N.Sinai¹, S.D.Cleary², M.L.Ballweg³, L.K.Nieman¹ and P.Stratton¹

Sinai et al. Human Reproduction 2002



Fibromyalgia
(OR=1.8)

ORIGINAL CLINICAL ARTICLE

WILEY

Endometriosis increased the risk of bladder pain syndrome/interstitial cystitis: A population-based study

Chia-Chang Wu MD, PhD^{1,2} | Shiu-Dong Chung MD, PhD^{3,4} |
Herng-Ching Lin PhD⁵

Wu et al. Neurourology and Urodynamics. 2018



**Bladder pain syndrome/
interstitial cystitis**
(aHR=3.74)

To Investigate the Risk of Herpes Zoster in Women With Endometriosis: A Taiwan National Population-Based Cohort Study

Chao-Yu Hsu^{1,2,3,4,5}, Der-Shin Ke¹, Cheng-Li Lin^{6,7} and Chia-Hung Kao^{8,9,10,11*}

Hsu et al. Front. Med. 2021



Herpes Zoster
(aHR=1.20)

Physical comorbidity of endometriosis

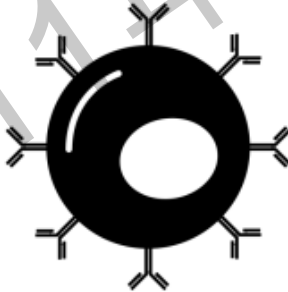
Cancer



CVD



Immune disorders



GI & others

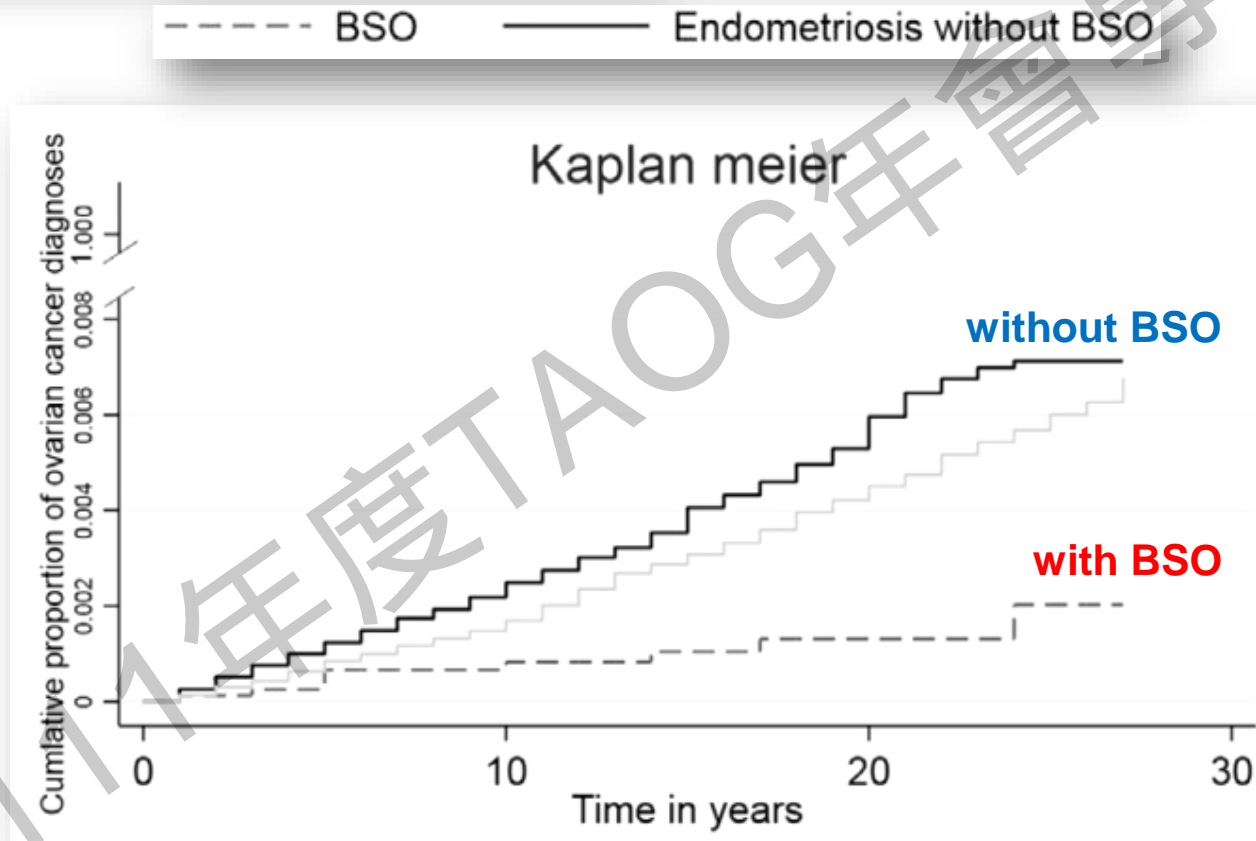


Incidence of ovarian cancer after bilateral salpingo-oophorectomy in women with histologically proven endometriosis

Marjolein Hermens, M.D.,^{2,3} Anne M. van Altena, M.D., Ph.D.,³ Johan Bulten, M.D., Ph.D.,⁵
Huib A. A. M. van Vliet, M.D., Ph.D.,^{4,6} Albert G. Siebers, Ph.D.,⁶ and Ruud L. M. Bekkers, M.D., Ph.D.^{4,6}

Hermens et al. Fertil Steril 2022

A retrospective nationwide cohort study
Endometriosis with BSO (n=7,984) vs.
Endometriosis without BSO (n=42,633)



Ovarian cancer

With BSO < without BSO

Oral contraceptive use by formulation and endometrial cancer risk among women born in 1947–1964: The Nurses' Health Study II, a prospective cohort study

Norah A. Burchardt^{1,2} · Amy L. Shafirir^{3,4} · Rudolf Kaaks¹ · Shelley S. Tworoger^{5,6} · Renée T. Fortner¹

Burchardt et al. European Journal of Epidemiology 2021

A prospective cohort study
107,069 women from the **NHS II**

Associations between OC and **EM cancer risk**

	Adjusted for age and calendar period		Multivariable-adjusted ^a	
	HR	95% CI	HR	95% CI
<i>Use of OCs</i>				
Never use	1.00	(ref.)	1.00	(ref.)
Ever use	0.67	(0.56–0.79)	0.77	(0.65–0.91)
Current use	0.53	(0.32–0.87)	0.60	(0.36–0.99)
Past use	0.67	(0.57–0.79)	0.77	(0.65–0.92)

OC use



**EM cancer
(OR=0.77)**

Oral contraceptive use by formulation and breast cancer risk by subtype in the Nurses' Health Study II: a prospective cohort study

Norah A. Burchardt, MD, MSc; A. Heather Eliassen, ScD; Amy L. Shafirir, ScD; Bernard Rosner, Rudolf Kaaks, PhD; Shelley S. Tworoger, PhD; Renée T. Fortner, PhD

Burchardt et al. Am J Obstet Gynecol 2022

A prospective cohort study
113,187 women from the **NHS II**

Associations between OC and **breast ca. risk**

Characteristics of OC use	Person-years	Invasive		
		Cases	HR	95% CI
Current OC use, restricted to premenopausal women ^b				
Never use	246,135	261	1.00	Ref
Current use	176,823	205	1.31	(1.09–1.58)
Current, duration of use				
≤5 y ^c	130,734	113	1.19	(0.95–1.49)
>5 y ^d	46,033	92	1.56	(1.23–1.99)
<i>P trend^e</i>				.07

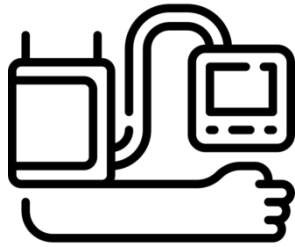
OC use



**Breast cancer
(OR=1.31)**

Obstetric comorbidity of endometriosis

Preeclampsia



Gestational diabetes



Placenta previa

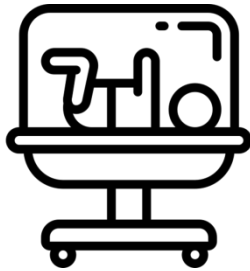


Cesarean section



Neonatal comorbidity of endometriosis

Preterm birth



PPROM



SGA



Neonatal death



Outlines of endometriosis comorbidity



1

Introduction



2

Physical
comorbidity



3

Psychological
comorbidity



4

Conclusions

Psychological comorbidity of endometriosis

Quality of life



Mental health



Social function



Sexuality



Psychological comorbidity of endometriosis

Quality of life



Mental health



Social function



Sexuality



RESEARCH ARTICLE

Systematic review of quality of life measures in patients with endometriosis

Nicolas Bourdel^{1,2*}, Pauline Chauvet^{1,2}, Valentina Billone³, Gianni Douridas¹, Arnaud Fauconnier⁴, Laurent Gerbaud⁵, Michel Canis^{1,2}

Bourdel et al. PLoS ONE 2019

A systematic review
201 studies, **endometriosis pts**
Quality of life measures

The generic instruments

Table 1. Studies found in a systematic review of endometriosis quality of life assessment and the quality of life scale used: The generic instruments.

Scale	Study references
SF-36 (The Short-Form-36 Health Survey) n = 72	Agarwal et al. 2015 [97], Angioni et al. 2015 [98], Angioni et al. 2015 [99], Augusto et al. 2016 [100], Bassi et al. 2011 [101], Berner et al. 2015 [102], Bodner et al., 1997 [43], Caruso et al., 2015 [103], Caruso et al., 2016 [104], Caruso et al., 2015 [105], Centini et al., 2013 [106], Chene et al., 2008 [107], Chene et al., 2012 [108], Chuamoor et al. 2012 [109], Darzi et al. 2015 [75], Darzi et al., 2009 [110], Darzi et al., 2010 [111], De Graaf et al., 2013 [112], De Graaf et al., 2015 [113], Deguara et al., 2013 [114], Di Donato et al., 2013 [115], Dubernard et al., 2008 [8], Dubernard et al., 2008 [116], Farfaras et al., 2014 [117], Friedl et al., 2015 [118], Friggé Sebe Petrelluzzi et al., 2012 [119], Grandi et al., 2015 [120], Heffer et al., 2005 [123], Hong et al., 2014 [122], Jia et al., 2013 [40], Jones et al., 2004 [4], Jones et al., 2001 [36], Laas et al., 2015 [123], Laursen et al., 2005 [124], Lepège et al., 1998 [14], Lovkvist et al., 2016 [125], Mabrouk et al., 2012 [126], Mabrouk et al., 2011 [127], Mabrouk et al., 2011 [28], Maiorana et al., 2012 [129], Marques et al., 2004 [130], Piketty et al., 2007 [131], Meis et al., 2014 [132], Miller et al., 2000 [133], Montanari et al., 2013 [134], Morotti et al., 2014 [135], Nnoaham et al., 2011 [85], Nogueira-Silva et al., 2015 [69], Notojima et al., 2011 [39], Nunes et al., 2014 [136], Petrelluzzi et al., 2008 [137], Pontis et al., 2016 [138], Rémorgida et al., 2007 [139], Ribeiro et al., 2014 [140], Roman et al., 2015 [141], Roman et al., 2012 [142], Rubi-Klein et al., 2010 [143], Callaghan et al., 2016 [144], Sesti et al., 2007 [145], Siedentopf et al., 2008 [146], Silveira da Cunha Araújo et al., 2014 [147], Strowitzki et al., 2010 [148], Strowitzki et al., 2010 [149], Strowitzki et al., 2012 [150], Stull et al., 2014 [60], Tammasakul et al., 2012 [151], Teixeira et al., 2017 [152], Touboul et al., 2015 [74], Tu et al., 2014 [153], Vercellini et al., 2002 [154], Zhao et al., 2012 [155], Zupi et al., 2004 [156].
SF-12 (The Short-Form-12 Health Survey) n = 16	Abbott et al., 2004 [66], Abbott et al., 2005 [157], Carey et al., 2014 [188], De Graaf et al., 2016 [159], Deguara et al., 2013 [114], Di Francesco et al., 2014 [160], Facchin et al., 2015 [161], Fourquet et al., 2011 [62], Garry et al., 2000 [3], Luisi et al., 2015 [163], Lyons et al., 2008 [164], Messner et al., 2016 [165], Mowwad et al., 2011 [166], Soto et al., 2017 [167], Vercellini et al., 2016 [168], Zupi et al., 2015 [169].
EQ-5D (The European Quality of Life-5 Dimensions questionnaire) n = 24	Abbott et al., 2004 [66], Bailly et al., 2013 [170], Bliert et al., 2016 [171], Daniels et al., 2009 [171], English et al., 2007 [172], English et al., 2014 [173], Ford et al., 2004 [174], Fritzer et al., 2014 [175], Gao et al., 2006 [78], Garry et al., 2000 [3], Kent et al., 2016 [165], Klein et al., 2014 [176], Li et al., 2014 [177], Lyons et al., 2006 [164], Meuleman et al., 2011 [178], Michalak et al., 2016 [186], Radosa et al., 2015 [187], Radosa et al., 2014 [179], Roman et al., 2016 [180], Roman et al., 2010 [181], Shakir et al., 2015 [188], Simoons et al., 2012 [8], Simoons et al., 2011 [182], The Luminal trial collaboration, 2003 [183].
NHP (The Nottingham Health Profile) n = 3	Bergqvist et al., 2001 [8], Burry et al., 1992 [189], Clarke et al., 1995 [20]
WHOQOL-BREF (The World Health Organization Quality of Life brief) n = 11	Cao et al., 2015 [189], Gallucci et al., 2016 [84], Kiykac Altinbas et al., 2015 [190], Lee et al., 2016 [191], Leonardo-Pinto et al., 2017 [192], Lin et al., 2014 [193], Sepulcri et al., 2009 [194], Souza et al., 2011 [195], Tripsi et al., 2011 [89], Yeta et al., 2015 [196], Zhao et al., 2013 [197].
Ferrans & Powers' Quality of Life Index (QLI) n = 2	Rannestad et al., 2001 [54], Laganà et al., 2015 [198]
Duke Health Profile [24] n = 3	Stratton et al., 2008, 2015 [26,27], Karp et al., 2011 [25]
15D n = 3	Taipale et al., 2009 [30], Setälä et al., 2012 [28], Küssi et al., 2013 [29]

SF-36=The Short-Form-36 Health Survey

The specific scales

Table 2. Studies found in a systematic review of endometriosis quality of life assessment and the quality of life scale used: The specific scales and self-developed measures.

Scale	Study references
EHP-30 (The 30-item Endometriosis Health Profile) n = 43	Ahn et al., 2009 [199], Al-Azemi et al., 2009 [200], Berbari et al., 2008 [201], Chauvet et al., 2017 [30], Chaong et al., 2014 [202], Darzi et al., 2009 [110], Flower et al., 2011 [203], Friedl et al., 2015 [118], Gallicchio et al., 2015 [204], Gao et al., 2006 [78], Gonçalves et al., 2017 [205], Hansen et al., 2013 [82], Hansen et al., 2014 [83], Jenkinson et al., 2008 [206], Jia et al., 2013 [40], Jones et al., 2001 [36], Jones et al., 2004 [4], Jones et al., 2004 [207], Jones et al., 2006 [7], Kent et al., 2016 [183], Khong et al., 2010 [209], Maiorana et al., 2012 [129], Meuleman et al., 2011 [178], Meuleman et al., 2011 [208], Meuleman et al., 2009 [5], Meuleman et al., 2014 [209], Middleton et al., 2017 [210], Mira et al., 2015 [211], Nogueira-Silva et al., 2015 [69], Notojima et al., 2011 [39], Protopoulos et al., 2014 [212], Rostami et al., 2015 [213], Selvi-Dogan et al., 2016 [214], Shakir et al., 2015 [188], Soliman et al., 2017 [215], Soto et al., 2017 [167], Tan et al., 2013 [116], Van de Burgi et al., 2011 [61], Van de Burgi et al., 2013 [65], Van der Houwen et al., 2014 [217], Vercellini et al., 2013 [218], Wayne et al., 2008 [219], Wicksstrom et al., 2013 [220].
EHP-5 (The 5-item Endometriosis Health Profile) n = 12	Acis et al., 2015 [221], Bailly et al., 2013 [170], Boukou et al., 2012 [222], Carr et al., 2014 [223], Fouconnier et al., 2017 [62], Fourquet et al., 2011 [162], Goshtrasebi et al., 2011 [70], Goyal et al., 2016 [224], Jones et al., 2004 [207], Minas et al., 2014 [225], Renault et al., 2009 [226], Sekak et al., 2015 [171].
Self-developed questionnaires (n = 1 for each scale)	Oehmke et al., 2008 [16] Trehan and Sanaullah 2009 [47] Kumar et al., 2011 [49] Leuridan et al., 2011 [52] Caccaroni et al., 2012 [54] Issa et al., 2012 [55] Fritzer et al., 2012 [57] Chapron et al., 2013 [58] Regidou et al., 1997 [85] Mathias et al., 1996 [44] Bodner et al., 1992 [43] Colwell et al., 1998 [42]

EHP-30=The 30-item Endometriosis Health Profile

SF-36 and **EHP-30** are the most two commonly used QoL scale in **endometriosis studies**

SF-36

Ware et al. Medical Care 1992

Concepts	No. of Items	No. of Levels	Meaning of Scores	
			Low	High
Physical functioning	10	21	Limited a lot in performing all physical activities including bathing or dressing	Performs all types of physical activities including the most vigorous without limitations due to health
Role limitations due to physical problems	4	5	Problems with work or other daily activities as a result of physical health	No problems with work or other daily activities as a result of physical health, past 4 weeks
Social Functioning	2	9	Extreme and frequent interference with normal social activities due to physical and emotional problems	Performs normal social activities without interference due to physical or emotional problems, past 4 weeks
Bodily pain	2	11	Very severe and extremely limiting pain	No pain or limitations due to pain, past 4 weeks
General mental health	5	26	Feelings of nervousness and depression all of the time	Feels peaceful, happy, and calm all of the time, past 4 weeks
Role limitations due to emotional problems	3	4	Problems with work or other daily activities as a result of emotional problems	No problems with work or other daily activities as a result of emotional problems, past 4 weeks
Vitality	4	21	Feels tired and worn out all of the time	Feels full of pep and energy all of the time, past 4 weeks
General health perceptions	5	21	Believes personal health is poor and likely to get worse	Believes personal health is excellent

8 concepts
36 items

EHP-30

Jones et al. Obstet Gynecol 2001

Scale
Core scales
Pain
Control and powerlessness
Emotional well being
Social support
Self-image
Modular scales
Work
Intercourse
Relationship with children
Medical profession
Treatment
Infertility

5 core scales
30 items

Does Endometriosis Disturb Mental Health and Quality of Life? A Systematic Review and Meta-Analysis

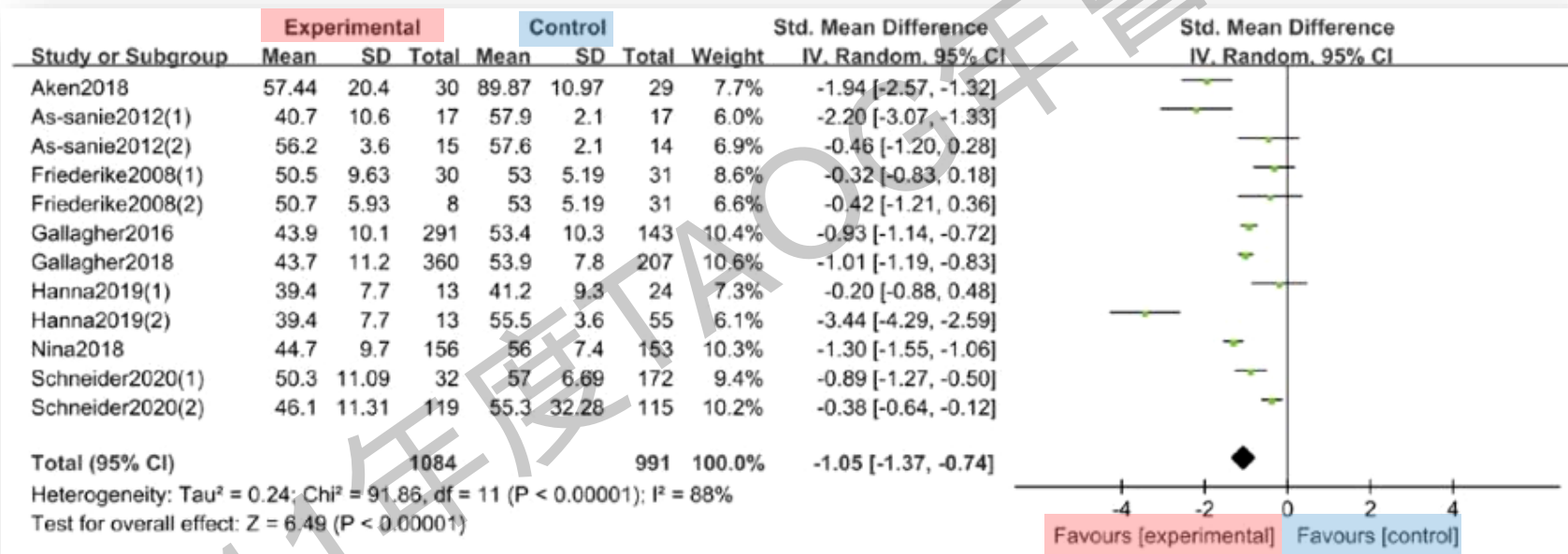
Yuehan Wang Bo Li Yang Zhou Yizi Wang Xue Han Shitai Zhang
Zheng He Ling Ouyang

Wang et al. Gynecol Obstet Invest 2021

12 studies

1,084 pts with **endometriosis** vs.
991 **controls**

Quality of life (Physical dimensions)



Physical dimensions
of QoL

Endometriosis < **Ctrl**

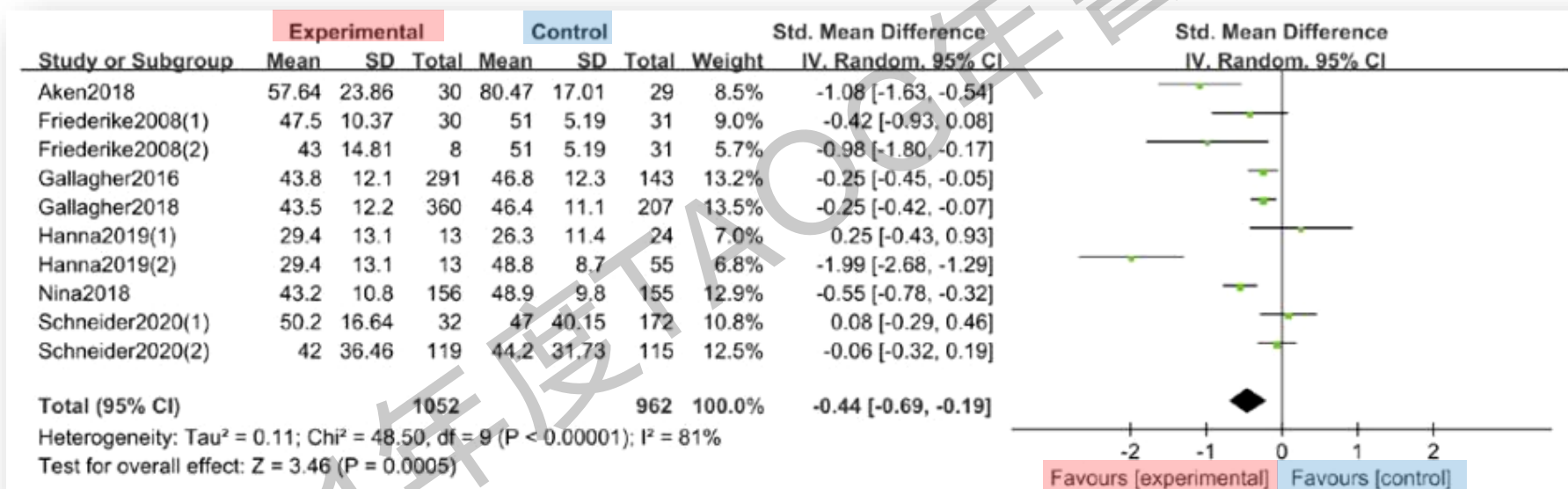
Does Endometriosis Disturb Mental Health and Quality of Life? A Systematic Review and Meta-Analysis

Yuehan Wang Bo Li Yang Zhou Yizi Wang Xue Han Shitai Zhang
Zheng He Ling Ouyang

Wang et al. Gynecol Obstet Invest 2021

10 studies
1,052 pts with **endometriosis** vs.
962 **controls**

Quality of life (Mental dimensions)



Mental dimensions
of QoL

Endometriosis < **Ctrl**

Clinical aspects and the quality of life among women with endometriosis and infertility: a cross-sectional study

Marina Pessoa de Farias Rodrigues^{1,2}, Fabia Lima Vilarino³, Alessandra de Souza Barbeiro Munhoz¹, Laércio da Silva Paiva^{2,4}, Luiz Vinicius de Alcantara Sousa^{2,4}, Victor Zaja^{1,3,5*} and Caio Parente Barbosa^{1,3,5}



Pessoa de Farias Rodrigues et al.
BMC Women's Health 2020

A cross-sectional study
106 pts with **endometriosis**
Stage I/II (n=26) and **Stage III/IV** (n=74)

Quality of life domains	Staging Endometriosis		p ^a
	Staging I/ II	Staging III/IV	
	Median scores (IQR)		
Physical Functioning	87.50 (25.00)	85.00 (28.00)	0.708
Role-Physical	100.00 (100.00)	100.00 (69.00)	0.794
Bodily Pain	73.00 (43.00)	57.00 (43.00)	0.352
Role-Emotional	66.67 (100.00)	66.67 (66.67)	0.360
	Mean scores (SD)		p ^b
General Health	58.69 (16.56)	60.54 (17.57)	0.629
Vitality	54.42 (14.72)	56.24 (11.38)	0.569
Social Functioning	66.34 (26.40)	66.20 (23.58)	0.980
Mental Health	59.54 (21.18)	59.23 (18.52)	0.946

**HRQoL
(PCS&MCS)**

Stage I/II = Stage III/IV

Cross-Sectional Survey of the Impact of Endometriosis Symptoms on Health-Related Quality of Life in Canadian Women

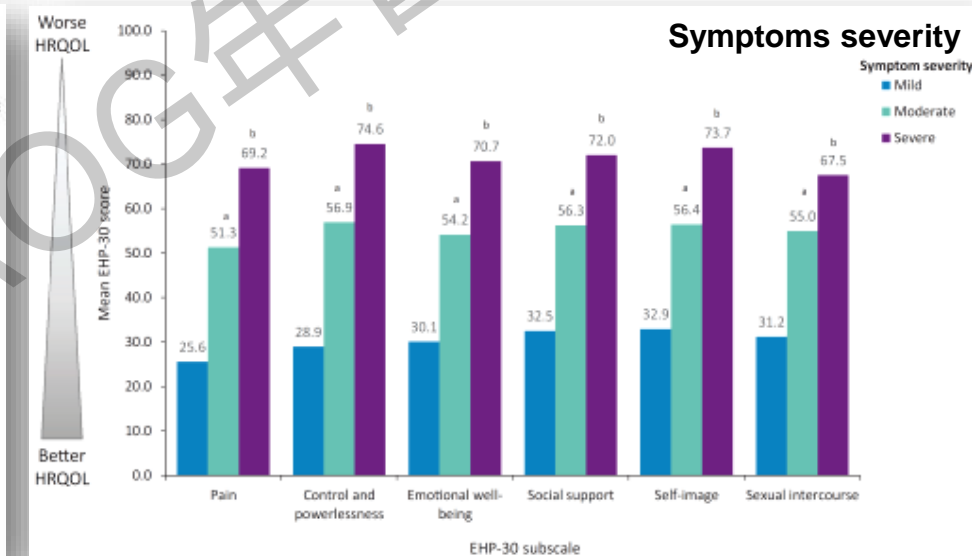
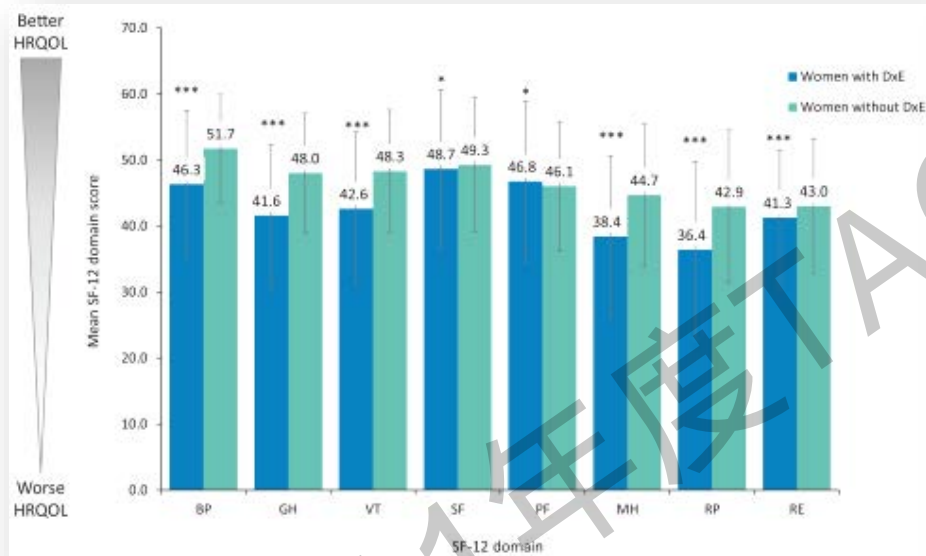
Ahmed M. Soliman, MS, PhD;¹ Sukhbir Singh, MD;² Yasmine Rahal, MSc;³ Catherine Robert, MBA;³ Isabelle Defoy, PhD;³ Paul Nisbet, PhD;⁴ Nicholas Leyland, MHCM, MD⁵

Soliman et al. J Obstet Gynaecol Can 2020

A cross-sectional study
2,004 pts with **endometriosis** and
26,528 **controls**

HRQOL: health-related quality of life

SF-12: 12-item Short Form Health Survey; EHP-30: Endometriosis Health Profile-30

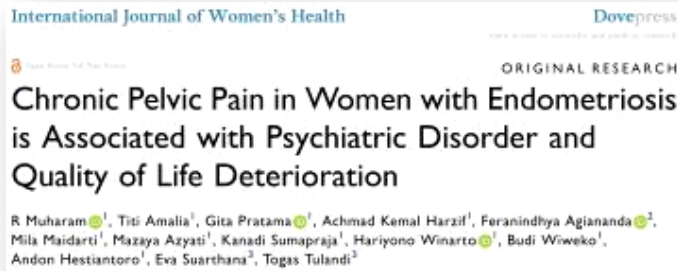


HRQoL

Endometriosis < Ctrl

HRQoL

Severe < Moderate < Mild

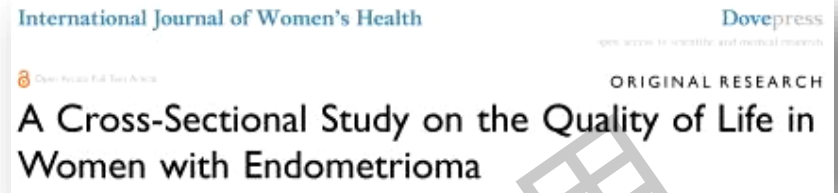


Muharam et al. International Journal of Women's Health 2022

A cross-sectional study
160 pts with **endometriosis**

Table 5 Multivariate Analysis of Quality of Life (EHP-30 Score) in Endometriosis Patients

Variable	Unstandardized β Coefficient (95% CI)	p-value*
Body Mass Index	5.52 (1.82–9.27)	0.007
Previous medication history	2.97 (–0.78–6.77)	0.125
VAS	13.33 (9.01–17.65)	<0.001
Psychiatric disorder	9.84 (6.07–13.60)	<0.001



Thammasiri et al. International Journal of Women's Health 2022

A cross-sectional study
99 pts with **ovarian endometrioma**

Table 3 Multivariable Linear Regression Analysis of the Clinical Factors Correlated with the Weighted Overall EHP-30 Score (n=99)

Analyzed Variable	Adjusted Coefficient	95% CI
Pain score	2.79	1.48, 4.18
Chronic pelvic pain	7.53	1.85, 13.20
Age	– 0.19	– 0.63, 0.25
Married	– 4.22	– 11.09, 2.66
Divorce	– 14.87	– 32.54, 2.82
BMI	0.07	– 0.64, 0.79



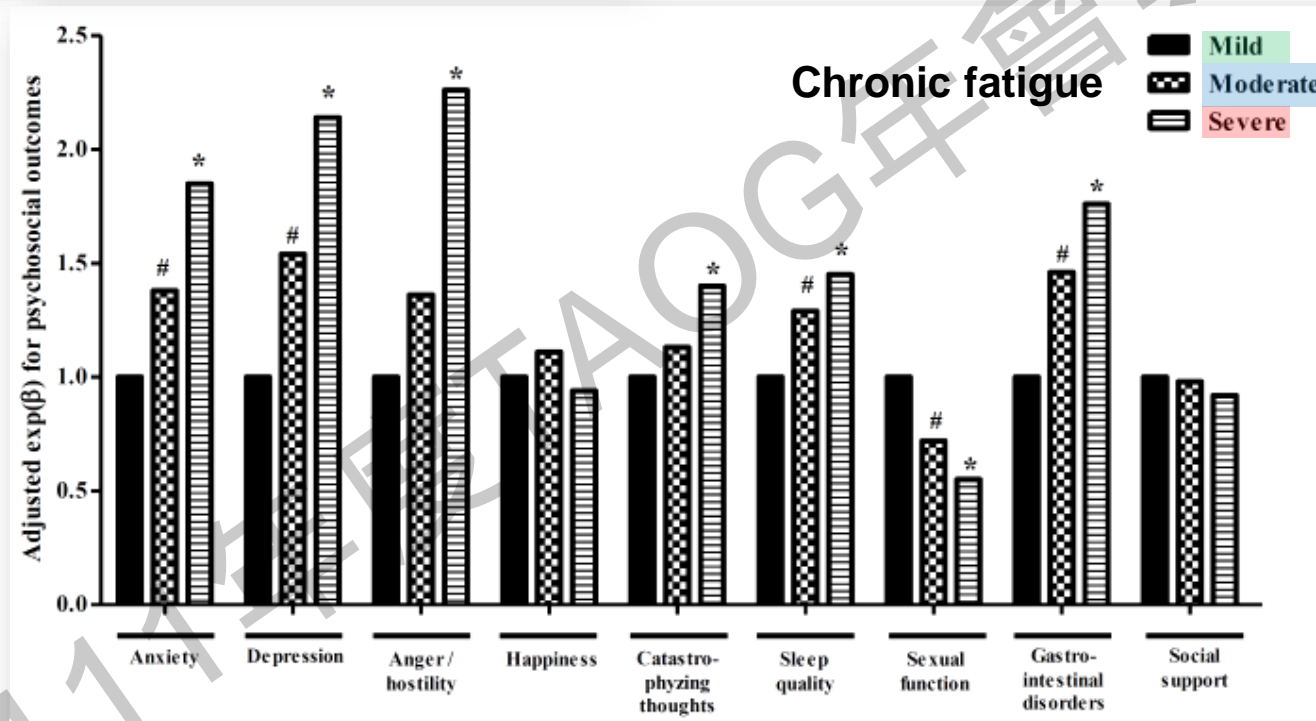
Article

Contribution of Chronic Fatigue to Psychosocial Status and Quality of Life in Spanish Women Diagnosed with Endometriosis

Antonio Mundo-López ^{1,2}, Olga Ocón-Hernández ^{3,4}, Ainhoa P. San-Sebastián ¹, Noelia Galiano-Castillo ^{3,5,6}, Olga Rodríguez-Pérez ¹, María S. Arroyo-Luque ¹, Manuel Arroyo-Morales ^{3,5,6}, Irene Cantarero-Villanueva ^{3,5,6}, Carolina Fernández-Lao ^{3,5,6,*} and Francisco Artacho-Cordón ^{1,3,6,7,*}

Mundo-López et al. Int. J. Environ. Res. Public Health 2020

A case-control study
230 pts with **endometriosis**
Chronic fatigue (Piper Fatigue Scale)



Quality of life

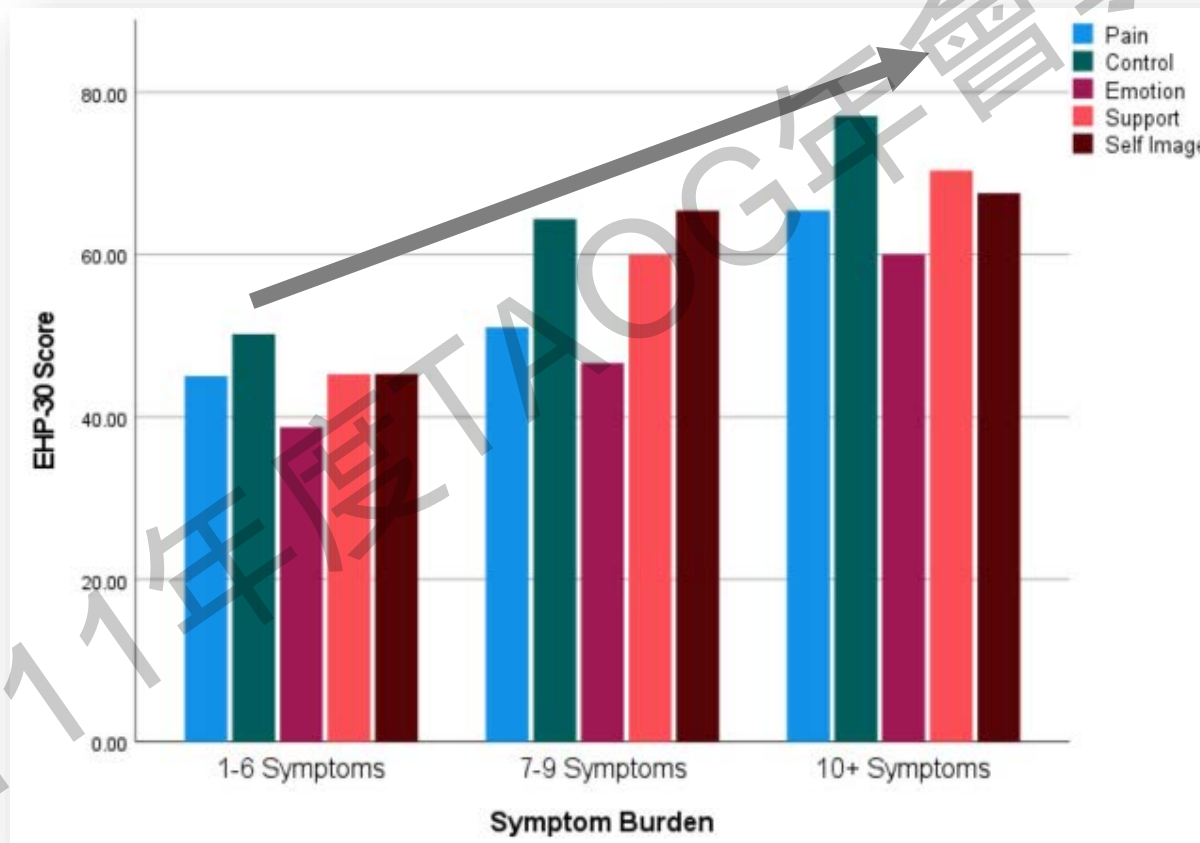
Severe < Moderate < Mild

Health-related quality of life in endometriosis: The influence of endometriosis-related symptom presence and distress

Journal of Health Psychology
1-15
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DOI: 10.1177/13591053221085051
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SAGE

Niekerk et al. Journal of Health Psychology 2022

A prospective questionnaire study
318 women with **endometriosis**
Endometriosis Health Profile (EHP-30)



Symptom burden were associated with **poor QoL**

Psychological comorbidity of endometriosis

Quality of life



Mental health



Social function



Sexuality



Does Endometriosis Disturb Mental Health and Quality of Life? A Systematic Review and Meta-Analysis

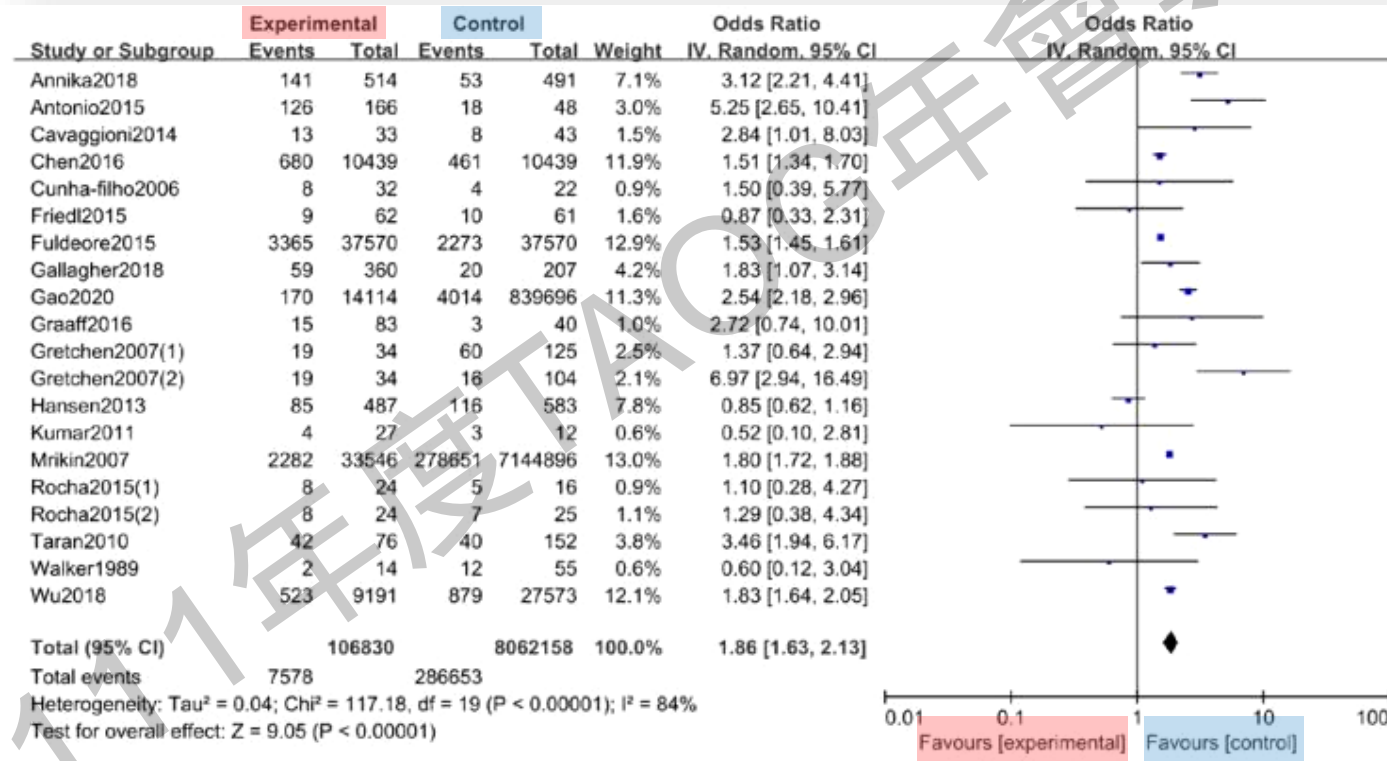
Yuehan Wang Bo Li Yang Zhou Yizi Wang Xue Han Shitai Zhang
Zheng He Ling Ouyang

Wang et al. Gynecol Obstet Invest 2021

20 studies

106,830 pts with **endometriosis** vs.
8,062,158 **controls**

Depression



Depression

Endometriosis > Ctrl
(OR=1.86)

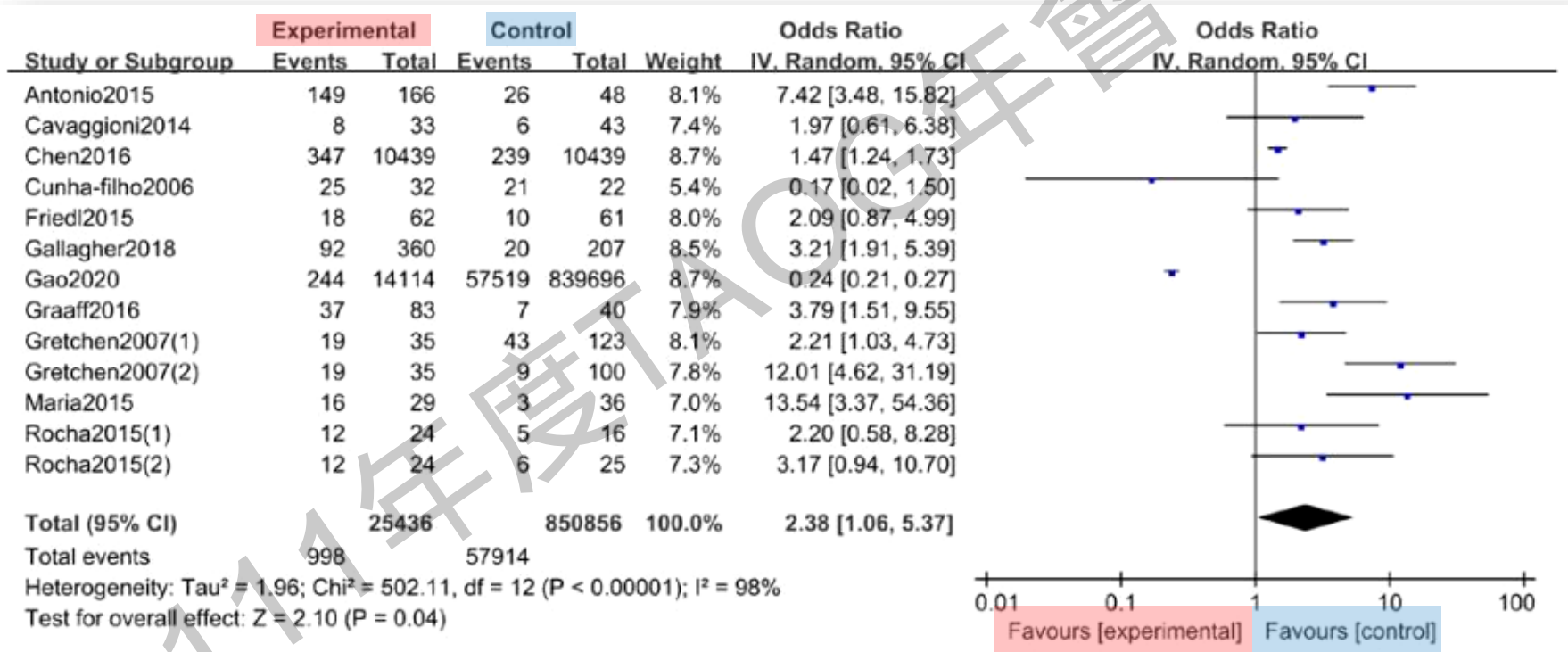
Does Endometriosis Disturb Mental Health and Quality of Life? A Systematic Review and Meta-Analysis

Yuehan Wang Bo Li Yang Zhou Yizi Wang Xue Han Shitai Zhang
Zheng He Ling Ouyang

Wang et al. Gynecol Obstet Invest 2021

13 studies
25,436 pts with **endometriosis** vs.
850,856 **controls**

Anxiety



Anxiety

Endometriosis > Ctrl
(OR=2.38)



Original Contribution

Depression, Anxiety, and Self-Directed Violence in Women With Endometriosis: A Retrospective Matched-Cohort Study

Stephanie J. Estes, Carrie E. Huisinigh*, Stephanie E. Chiuve, Natalia Petruski-Ivleva, and Stacey A. Missmer

Estes et al. Am J Epidemiol. 2021

A retrospective matched-cohort study
Optum's Clinformatics DataMart
72,677 women **with endometriosis** vs.
147,251 women **without endometriosis**

Exposure Status	No.	No. of Events	Incidence Per 1,000 PY	Crude		Multivariable Model 1 ^b		Multivariable Model 2 ^c	
				HR	95% CI	HR	95% CI	HR	95% CI
<i>Incident Anxiety</i>									
Overall									
Endometriosis	72,677	8,377	57.1	1.42	1.38, 1.45	1.38	1.34, 1.42	1.25	1.21, 1.29
No endometriosis	147,251	14,840	39.8	1.00	Referent	1.00	Referent	1.00	Referent
Age 18–34 years									
Endometriosis	38,741	4,875	64.5	1.43	1.38, 1.48	1.36	1.31, 1.41	1.35	1.30, 1.40
No endometriosis	75,931	7,833	44.4	1.00	Referent	1.00	Referent	1.00	Referent
Age 35–50 years									
Endometriosis	33,936	3,502	49.3	1.37	1.31, 1.42	1.35	1.29, 1.41	1.34	1.28, 1.39
No endometriosis	71,320	7,007	35.6	1.00	Referent	1.00	Referent	1.00	Referent
<i>Incident Depression</i>									
Overall									
Endometriosis	72,677	7,105	47.7	1.48	1.44, 1.52	1.48	1.44, 1.53	1.31	1.27, 1.36
No endometriosis	147,251	11,933	31.5	1.00	Referent	1.00	Referent	1.00	Referent
Age 18–34 years									
Endometriosis	38,741	4,287	56.1	1.56	1.50, 1.63	1.52	1.46, 1.59	1.50	1.44, 1.56
No endometriosis	75,931	6,289	35.1	1.00	Referent	1.00	Referent	1.00	Referent
Age 35–50 years									
Endometriosis	33,936	2,818	38.9	1.35	1.29, 1.41	1.38	1.31, 1.45	1.34	1.28, 1.41
No endometriosis	71,320	5,644	28.3	1.00	Referent	1.00	Referent	1.00	Referent
<i>Incident Self-Directed Violence</i>									
Overall									
Endometriosis	72,677	151	0.91	2.32	1.86, 2.90	2.03	1.60, 2.58	1.70	1.30, 2.23
No endometriosis	147,251	162	0.39	1.00	Referent	1.00	Referent	1.00	Referent
Age 18–34 years									
Endometriosis	38,741	101	1.17	2.39	1.80, 3.16	1.98	1.47, 2.67	3.26	1.92, 5.53
No endometriosis	75,931	96	0.49	1.00	Referent	1.00	Referent	1.00	Referent
Age 35–50 years									
Endometriosis	33,936	50	0.63	2.09	1.45, 3.02	1.83	1.23, 2.72	2.01	1.02, 3.95
No endometriosis	71,320	66	0.30	1.00	Referent	1.00	Referent	1.00	Referent

• Anxiety
Endometriosis > Ctrl
(HR=1.38)

• Depression
Endometriosis > Ctrl
(HR=1.48)

• Self-directed violence
Endometriosis > Ctrl
(HR=2.03)

Contents lists available at ScienceDirect


Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Risk of bipolar disorder in patients with endometriosis: A nationwide population-based cohort study

Shih-Fen Chen^a, Yu-Cih Yang^b, Chung-Y Hsu^c, Yu-Chih Shen^{d,*}

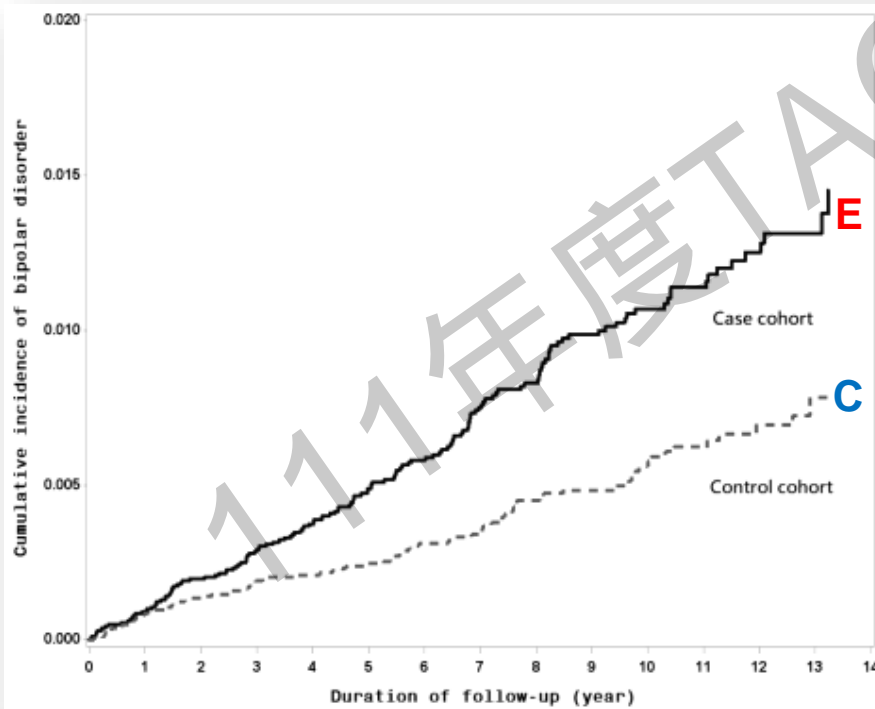


Chen et al. Journal of Affective Disorders 2020

A retrospective matched-cohort study
Taiwan NHIRD

17,832 women **with endometriosis** vs.
17,832 women **without endometriosis**

	BDn = 233	Person years	IR ^a	Crude ^b HR (95%CI)	Adjusted ^c HR (95%CI)
EM					
No	81	144,472	0.56	1 (Reference)	1 (Reference)
Yes	152	144,783	1.04	1.87 (1.43-2.46)*	2.34 (1.75-3.12)*



Bipolar disorder

Endometriosis > Ctrl
(aHR=2.34)

Systematic Reviews

Depressive symptoms among women with endometriosis: a systematic review and meta-analysis

Pietro Gambadauro, MD, MSc (Med Ed), PhD; Vladimir Carli, MD, PhD; Gergő Hadlaczky, MSc, PhD

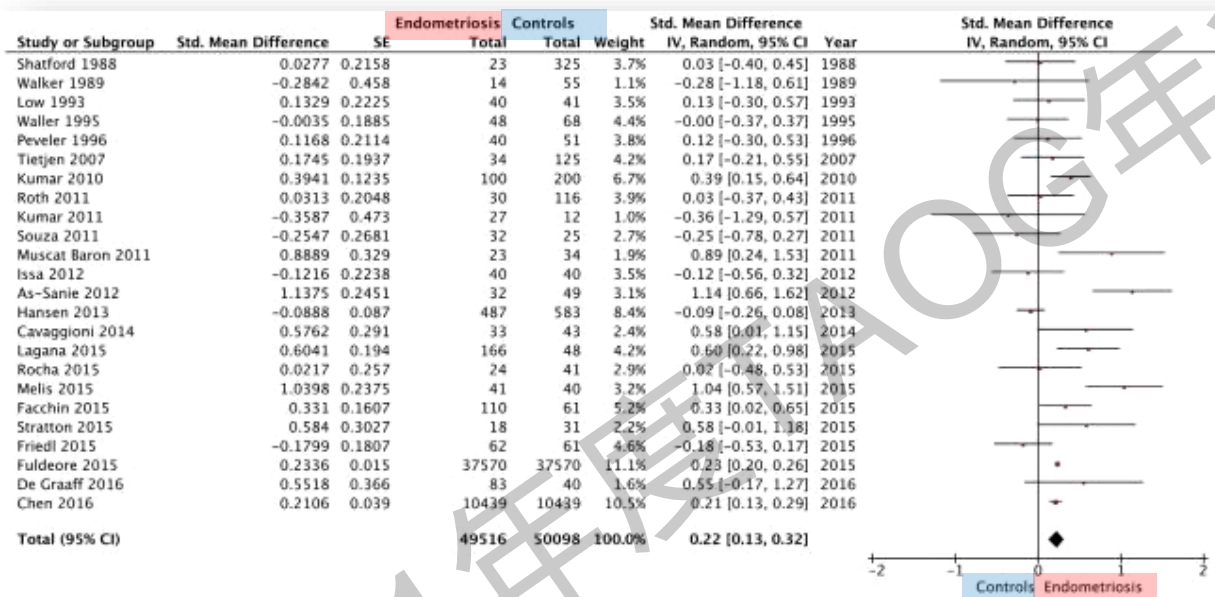
Gambadauro et al. AJOG 2019

24 studies

49,516 women **with endometriosis (EM)** vs.

50,098 women **without endometriosis**

Depression

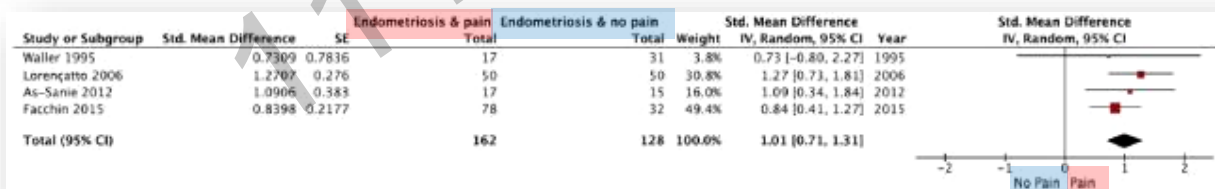


Depression

EM > Ctrl

Depression

EM with pain > EM with no pain



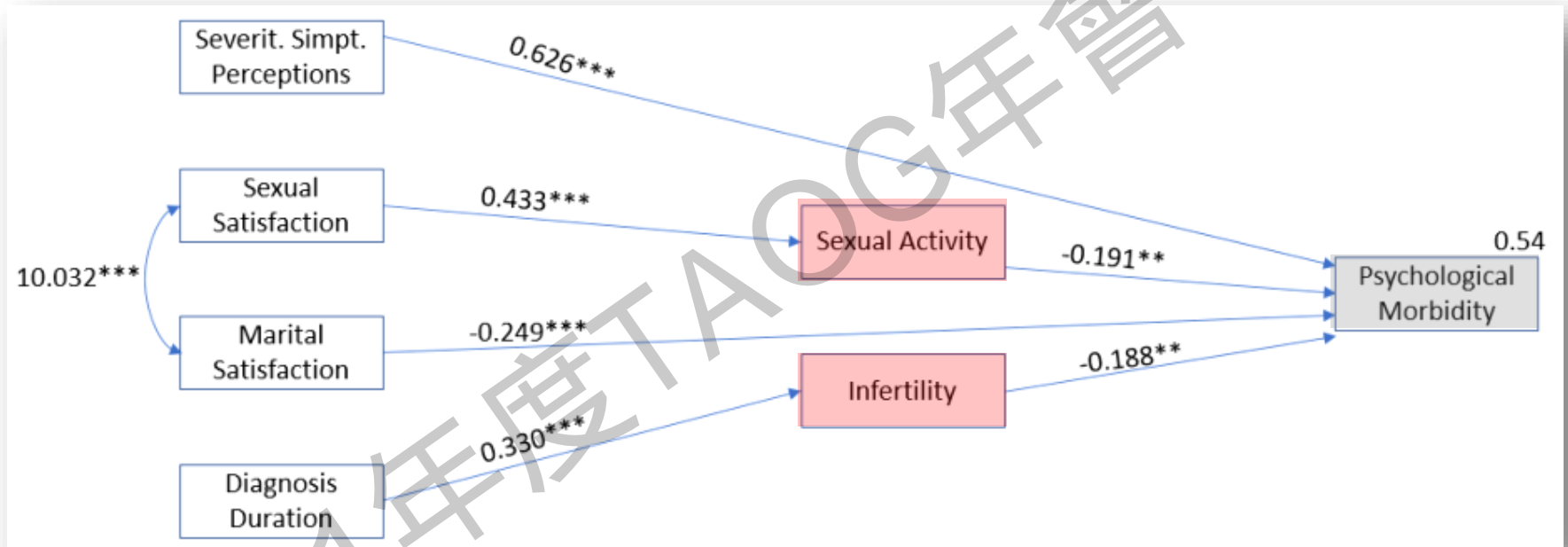
Article

Psychological Morbidity in Endometriosis: A Couple's Study

Maria Graça Pereira ^{1,*}, Inês Ribeiro ², Helder Ferreira ³, Filipa Osório ^{4,5}, Cristina Nogueira-Silva ^{6,7,8} and Ana C. Almeida ¹

Pereira et al. Int. J. Environ. Res. Public Health 2021

A cross-sectional study
105 women with **endometriosis and their partners**



Sexual dysfunction and **infertility** were associated with **poor mental health**

Psychological comorbidity of endometriosis

Quality of life



Mental health



Social function



Sexuality



Quantification of the impact of endometriosis symptoms on health-related quality of life and work productivity

Jessica Fourquet, M.P.H.,^a Lorna Báez, M.P.H.,^b Michelle Figueroa, M.P.H.,^b R. Iván Iriarte, M.S., M.D.,^b and Idhaliz Flores, Ph.D.³

Fourquet et al. Fertil Steril 2011

A cross-sectional quantitative study
193 pts with **endometriosis** (surgical Dx)

Impact of endometriosis-related symptoms on productivity loss and daily life activities, Work Productivity and Activity Impairment Survey (WPAI).

Impact of endometriosis symptoms	Not affected (0), n (%)	Lightly affected (1–3), n (%)	Moderately affected (4–6), n (%)	Extremely affected (7–10), n (%)	Mean, median (± SD)
Loss of productivity	10 (9.8)	22 (21.6)	26 (25.5)	44 (43.1)	5.3, 6.0 (3.1)
Daily life activities	12 (7.9)	15 (9.9)	45 (29.6)	80 (52.6)	5.9, 7.0 (2.9)

Work productivity

≥ Moderately affected: **68.6%**

Daily life activities

≥ Moderately affected: **82.2%**

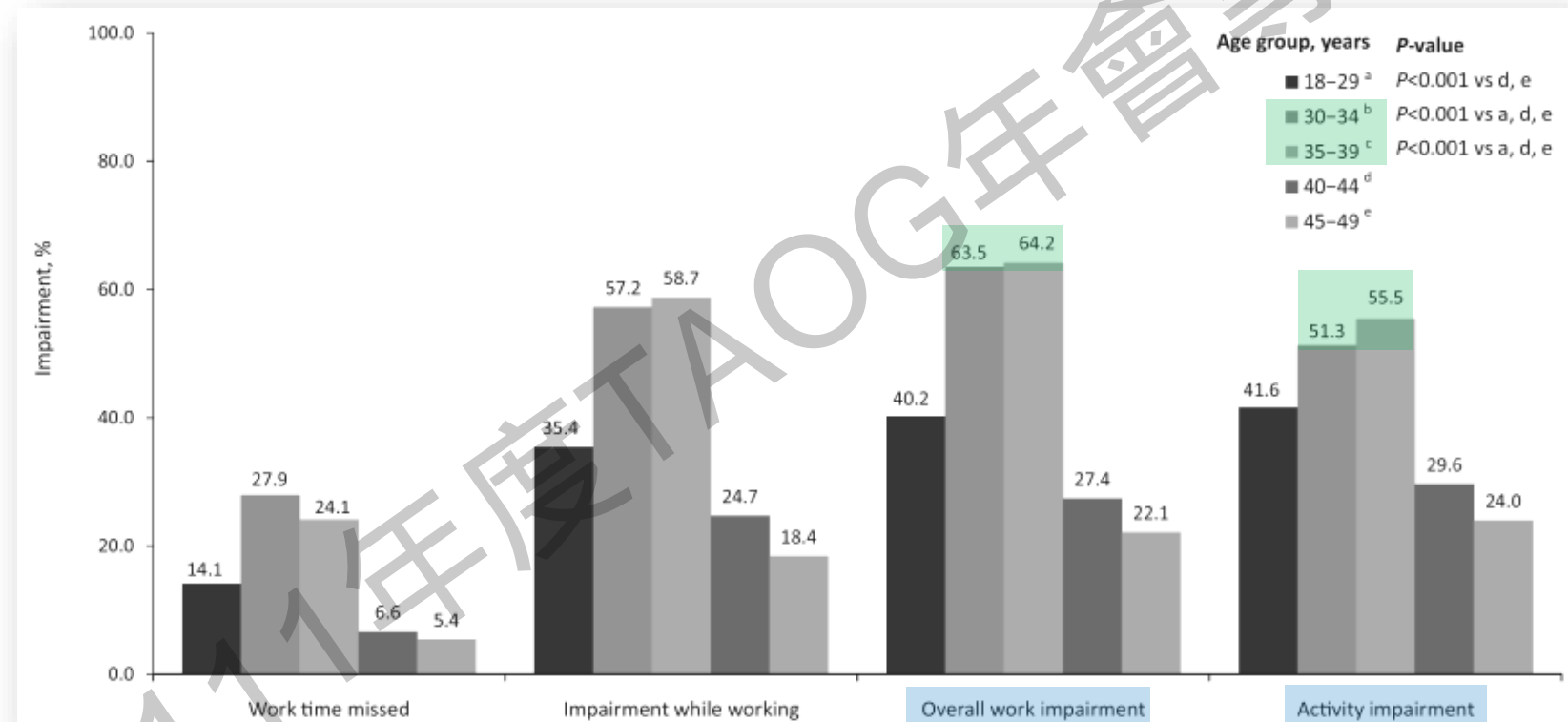
Impact of Endometriosis on Fatigue and Productivity Impairment in a Cross-Sectional Survey of Canadian Women

Ahmed M. Soliman, MS, PhD;¹ Yasmine Rahal, MSc;² Catherine Robert, MBA;² Isabelle Defoy, PhD;² Paul Nisbet, PhD;² Nicholas Leyland, MHCm, MD;⁴ Sukhbir Singh, MD²

Soliman et al. J Obstet Gynaecol Can 2021

A cross-sectional study
2,004 **endometriosis pts** and
26,528 **controls**

Work Productivity and Activity Impairment –Specific Health Problem (WPAI-SHP) questionnaire



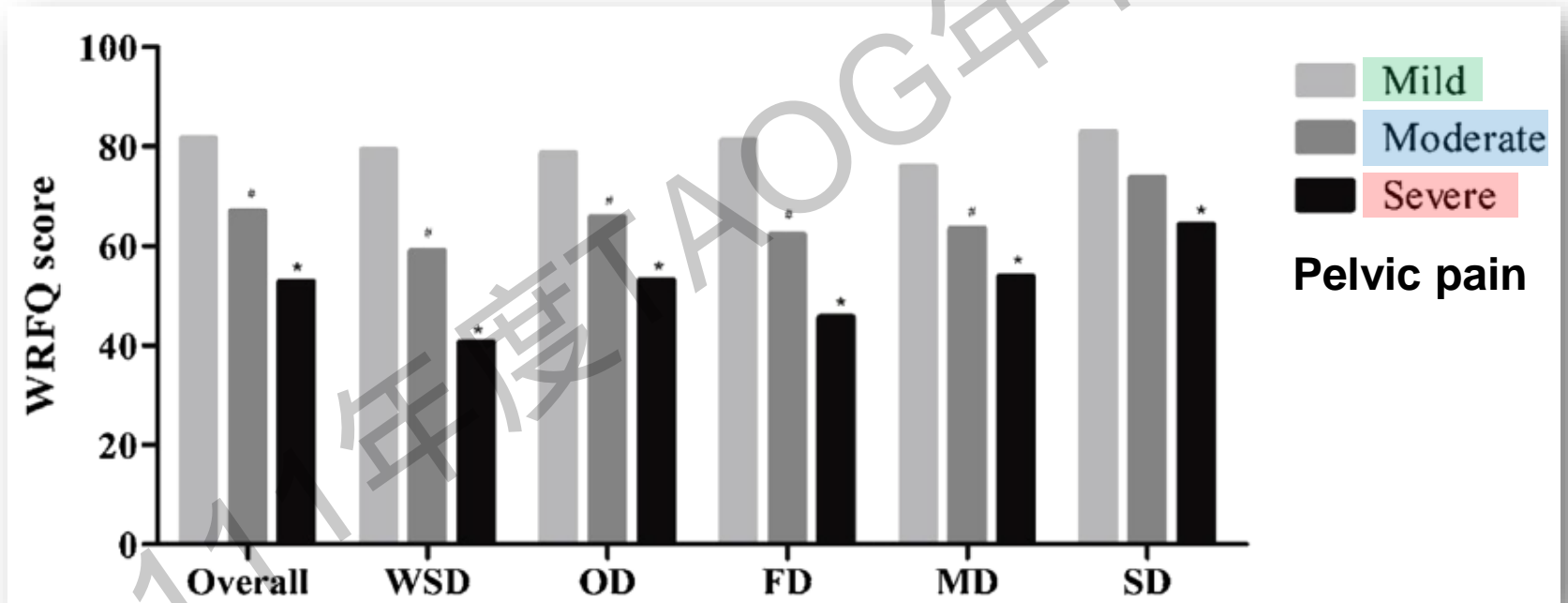
Endometriosis impairs **work productivity** and **activity** most in middle age group (**30-39 years**)

Mundo-López et al. European Journal of Obstetrics & Gynecology and Reproductive Biology 2021

A cross-sectional study
 148 pts with **endometriosis**

WRFQ=Work Role Functioning Questionnaire

WSD: work scheduling demands; OD: output demands; PD: physical demands;
 MD: mental demands; SD: social demands



WRFQ score

Severe < Moderate < Mild



Mundo-López et al. European Journal of Obstetrics & Gynecology and Reproductive Biology 2021

A cross-sectional study
148 pts with **endometriosis**

Multivariate linear regression analysis for predictors of **work performance status**

	β	$\exp(\beta)$	95 %CI		p-value
NRS Pelvic pain					
<i>Moderate</i>	-0.10	0.90	0.77	1.06	0.198
<i>Severe</i>	-0.25	0.78	0.63	0.96	0.019
PSQI sleep quality (Ln)	-0.19	0.83	0.72	0.95	0.010
HADS depression (Ln)	-0.22	0.80	0.71	0.91	0.001
MOS-SSS social support (Ln)	0.23	1.26	0.99	1.60	0.057

Pelvic pain, sleep quality and **depression** were **negatively associated** with **work performance status**

Psychological comorbidity of endometriosis

Quality of life



Mental health



Social function



Sexuality



Endometriosis decreases female sexual function and increases pain severity: a meta-analysis

Can Shi¹ · Hongge Xu¹ · Ting Zhang¹ · Yingchun Gao¹

Shi et al. Archives of Gynecology and Obstetrics 2022

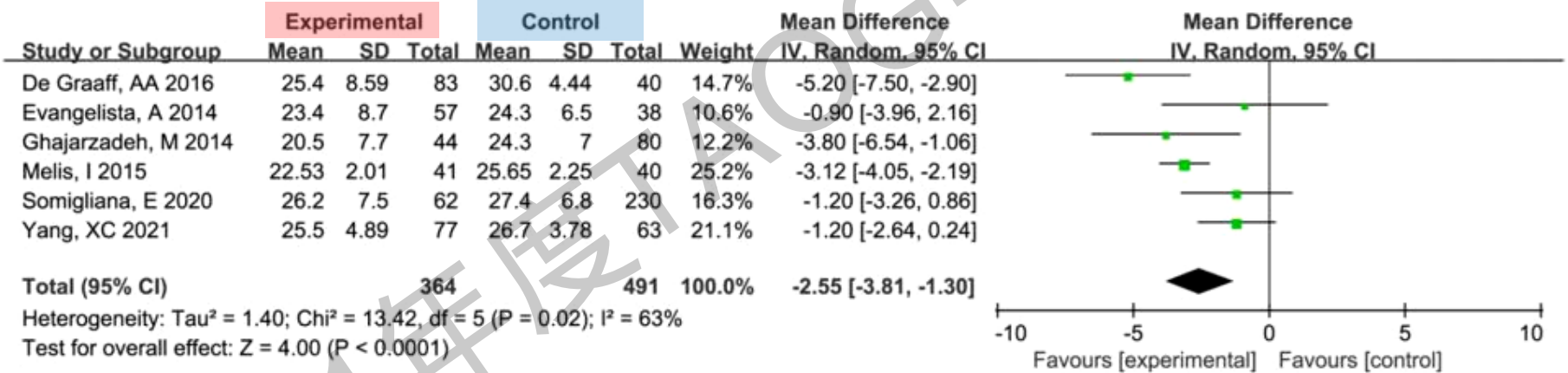
6 studies

364 pts with **endometriosis** vs.
491 **controls**

FSFI, Female Sexual Function Index

Sexual function

FSFI: total score



**Sexual function
(FSFI score)**

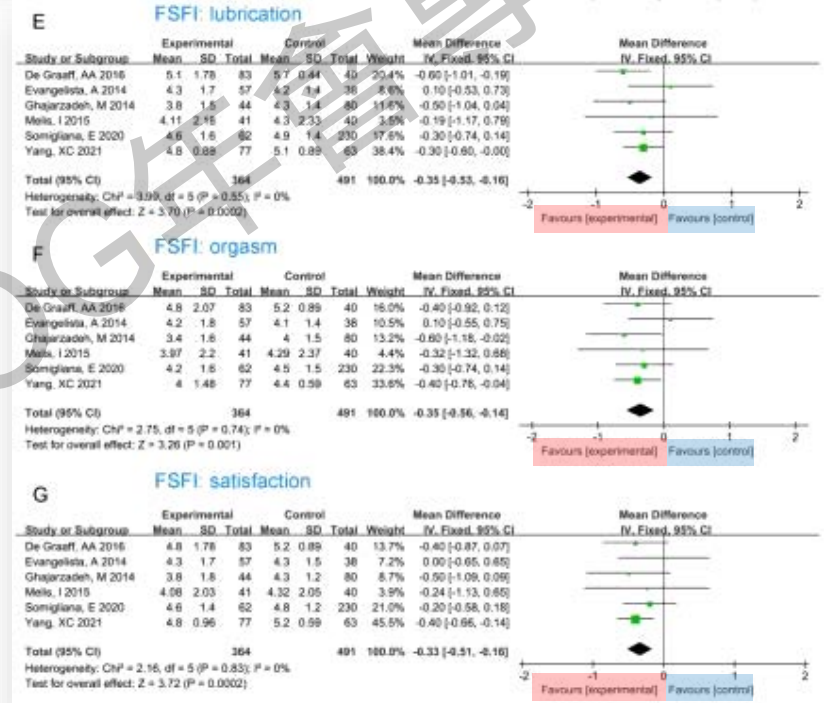
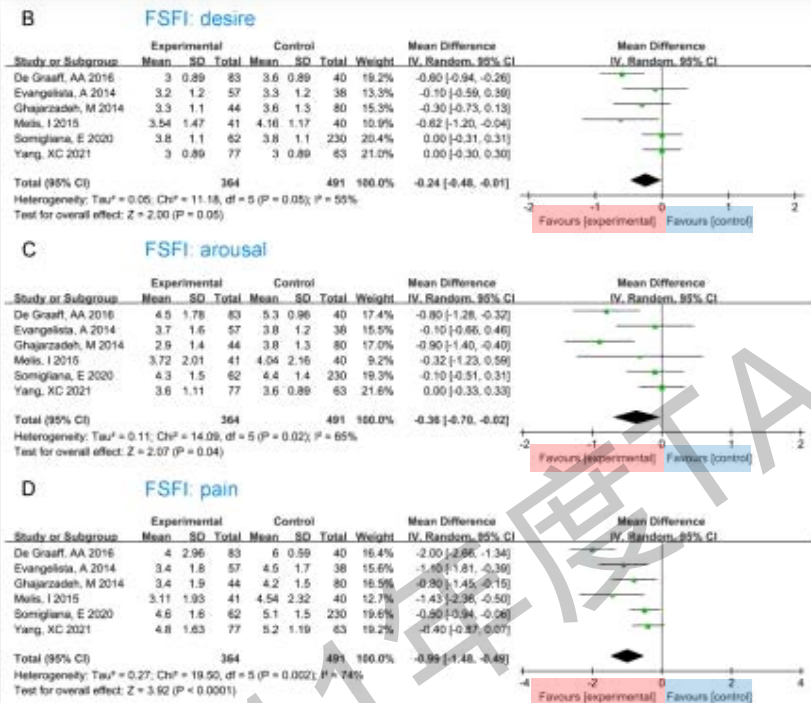
Endometriosis < Ctrl

Endometriosis decreases female sexual function and increases pain severity: a meta-analysis

Can Shi¹ · Hongge Xu¹ · Ting Zhang¹ · Yingchun Gao¹

6 studies

364 pts with **endometriosis** vs. 491 **controls**



- Desire
- Arousal
- Pain
- Lubrication
- Orgasm
- Satisfaction

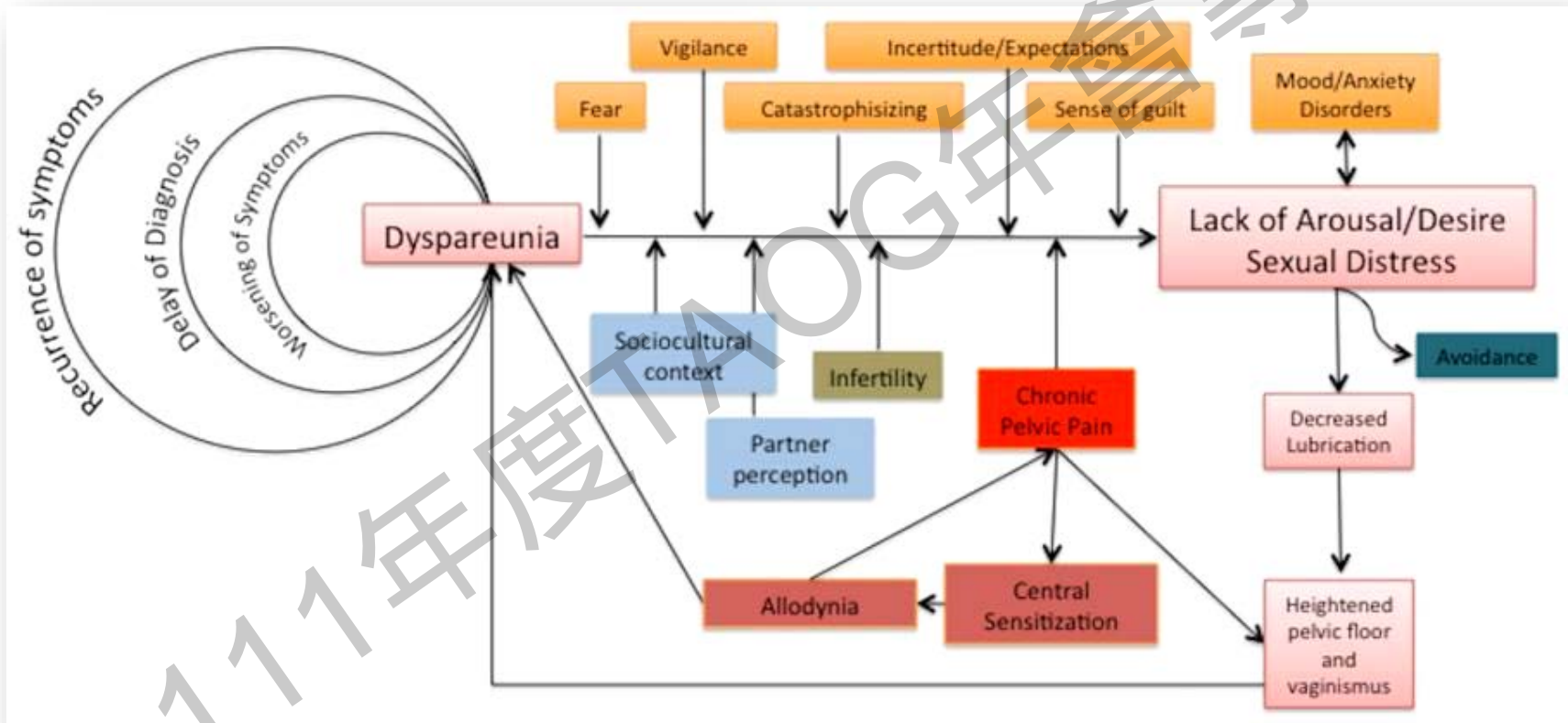
Endometriosis < Ctrl

Sexual function in endometriosis patients and their partners: effect of the disease and consequences of treatment

Nicola Pluchino^{1,2*}, Jean-Marie Wenger¹, Patrick Petignat¹, Reshef Tal¹, Mylene Bolmont¹, Hugh S. Taylor², and Francesco Bianchi-Demicheli¹

Pluchino et al. Human Reproduction Update 2016

A review



Dyspareunia is a major factor leading to **sexual distress**

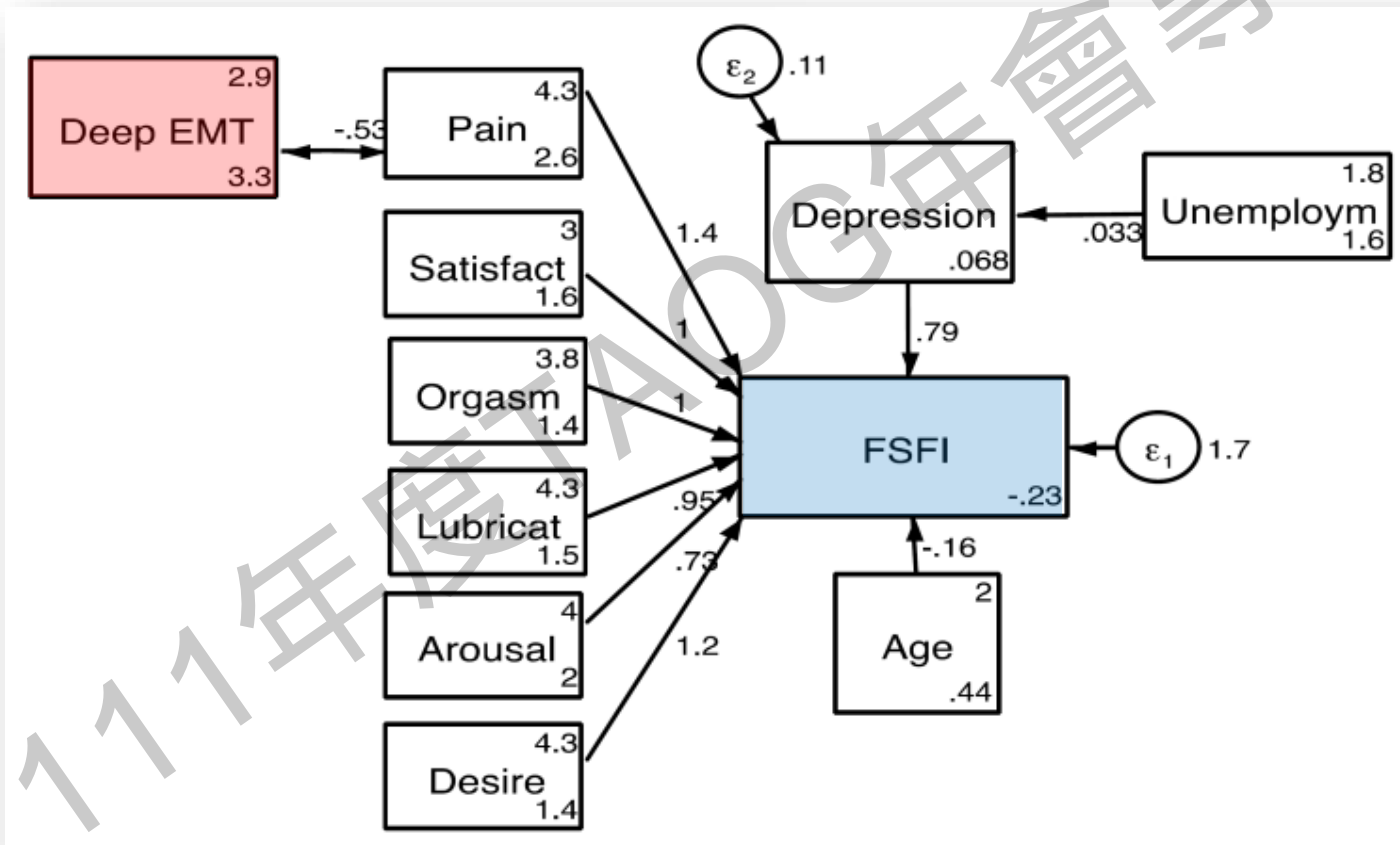
Article

Correlates of Sexual Function in a Sample of Spanish Women with Endometriosis

Ernesto González-Mesa ^{1,2,*}, Davinia Moya-Bejarano ^{2,*}, Carmen Aisha Butrón-Hinojo ³, Pilar Marín-Sánchez ⁴, Marta Blasco-Alonso ², Jesús Salvador Jiménez-López ², Emilia Villegas-Muñoz ² and Daniel María Lubián-López ³

González-Mesa et al. J. Clin. Med. 2021

A multicenter cross-sectional study
196 women with endometriosis
Female Sexual Function Inventory (FSFI)



DIE was a strong predictive factor for **poor sexual function**



Cozzolino et al. Sexual & Reproductive Healthcare 2018

A prospective study
170 women with DIE
Female Sexual Function Index (FSFI)

Correlation between the score of Female Sexual Function Index with the different sites of endometriosis lesions (LUS uterosacral ligaments, SRV septum rectovaginal y:yes, n: no).

Endometriotic site	Cat	N	Mean	Std dev	Lower quartile	Median	Superior quartile	Minimum	Maximum	P-value
LUS Nodule	n	38	20.64	8.32	17.50	21.45	27.40	1.80	34.20	.704
	y	131	20.46	10.00	13.30	23.90	28.25	1.20	35.40	
Vaginal Nodule	n	139	22.47	9.43	14.05	22.05	27.55	1.20	35.40	.122
	y	30	20.08	10.37	18.30	26.45	29.90	1.80	34.80	
SRV	n	72	21.68	9.25	13.50	20.90	26.10	1.20	32.20	.029
	y	98	18.91	9.71	16.20	25.20	29.40	1.80	35.40	
Bowel	n	109	21.03	9.30	14.20	22.00	27.60	1.20	35.40	.405
	y	61	20.19	10.13	16.00	24.40	28.90	1.80	34.80	
Sacral plexus	n	159	20.71	9.38	15.30	23.10	27.90	1.20	35.40	.505
	y	11	17.56	12.30	4.80	18.00	31.50	3.60	33.50	
Pudendalnerves	n	162	20.58	9.41	14.60	23.00	27.80	1.20	35.40	.958
	y	8	18.95	13.38	4.20	21.00	32.05	3.60	33.50	
Parametria	n	130	20.95	9.10	15.35	23.15	27.90	1.20	35.40	.47
	y	40	19.03	11.06	4.80	22.90	28.70	1.80	33.50	

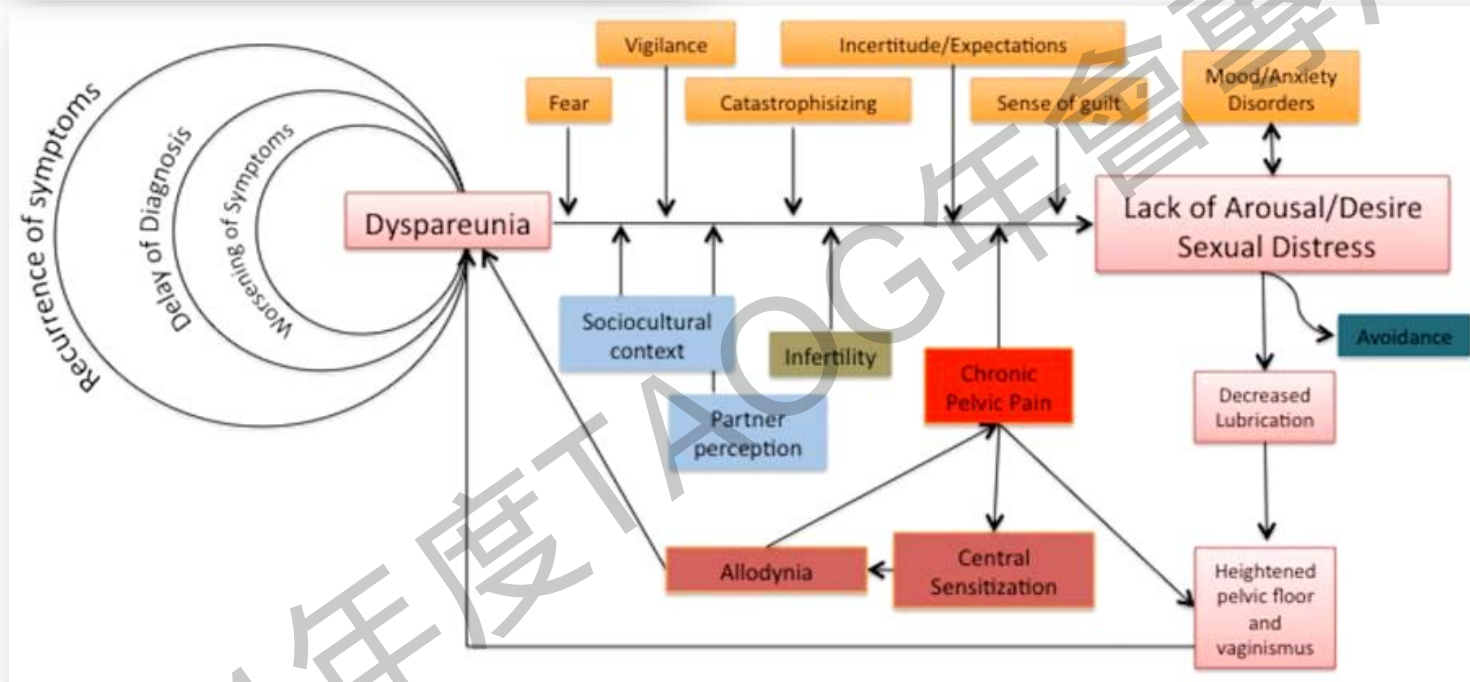
Rectovaginal septum endometriosis was mostly associated with **sexual dysfunction**

Sexual function in endometriosis patients and their partners: effect of the disease and consequences of treatment

Nicola Pluchino^{1,2,*}, Jean-Marie Wenger¹, Patrick Petignat¹, Reshef Tal¹, Mylene Bolmont¹, Hugh S. Taylor¹, and Francesco Bianchi-Demicheli¹

Pluchino et al. Human Reproduction Update 2016

A review



Dyspareunia is a major factor leading to sexual distress, which can be enhanced by

- **Partner perception, sociocultural context**
- **Fertility concerns**
- **Chronic pelvic pain: allodynia, vaginismus**
- **Personality and mental health**

Psychological comorbidity of endometriosis

Quality of life



Mental health



Social function



Sexuality

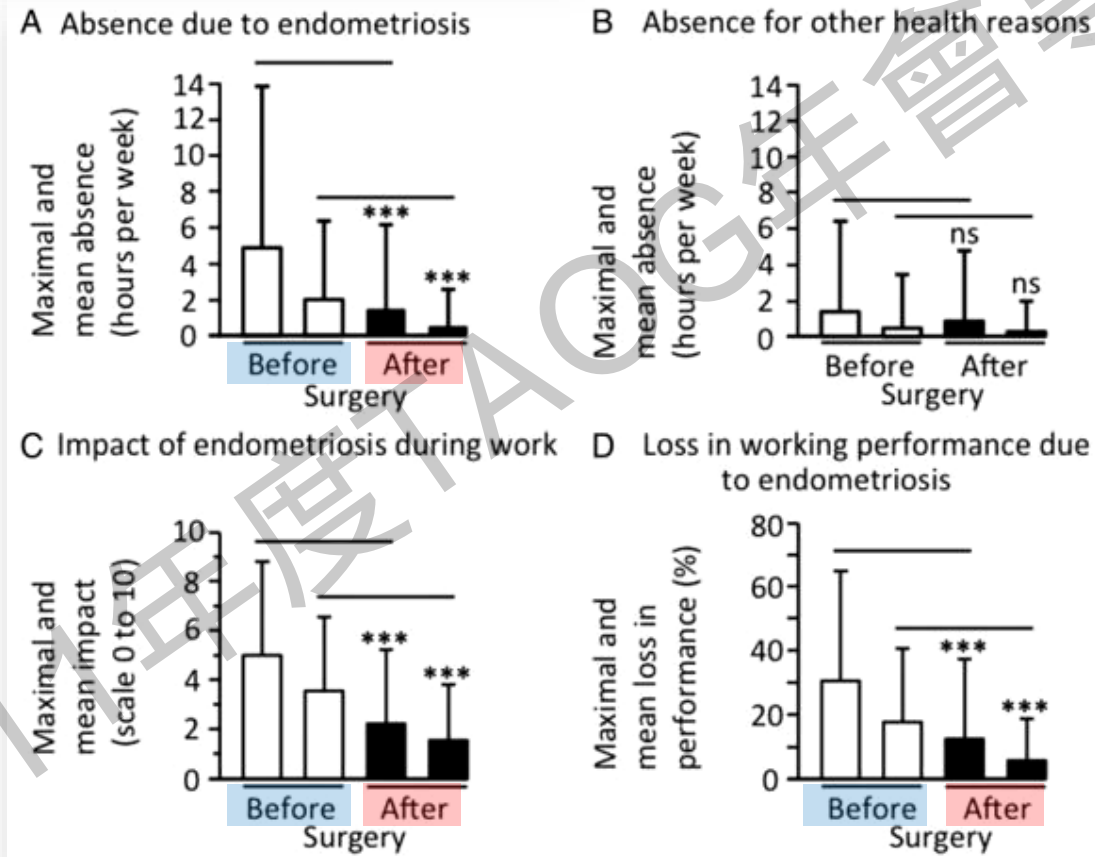


Minimally invasive surgery when treating endometriosis has a positive effect on health and on quality of work life of affected women

M.F. Wulschleger^{1,*}, S. Imboden², J. Wanner², and M.D. Mueller²

Wulschleger et al. Human Reproduction 2015

A retrospective questionnaire-based study
211 women with **endometriosis** and a
history of **laparoscopic surgery**



Work productivity loss

After surgery < Before surgery

Sexual function in endometriosis patients and their partners: effect of the disease and consequences of treatment

Nicola Pluchino^{1,2,*}, Jean-Marie Wenger¹, Patrick Petignat¹, Reshef Tal¹, Mylene Bolmont¹, Hugh S. Taylor¹, and Francesco Bianchi-Demicheli¹

Pluchino et al. Human Reproduction Update 2016

A review

Table I List of studies investigating the effect of **surgical management** of endometriosis on sexual function.


Reference	Type of study	Number of patients	Type of lesion	Follow-up	Measuring instrument	Result	Note
Giary et al. (2000)	Prospective, Observational	57	AFS I-IV	4 months	The Sexual Activity Questionnaire	Improved pleasure, habit, discomfort	
Vercellini et al. (2003)	RCT	37 without USL resection + 28 with USL resection	AFS I-IV	1 year	Revised Sabbatsberg Sexual Rating Scale	Index score improved in both groups	No effect of USL resection.
Albosta et al. (2003)	Prospective, Observational	125	AFS I-IV and mixed deep lesions	2-5 (3.2) years	The Sexual Activity Questionnaire	Improved pleasure, habit, discomfort	Results are not controlled for type of procedure
Ferrero et al. (2005)	Prospective, Observational	34	AFS I-IV and mixed deep lesions	1 year	Sexual Satisfaction Subscale of the Demogis Sexual Functioning Inventory	Improved variety in sexual life, frequency of intercourse, relaxed more easily during sex, more satisfying orgasms and more relaxed and fulfilled after sex	
Setata et al. (2012)	Prospective, Observational	22	Deep Lesions involving the vagina	1 year	McClay Female Sexuality Questionnaire	Improved sexual satisfaction and sexual problems; satisfaction with partner unchanged	Results are not controlled for hormone use
Matrouk et al. (2012)	Prospective, Observational	103	Mixed deep lesions	6 months	SHOW-Q	Improved satisfaction, desire, pelvic pain. Orgasm unchanged	All patients received post-operative COC.
Muslemian et al. (2011)	Retrospective, Observational	30	Deep lesions involving the bowel (bowel resection)	27 (range: 16-40) months	The Sexual Activity Questionnaire	Improved pleasure, habit, discomfort	
Duboisson et al. (2013)	Prospective	20	Mixed deep lesions	23.3 months	Brief Index of Sexual Functioning for Women	Improved desire, arousal, pleasure, orgasm, relational satisfaction	Results are not controlled for hormone use and type of procedure (bowel resection)
Kossi et al. (2013)	Prospective, Observational	26	Deep lesions involving the bowel (bowel resection)	1 year	McClay Female Sexuality Questionnaire	Improved sexual satisfaction; sexual problems and satisfaction with partner unchanged	Results are not controlled for hormone use
Vercellini et al. (2013)	Prospective	51	AFS I-IV and mixed deep lesions. Second-line surgery	1 year	FSFI	Improved all domains. Score remained below the threshold for sexual dysfunction	
Van den Broeck et al. (2013)	Prospective	76 with bowel resection + 127 without bowel resection	AFS II-IV and deep lesions	18 months	Short sexual functioning Scale	Improved arousal, sexual desire, orgasm problems and pain during intercourse. Relationship satisfaction unchanged	
Morelli et al. (2015)	Retrospective	10	Deep lesions involving the bowel	1 year	FSFI	Improved pain; other domains unchanged	Results are not controlled for hormone use

Table II List of studies investigating the effect of **hormonal management** of endometriosis on sexual function.

Reference	Type of study	Number of patients (Intervention)	Type of lesion/ inclusion criteria	Follow-up	Measuring instrument	Result	Note
Vercellini et al. (2002)	RCT	45 (CA) + 45 (EE + DSG)	Pain recurrence/persistence after surgery (< 1 year)	6 months	Sabbatsberg Sexual Rating Scale	Improved in both groups. Libido decreased in 13% of CA group.	
Guzek et al. (2011)	RCT	26 (EE + NETA) + 21 (LA + NETA)	Pain recurrence/persistence after surgery	1 year (19 patients)	Index of Sexual Satisfaction	Improved only in LA+NETA group after 1 year.	
Vercellini et al. (2013)	Prospective	103 (NETA)	Deep dyspareunia recurrence/persistence after surgery (mixed lesions)	1 year	FSFI	Improved all domains. Score remained below the threshold for sexual dysfunction.	
Morelli et al. (2014)	Prospective	25 (DNG)	Rectovaginal lesions in patients not responsive to NETA	6 months	FSFI	Improved total score. Mean score remained below the threshold for sexual dysfunction.	Two doses of NETA had been used.
Vercellini et al. (2016)	Retrospective, before and after	90 (NETA) + 90 (DNG)	Mixed lesions	6 months	FSFI	Improved total score in both groups. Score remained below the threshold for sexual dysfunction in both groups.	Results are not adjusted for type of lesion.

Surgical or **hormonal** treatments **improve pain**, but **do not consistently improve sexual function**

Analysis of preoperative and postoperative quality of life, sexual function, and sleep in patients with endometriosis: a prospective cohort study

Belfin Nur Arici Halici¹ · Fatih Aktöz² · Meric Kabakci³ · Gurkan Kiran¹ · Pinar Ozcan¹ 

Halici et al. Archives of Gynecology and Obstetrics 2022

A prospective cohort study
56 women with **endometriosis**
Pre-op and **post-op** evaluation

Parameters	Preoperatively	Postoperatively	<i>p</i> value
VAS score			
Dysmenorrhea	7.79 ± 1.26 ^a	2.73 ± 1.49 ^a	<0.001*
Dyspareunia	6.66 ± 2.48 ^a	3.27 ± 1.40 ^a	<0.001*
Chronic pelvic pain	6.98 ± 1.73 ^a	3.04 ± 1.26 ^a	<0.001*
PSQI score	6.54 ± 3.15 ^a	3.18 ± 1.08 ^a	<0.001*
PSQI groups			
< 5	13 (23.2%) ^b	53 (94.6%) ^b	
> 5	43 (76.8%) ^b	3 (5.4%) ^b	
PSQI subgroups			
Subjective sleep quality	1.34 ± 0.85 ^a	0.77 ± 0.60 ^a	<0.001*
Sleep latency	1.64 ± 0.98 ^a	0.89 ± 0.59 ^a	<0.001*
Sleep duration	0.54 ± 0.66 ^a	0.30 ± 0.46 ^a	<0.001*
Sleep efficiency	0.48 ± 0.71 ^a	0.21 ± 0.41 ^a	<0.001*
Sleep disturbances	1.48 ± 0.71 ^a	0.75 ± 0.43 ^a	<0.001*
Use of sleep medication	0.18 ± 0.47 ^a	0.04 ± 0.18 ^a	<0.001*
Daytime dysfunction	0.80 ± 0.92 ^a	0.18 ± 0.43 ^a	<0.001*
MEQ score	48.95 ± 10.58 ^a	52.98 ± 9.0 ^a	<0.001*
EHP-30 score	52.66 ± 19.1 ^a	29.41 ± 11.3 ^a	<0.001*
FSFI score	11.56 ± 6.17 ^a	16.57 ± 6.13 ^a	<0.001*

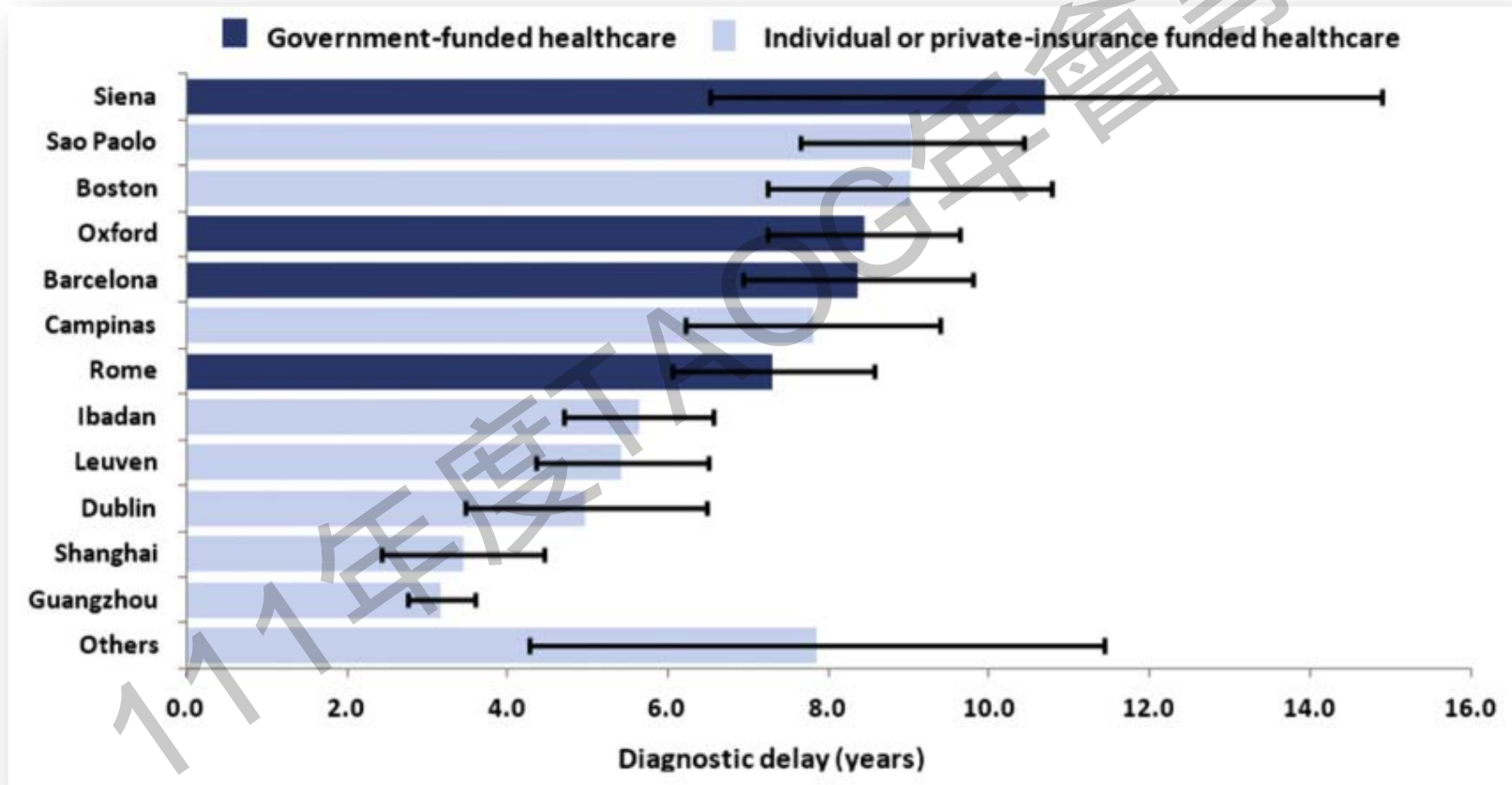
Sleep
QoL
Sexual function

Post-op > **Pre-op**

Delayed diagnosis is common in women with endometriosis

16 centers in 10 countries

Nnoaham et al. Fertil Steril 2011

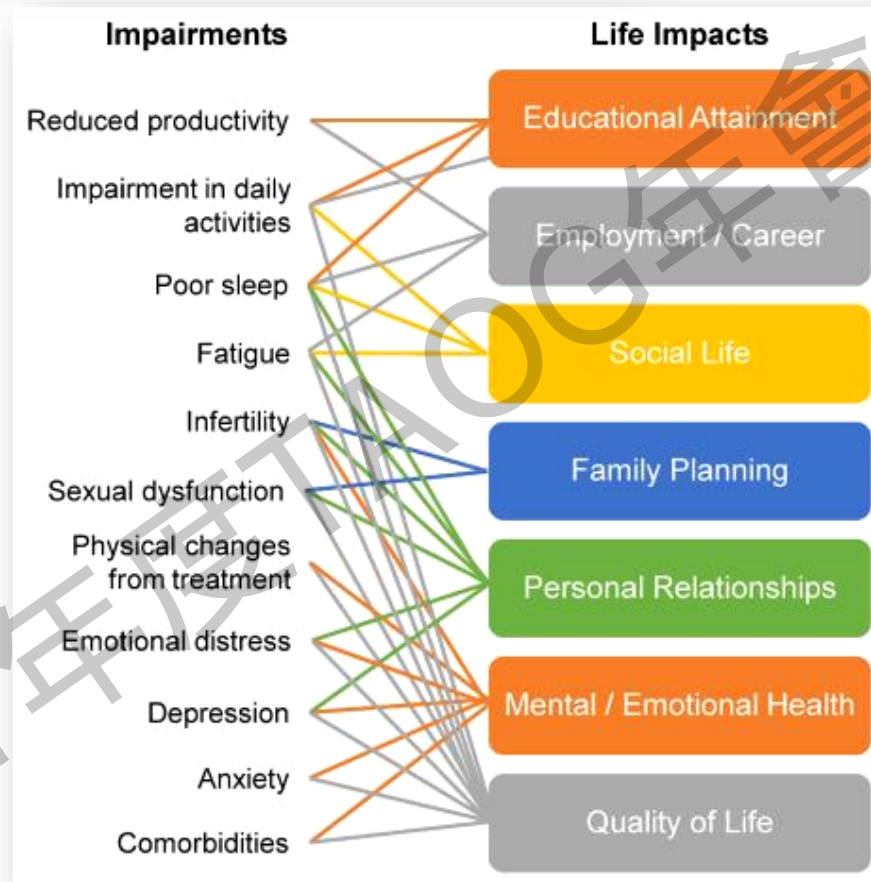


Endometriosis is usually **delayed diagnosed 7 yrs** (3~11 yrs)

Impact of Endometriosis on Life-Course Potential: A Narrative Review

Missmer et al. International Journal of
General Medicine 2021

A review



Endometriosis-associated impairments



Life impacts

BMJ Open Impact of endometriosis on women's life decisions and goal attainment: a cross-sectional survey of members of an online patient community

Stacey A Missmer,^{1,2,3} Frank Tu,^{4,5} Ahmed M Soliman,⁶ Stephanie Chiuvè,⁶ Sarah Cross,⁶ Samantha Eichner,⁶ Oscar Antunez Flores,⁶ Andrew Horne,⁷ Beth Schneider,⁸ Sawsan As-Sanie⁹

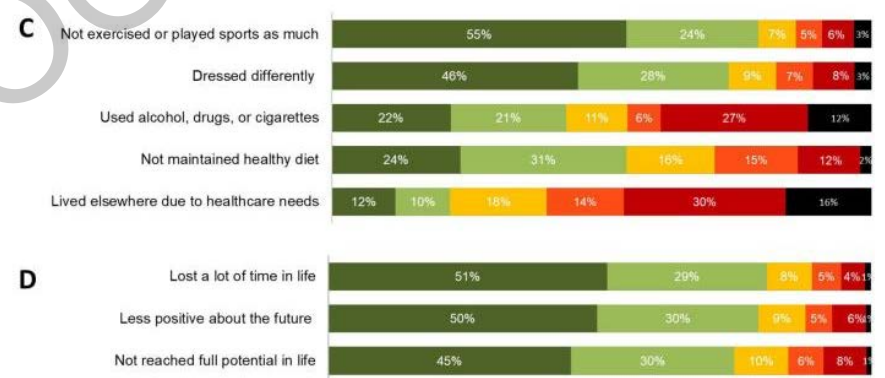
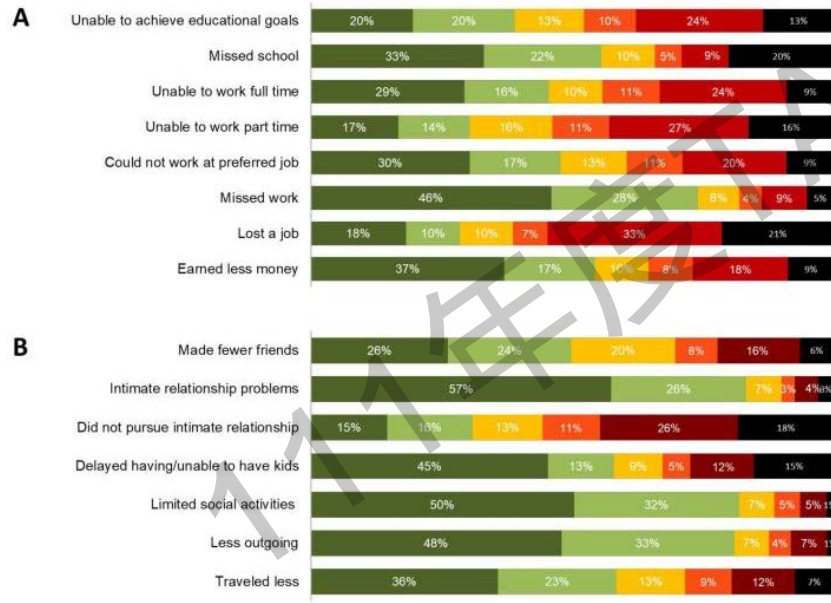
Missmer et al. BMJ Open 2022

A **anonymous online survey** through the social media network
743 women with **self-reported endometriosis**



(A) educational and professional achievements
(B) social life and relationships

(C) physical well-being
(D) overall life course



Most of women **agrees with** the impact of endometriosis on **life course**

Outlines of endometriosis comorbidity



1

Introduction



2

Physical comorbidity



3

Psychological comorbidity



4

Conclusions

Reasons for comorbidity of endometriosis

Altered milieu



Shared factors



Clinical presentation



Treatment-related



Physical comorbidity of endometriosis

- ↑ Ovarian ca.
- ? EM/breast ca.
- ↑ Thyroid ca.
- ↓ Cervical ca.

Cancer



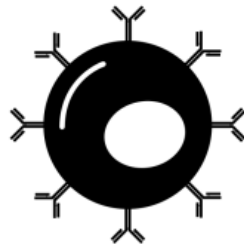
CVD



- ↑ CVD
- ↑ CAD/IHD
- ↑ CVA
- ↓ Mortality

- ↑ Autoimmune
(SLE, RA, SS, MS, IBD)
- ↑ Allergies
- ↑ Asthma

Immune disorders



GI & others



- ↑ IBS
- ↑ Bowel obs.
- ↑ Fibromyalgia
- ↑ IC

Psychological comorbidity of endometriosis

Quality of life

Mental health

↓ Quality of life



↑ Depression
↑ Anxiety

Social function

Sexuality

↓ Work productivity
↓ Daily activities



↓ Sexual function

Potential factors mediating the impact of endometriosis on life course

Age at symptom onset and eventual diagnosis
Delay in diagnosis
Social/family/spouse support
Psychological considerations (eg, abuse/early traumatic exposures, stress, anxiety, depression)
Severity, frequency, and predictability ^a of pain
Opioid use
Infertility
Pregnancy/successful livebirth
Comorbidities and their symptoms
Response (or non-response) to treatment
Number of surgeries
Geographic location
Financial status
Access to healthcare
Hysterectomy
Menopause
Patient resilience
Complementary and alternative medicine coping mechanisms, including mindfulness training or other mind-body interventions
Predisposition to pain/chronic pain syndromes

Ways to minimize impact of endometriosis on life course



Early diagnosis



Effective intervention



Long-term care & support



感謝聆聽 敬請指教



Further Evidence for Hypercoagulability in Women With Ovarian Endometriomas

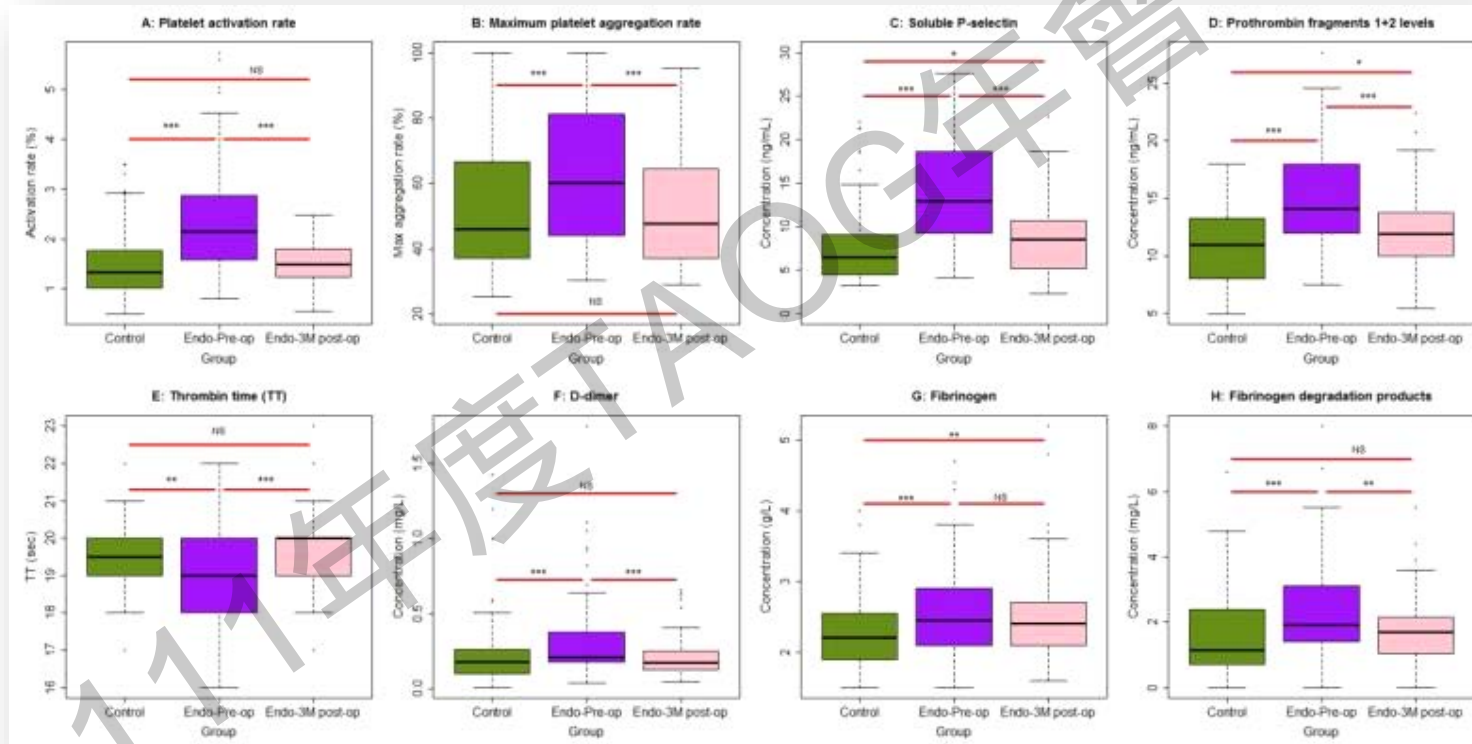
Reproductive Sciences
2018, Vol. 25(11) 1540-1548
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DOI: 10.1177/1933719118799195
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SAGE

Ding et al. Reproductive Sciences 2018

Ding Ding, MD, PhD¹, Xishi Liu, MD, PhD^{1,2},
and Sun-Wei Guo, PhD^{1,2}

A cross-sectional study

100 women with **pre-operative ovarian endometriomas (OMA)** and **post-operation**
100 women **without endometriosis**



PLT activation/aggregation rate
D-dimer, FDPs

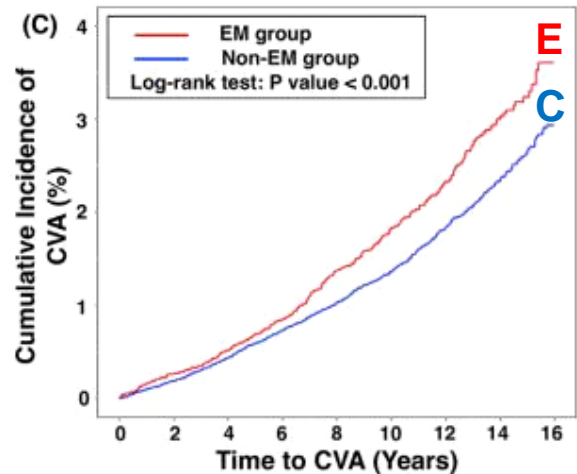
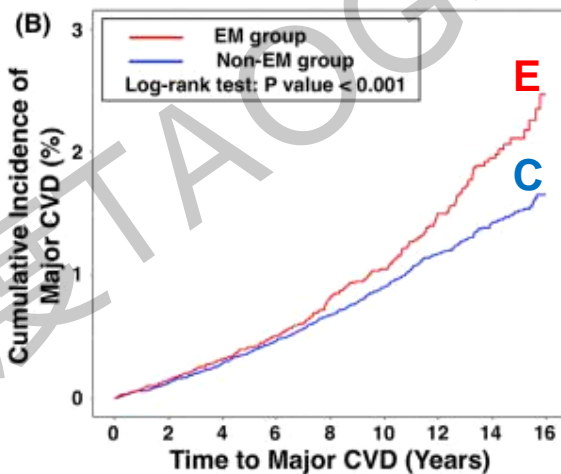
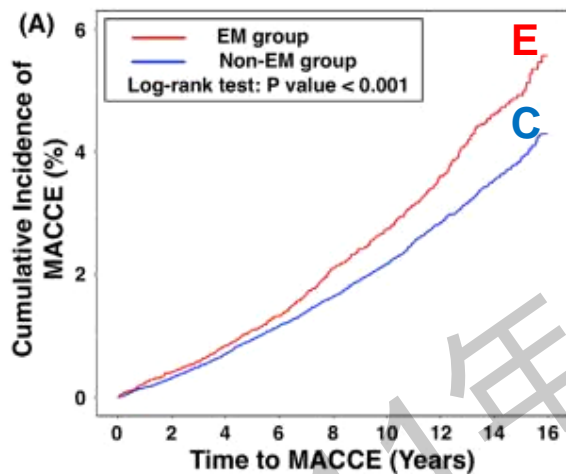
- **Pre-op OMA > Ctrl**
- **Post-op < Pre-op OMA**



Chiang et al. Journal of the Formosan Medical Association 2021

A retrospective population-based cohort study (NHIRD)
17,543 **Endometriosis (EM)** vs. 70,172 **without EM**

MACCE: major adverse cardiovascular and cerebrovascular events
Major CVD: AMI or HF
CVA: acute ischemic or hemorrhagic stroke



MACCE
CVD
CVA

Endometriosis > Ctrl

Available online at www.sciencedirect.com
ScienceDirect
 Journal homepage: www.jfma-online.com

Original Article

Risk of major adverse cardiovascular and cerebrovascular events in Taiwanese women with endometriosis

Hsin-Ju Chiang ^{a,b}, Kuo-Chung Lan ^a, Yao-Hsu Yang ^{c,d}, John Y. Chiang ^{e,f}, Fu-Tsai Kung ^a, Fu-Jen Huang ^a, Yu-Ju Lin ^a, Yu-Ting Su ^a, Pei-Hsun Sung ^{g,h,*}

Chiang et al. Journal of the Formosan Medical Association 2021

A retrospective population-based cohort study (NHIRD)
 17,543 **Endometriosis (EM)** vs. 70,172 **without EM**

Table 3 Cox regression multivariate analysis^a for identifying the predictors of MACCE, including major CVD and CVA.

	MACCE			Major CVD			CVA		
	aHR	95% CI	P-value	aHR	95% CI	P-value	aHR	95% CI	P-value
EM									
No	1.00			1.00			1.00		
Yes	1.17	1.05–1.29	0.0053	1.19	1.01–1.40	0.0385	1.16	1.02–1.31	0.0285
Age (year)									
18–34	1.00			1.00			1.00		
35–50	3.39	2.94–3.91	<0.0001	3.06	2.45–3.83	<0.0001	3.74	3.12–4.49	<0.0001
Level of urbanization									
1 (rural)	1.00			1.00			1.00		
2	1.03	0.85–1.26	0.7533	0.98	0.72–1.33	0.8773	1.12	0.88–1.43	0.3671
3	0.86	0.73–1.02	0.0868	0.83	0.64–1.08	0.1616	0.91	0.73–1.13	0.3901
4 (urban)	0.84	0.70–1.00	0.0463	0.89	0.68–1.17	0.3977	0.83	0.66–1.04	0.1015
Level of income									
1 (lowest)	1.00			1.00			1.00		
2	0.83	0.71–0.97	0.0197	0.81	0.64–1.04	0.0928	0.82	0.67–1.00	0.0445
3	0.99	0.87–1.12	0.8288	0.95	0.78–1.15	0.5963	0.99	0.85–1.16	0.9075
4 (highest)	0.74	0.63–0.86	<0.0001	0.59	0.46–0.76	<0.0001	0.79	0.65–0.95	0.0125
Comorbidity									
Hypertension	3.70	3.35–4.10	<0.0001	4.80	4.08–5.65	<0.0001	3.20	2.82–3.63	<0.0001
Diabetes mellitus	1.42	1.25–1.60	<0.0001	1.66	1.39–1.99	<0.0001	1.32	1.13–1.55	0.0004
Dyslipidemia	1.01	0.90–1.13	0.9261	0.96	0.81–1.14	0.6439	1.03	0.90–1.19	0.6443
Gout	1.12	0.93–1.35	0.2468	1.35	1.04–1.76	0.0251	1.01	0.79–1.30	0.9099
Amenorrhea	0.99	0.89–1.10	0.8861	0.86	0.72–1.02	0.0761	1.06	0.93–1.21	0.3742

MACCE

Endometriosis > Ctrl (aHR=1.17)

CVD

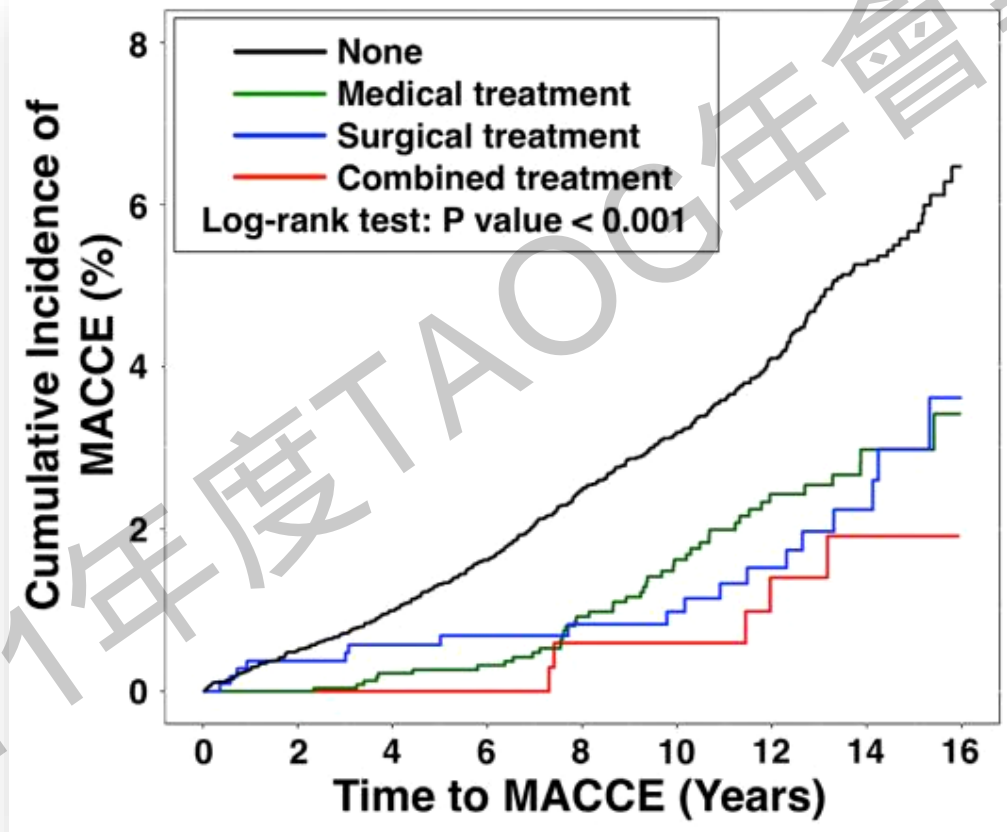
Endometriosis > Ctrl (aHR=1.19)

CVA

Endometriosis > Ctrl (aHR=1.16)

A retrospective population-based cohort study (NHIRD)
17,543 **Endometriosis (EM)** vs. 70,172 **without EM**

MACCE: major adverse cardiovascular and cerebrovascular events



MACCE **Medical, surgical, combined** Tx < Non-Tx

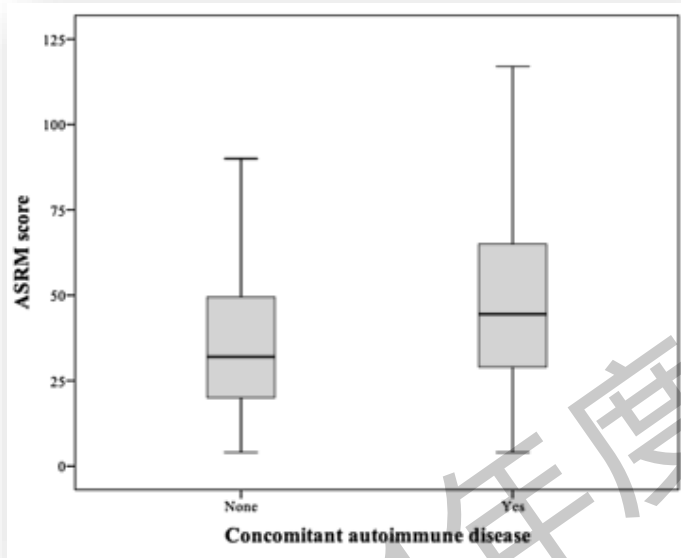
OPEN Concomitant autoimmunity may be a predictor of more severe stages of endometriosis

Valeria Stella Vanni^{1,2}, Roberta Villanacci¹, Noemi Salmeri¹, Enrico Papaleo¹, Diana Delprato¹, Jessica Ottolina¹, Patrizia Rovere-Querini^{1,2}, Stefano Ferrari¹, Paola Viganò¹ & Massimo Candiani¹

A retrospective cohort study
384 women with **endometriosis**

Cases (n=96): endometriosis and an **autoimmune disease**

Controls (n=288): endometriosis **without history of autoimmunity**



ASRM score

Cases > Ctrl

Risk factors for **stage IV of endometriosis**

Parameters	Univariate logistic regression			Multiple logistic regression		
	Odds ratio	95% CI ^a	p-value	Odds ratio	95% CI ^a	p-value
Age at evaluation (years)	1.01	0.97–1.04	0.65			
Age at diagnostic LS (years)	0.97	0.94–1.01	0.23			
Age at symptoms onset (years)	0.97	0.94–1.01	0.19			
Time from LS (years)	1.01	0.97–1.05	0.48			
Number of LS procedures*	2.81	1.45–5.43	0.002	2.70	1.37–5.30	0.050
Number of clinical evaluations	0.91	0.79–1.05	0.20			
Autoimmunity*	2.63	1.64–4.21	0.000	2.54	1.57–4.10	0.004
Hormone therapy	1.26	0.95–1.67	0.11			

Autoimmune disease was an independent risk factors for **stage IV of endometriosis**