GEMs
GOOD EVIDENCE MATTERS

# GEMs of the Week

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## What's in this week's issue?

**Week of October 18 - 22, 2021**

### SPOTLIGHT: Is There a Connection Between Endometriosis and Other Autoimmune Diseases?

# Is There a Connection Between Endometriosis and Other Autoimmune Diseases?

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

**The Association Between Endometriosis and Autoimmune Diseases: A Systematic Review and Meta-Analysis**

Shigesi N, Kvaskoff M, Kirtley S, et al. The association between endometriosis and autoimmune diseases: a systematic review and meta-analysis. *Hum Reprod Update*. 2019; 25(4):486–503. doi: 10.1093/humupd/dmz014.



KEY TAKEAWAY: There appears to be an association between endometriosis and autoimmune diseases such as systemic lupus erythematosus, Sjogren syndrome, rheumatoid arthritis, celiac disease, multiple sclerosis, and inflammatory bowel disease.

STUDY DESIGN: Meta-analysis of 26 studies (12 case-control, 6 cross-sectional, 4 prospective cohort, 2 retrospective cohort; N=166,286)

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Endometriosis is an often painful disorder characterized by the growth of endometrium outside of the uterus. It has been suggested that there exists an association between endometriosis and autoimmune diseases, yet there exists a lack of systematic review on the subject.

PATIENTS: Adult females
INTERVENTION: Those with endometriosis
CONTROL: Those without endometriosis
OUTCOME: Autoimmune disease

METHODS (BRIEF DESCRIPTION):

- A search of four databases was completed (Medline, Embase, Web of Science, and CINAHL) in April 2018, using search terms related to 'endometriosis' and 'autoimmune diseases'.
- Inclusion Criteria: Peer-reviewed, population-based articles published in English-language journals reporting an association between endometriosis and any autoimmune diseases.
- 26 articles met inclusion criteria; 14 of those articles allowed for quantitative synthesis.
- Meta-analyses were conducted, and Forest plots were constructed if there were at least 3 studies reporting an autoimmune disease connection.
- The GRADE criteria were used for a quality of evidence assessment.
- Some studies looked at the presence of endometriosis in patients with known autoimmune diseases, whereas other studies looked at the presence of autoimmune disease in patients with known endometriosis.

INTERVENTION (# IN THE GROUP): 116,286
COMPARISON (# IN THE GROUP): 2,122,480

FOLLOW UP PERIOD: Ranged from 1 to 22 years

RESULTS:

- Patients with endometriosis had an increased risk for the following compared to patients without endometriosis:
  - Systematic lupus erythematosus (4 studies, N=103,752; OR 1.4; 95% CI, 1.1–1.7 & 2 studies, N=152,114; RR 1.7; 95% CI, 1.1–2.8)
  - Sjogren syndrome (4 studies, N=37,857; OR 1.8; 95% CI, 1.4–2.2 & 1 study, N=37,661; RR 1.6; 95% CI, 1.2–2.0)
  - Celiac disease (2 studies, N=2,113; OR 4.0; 95% CI, 1.5–11)
  - Multiple sclerosis (1 study, N=3,680; OR 7.1; 95% CI, 4.4–11)
  - Inflammatory bowel disease (1 study, N=1,847,011)
    - Ulcerative colitis (OR 2.0; 95% CI, 1.7–2.3)
    - Crohn's disease (OR 2.2; 95% CI, 1.7–2.6)
    - Irritable bowel syndrome (OR 2.1; 95% CI, 1.8–2.3)
- While two studies reported an increased odds of rheumatoid arthritis in patients with endometriosis compared to those without (N=105,175; OR 1.5; 95% CI, 1.2–1.9), two other studies did not report any significantly increased risk (N=145,789; RR 1.5; 95% CI, 0.7–3.0).
- Patients with endometriosis did not have an increased risk of autoimmune thyroid disease compared to patients without endometriosis (3 studies, N=28,818; OR 1.3; 95% CI, 1.0–1.7).

LIMITATIONS:

- Poorly defined ethnicity and limited genotyping loci.
- Difficulty establishing timeline between endometriosis and autoimmune disease, so unable to determine causality.
- Suboptimal control selection in cross-sectional and case-control studies.
- Recruitment of women with gynecological conditions that increase risk of association with endometriosis.
- Small sample size of some of the included studies.

- Heterogeneity of how the diagnosis of endometriosis was established (laparoscopy-confirmed vs self-report).
- Included studies had low or very low quality of evidence per GRADE criteria due to the risk of bias.
- Limited data on post-menopausal women.

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# Are Two Steps Better Than One? A Look at One vs Two-Step Gestational Diabetes Screening

**A Pragmatic, Randomized Clinical Trial of Gestational Diabetes Screening**

Hillier TA, Pedula KL, Ogasawara KK, et al. A Pragmatic, Randomized Clinical Trial of Gestational Diabetes Screening. *N Engl J Med*. 2021; 384(10):895–904.
doi:10.1056/NEJMoa2026028


KEY TAKEAWAY: When screening for gestational diabetes mellitus (GDM), one-step screening versus two-step screening did not affect maternal or neonatal outcomes. However, the one-step screening doubled the incidence of diagnosis of GDM.
STUDY DESIGN: Multisite randomized clinical trial
LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: GDM is a common pregnancy complication affecting 6–25% of pregnant women. It is associated with increased risks to both mother and baby, including higher risks for still-births, neonatal deaths, and large-for-gestational-age (LGA) infants. There is consensus on when to screen (24–28 weeks' gestation), but not on the best method to diagnose GDM.

PATIENTS: Pregnant women without pre-existing diabetes mellitus
INTERVENTION: One-step GDM screening
CONTROL: Two-step GDM screening
OUTCOME: Diagnosis of GDM, incidence of LGA infants, composite measure of perinatal outcomes (stillbirth, neonatal death), gestational hypertension or preeclampsia, rate of primary cesarean delivery

METHODS (BRIEF DESCRIPTION):

- All pregnant women without pre-existing diabetes mellitus were randomly assigned to one-step versus two-step screening for GDM.
- One-step screening consisted of a fasting 75 g glucose load with blood glucose level measured one and two hours later.
- Two-step screening started with a one-hour glucose challenge. At one hour, GDM was diagnosed for glucose levels >200. Otherwise, women with increased glucose levels were asked to complete a subsequent fasting three-hour glucose tolerance test utilizing a 100 g glucose load.
- Relative risk was estimated for primary outcomes using generalized linear log-binomial models adjusted for errors due to multiple pregnancies per woman.
- Intention-to-treat analyses were completed utilizing both unadjusted and adjusted models to account for GDM diagnosis, group-by diagnosis interaction, and other covariates (such as excessive gestational weight gain) that may have affected the outcome.
- Inverse probability weighting was used to account for nonadherence.

INTERVENTION (# IN THE GROUP): 11,922
COMPARISON (# IN THE GROUP): 11,870

FOLLOW UP PERIOD: First perinatal visit through the peripartum period

RESULTS:

- One-step screening led to more GDM diagnoses than two-step screening (17% vs 8.5%; RR 1.9; 97.5% CI, 1.8–2.1)
- There was no difference between one-step screening and two-step screening for the following outcomes:
  - LGA infants (8.9% vs 9.2% ; RR 0.95; 97.5% CI, 0.87–1.1)
  - Perinatal composite outcome (3.1 vs 3.0; RR 1.0; 97.5% CI, 0.88–1.2)
  - Gestational hypertension or preeclampsia (14 vs 14; RR 1.0; 97.5% CI, 0.93–1.1)
  - Primary cesarean section (24 vs 25; RR 0.98; 97.5% CI, 0.93–1.0)
  - Macrosomia, small-for-gestational-age, neonatal respiratory distress, neonatal jaundice requiring treatment, neonatal hypoglycemia, shoulder dystocia, bone fracture, or nerve palsy, or maternal receipt of insulin or hypoglycemic medication

LIMITATIONS:

- Lower adherence to one-step approach.
- The two research sites used different thresholds (130 mg/dL vs 140 mg/dL) as part of the two-step protocol.

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# What Can We Do for Patellar Tendinopathy?

**Non-surgical Treatment of Patellar Tendinopathy: A Systematic Review of Randomized Controlled Trials**

Vander Doelen T and Jelley W. Non-surgical Treatment of Patellar Tendinopathy: A Systematic Review of Randomized Controlled Trials. *J Sci Med Sport*. 2019; 23(2): 118–124. doi:10.10.16/j.jsams.2019.09.008



KEY TAKEAWAY: There are several effective non-surgical interventions available to help reduce pain and improve function in patellar tendinopathy.

STUDY DESIGN: Systematic review of 9 RCTs, N=336

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Patellar tendinopathy is a very common pathology affecting 14% of elite athletes at some point in their athletic careers and may result in chronic impairment. Volleyball and basketball players have an even higher prevalence of being affected due to the high impact loading of the knee extensors.

PATIENTS: Athletes of all ages with patellar tendinopathy

INTERVENTION: Non-surgical treatments

CONTROL: Other non-surgical treatments and no treatment/placebo at baseline and after intervention

OUTCOME: Pain level

Secondary Outcome: Knee function

METHODS (BRIEF DESCRIPTION):

- Systematic review of RCTs investigating treatments for patients with patellar tendinopathy between 2012 and 2017.
- Unable to perform meta-analysis due to study diversity.
- Patients were randomly assigned to receive a single intervention or a combination of interventions.
- Nonsurgical interventions included isometric exercise (N=24), isotonic exercise (N=27), sports taping (N=34), patellar strapping (N=21), dry needling (DN; N=43), platelet-rich plasma (PRP) injection (N=33), autologous blood injection (ABI; N=11), saline injection (N=11), and extracorporeal shockwave therapy (ESWT; N=97). 138 individuals used eccentric exercise in combination with different interventions.
- Visual analog scale (VAS) was required to assess pain before and after intervention, ranging from 0 (no pain) to 10 (extreme pain).
- Victorian Institute of Sport Assessment – Patellar Tendinopathy (VISA-P) was optional to assess knee symptoms and function before and after intervention, ranging from 0 (non-functional) to 100 (pain-free full function).
- Minimal clinically important difference defined as 3.0–3.5 on VAS and 13 points on VISA-P.
- Patients were evaluated at different time points depending on the type of intervention.
- P-values and confidence intervals were not reported for differences between interventions in VAS and VISA-P scores for any of the included studies.

INTERVENTION (# IN THE GROUP): 336

COMPARISON (# IN THE GROUP): Not provided

FOLLOW UP PERIOD: Immediately after intervention up to one year following intervention

RESULTS:

- Isometric exercise resulted in a greater reduction in pain compared to isotonic exercise immediately after intervention (1 study, n=6; Isometric VAS initial 7.0, post 0.17; Isotonic VAS initial 6.3, post 3.8).
  - This was maintained after 4 weeks of the exercise program (1 study, n=20; Isometric VAS baseline 5, after 3.2; isotonic VAS baseline 5, after 4.1).
- The following interventions reduced pain immediately after intervention and for up to two hours after intervention (1 study, n=97):
  - Patellar strapping (MD from baseline –14 mm; MD from control –8 mm)
  - Non-stretch tape (MD from baseline –13 mm; MD from control –10 mm)
  - Placebo taping (MD from control –7 mm)
- ABI and saline injections had equivalent improvement after 1 year (1 study, n=22; ABI VAS initial 7.5, 1 year 3.1; Saline VAS initial 7.9, 1 year 3.3).
- Eccentric exercise + PRP injection + DN at 12 weeks showed better functional improvement compared to eccentric exercise + DN alone (1 study, n=23; exercise+PRP+DN baseline 41, 12 weeks 66; exercise+DN baseline 47, 12 weeks 52).
  - However, this difference was not sustained at 26 weeks (1 study, n=23; exercise+PRP+DN 26 weeks 68; exercise+DN 84).

- ESWT had no difference compared to placebo and was less effective than PRP injections at 6 and 12 month follow up in another study (1 study, n=46; PRP baseline 55, 1 year 91; ESWT baseline 56, 1 year 78).

LIMITATIONS:

- The study compared multiple unique interventions, with varied periods of follow up, making it difficult to draw conclusions on superiority of one intervention over another. Combining interventions increases the likelihood of confounding and makes it difficult to determine which intervention is responsible for improvements.
- Outcome measures were all subjective.
- No meta-analysis was performed, and no measures of statistical significance were present.
- Several of the studies were small sample size (n<30) reducing the power, and several studies were predominantly male reducing the applicability.

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# Does Cannabis Use in Adolescence Change the Brain?

**Association of Cannabis Use During Adolescence with Neurodevelopment**

Albaugh MD, Ottino-Gonzalez J, Sidwell A, et al. Association of Cannabis Use During Adolescence with Neurodevelopment [published online ahead of print, 2021 Jun 16]. *JAMA Psychiatry*. 2021; 78(9):1–11. doi:10.1001/jamapsychiatry.2021.1258



KEY TAKEAWAY: Cannabis use in adolescence is associated with cortical thinning in the frontal cortex and impulsiveness.

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: It is estimated that 7.4–8.2% of adolescents have engaged in cannabis use, however, there are few human studies that investigate effects that occur on brain development and behavioral changes in this population.

PATIENTS: European adolescents around 14 years old

INTERVENTION: Cannabis use (any method of administration)

CONTROL: No marijuana use

OUTCOME: Cerebral cortex thickening

Secondary Outcome: Impulsiveness

METHODS (BRIEF DESCRIPTION):

- 799 participants included male (44%) and female (56%) cannabis-naïve adolescents of European nationality between the 14 years old at baseline and 19 years old at follow up.
- European School Survey Project on Alcohol and Other Drugs (ESPAD), a self-report questionnaire, was collected at baseline and at 5-year follow-up.
- MRI scans were performed at baseline and repeated at 5-year follow-up.
- Data were collected from the IMAGEN, which is a European research project examining how biological, psychological, and environmental factors during adolescence may influence brain development and mental health.
- MRI brain images were prepared based on the Alzheimer's Disease Neuroimaging Initiative standardized protocol. The images were then superimposed with cannabinoid receptor mapping data to assess cannabis-associated changes.
    - Cortical thickness on MRI was analyzed using random field theory correction to account for multiple comparisons.
- Impulsiveness was measured with the Barratt Impulsiveness Scale, a 30-item questionnaire was administered (scores range 30 to 120 with higher scores representing more impulsiveness).

INTERVENTION (# IN THE GROUP): 369

- 208 light users (1–9 uses)
- 161 heavy users (≥10 uses)

COMPARISON (# IN THE GROUP): 430

FOLLOW UP PERIOD: 5 years

RESULTS:

Primary Outcome –

- Cannabis users had increased cortical thinning in areas associated with CB1 receptors and increased age-associated cortical thinning.
    - Non-users and light users lost 0.75–1.0 mm/year while heavy users lost 1.0–1.3 mm/year ($P$<.001).
- Cannabis users had increased attentional impulsiveness at 5-years compared with non-users ($b$=–0.119; $P$=.003).
    - This persisted when controlling for baseline parent and self-reported ADHD symptoms.

LIMITATIONS:

- Cannabis use is self-reported.
- Lack of information regarding type of cannabis products used (cannabis oil vs edible vs leaf).
- No definitive way to determine whether cortical thinning was due to cannabis use alone compared to other pre-existing factors.
- Cortical thickening is a disease-oriented outcome, not a patient-oriented outcome.

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# Eggs: Good or Bad for Cardiovascular Health?

**Association Between Egg Consumption and Risk of Cardiovascular Outcomes: A Systematic Review and Meta-Analysis**

Krittanawong C, Narasimhan B, Wang Z, et al. Association Between Egg Consumption and Risk of Cardiovascular Outcomes: A Systematic Review and Meta-Analysis. *Am J Med*. 2021; 134(1):76-83.e2. doi: 10.1016/j.amjmed.2020.05.046. Epub 2020 Jul 10.



KEY TAKEAWAY: Consumption of more than one egg per day was not associated with an increased risk of overall cardiovascular disease but was associated with a significant reduction in risk of coronary artery disease.

STUDY DESIGN: Systematic review and meta-analysis of observational trials

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Eggs are a source of nutrients and protein, but there is some concern about their contribution to elevated cholesterol levels. In 2000, American Heart Association (AHA) Dietary Guidelines recommended a daily cholesterol intake of less than 300 mg. One egg has 186 mg of cholesterol. In 2015 the AHA Dietary Guidelines removed this recommendation due to the lack of direct evidence. Previous studies on the association between egg consumption and cardiovascular disease risk have been inconclusive.

PATIENTS: International patients

INTERVENTION: Consumption of more than one egg per day

CONTROL: Consumption of zero or one egg per day

OUTCOME: Combined cardiovascular events (coronary artery disease, acute myocardial infarction, acute coronary syndrome, stroke, heart failure)

METHODS (BRIEF DESCRIPTION):

- A systematic search was completed of Ovid MEDLINE, Ovid Embase, Ovid Cochrane, Scopus, and Web of Science from 166 through January 2020 for observational studies that reported the association between egg consumption and cardiovascular disease and cardiovascular events.
- Twenty-three prospective studies were identified containing 1.4 million patients.

INTERVENTION (# IN THE GROUP): 123,660

COMPARISON (# IN THE GROUP): 1,292,179

FOLLOW UP PERIOD: Mean of 12 years

RESULTS:

- Consuming more than one egg per day was not associated with a significantly higher risk of overall cardiovascular disease events (23 studies, N=1,415,839; pooled HR 0.99; 95% CI, 0.93–1.1).
- Consuming more than one egg per day was associated with a significantly lower risk of coronary artery disease (23 studies, N=1,415,839; pooled HR 0.89; 95% CI, 0.86–0.93).

LIMITATIONS:

- Changes in dietary patterns in long follow-up period, particularly in the United States following 2015 change in AHA Dietary Guidelines.
- Possible measurement errors from self-reported data.
- Limitation of statistical power for subgroup analysis.
- Observational findings cannot establish causality.

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# Should We "Carb Load" Prior to Resistance Training?

**Acute Maltodextrin Supplementation during Resistance Exercise**

Wilburn DT, Machek SB, Cardaci TD, Hwang PS, Willoughby DS. Acute Maltodextrin Supplementation During Resistance Exercise. J Sports Sci Med. 2020; 19(2):282–288. Published 2020 May 1.



KEY TAKEAWAY: Carbohydrate supplementation prior to short resistance exercise sessions does not increase performance.

STUDY DESIGN: Double blind, cross over, repeated measures design, randomized trial

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Multiple previous studies have shown that endurance performance is negatively impacted by low glycogen stores. Carbohydrate consumption can increase aerobic based exercise and has positive ergogenic effects in resistance training that is longer than 50 minutes. The dosage of carbohydrate intake, timing, and mechanism is still understudied.

PATIENTS: Men with low cardiovascular risk

INTERVENTION: Carbohydrate supplementation (maltodextrin)

CONTROL: Non-caloric placebo

OUTCOME: Repetitions to fatigue

Secondary Outcomes: Serum glucose, glycogenolysis, performance

METHODS (BRIEF DESCRIPTION):

- Men who exercised 3 times per week for at least a year with low risk for cardiovascular disease without contraindications per the American College of Sports Medicine were included.
  - Average age: 22 years old
  - Average leg press strength to body weight ratio: 5.98
- Random double-blind assignment to:
  - Maltodextrin carbohydrate supplement at 2 g per kg of body mass mixed with Crystal Light
  - Non-caloric placebo mixed with Crystal Light
- Supplement or placebo administered 30 minutes before resistance training.
- 7- to 10-day muscle recovery and washout period between sessions.
- Controlled diet and exercise for all participants.
- Blood samples were analyzed before supplement ingestion, 30 minutes following ingestion, immediately post exercise, and one hour post exercise.
- Vastus lateralis muscle biopsies of the dominant leg were completed at visits 3 and 4 immediately post exercise and one hour after.

INTERVENTION (# IN THE GROUP): 10

COMPARISON (# IN THE GROUP): 10

FOLLOW UP PERIOD: Not available

RESULTS:

Primary Outcome –

- Supplementation did not significantly impact repetitions to fatigue in resistance training compared to placebo (54 vs 52; *P*=.799).

Secondary Outcomes –

- Carbohydrate supplementation did not affect serum glucose, glycogenolysis, or performance.

LIMITATIONS:

- Small sample size.
- Limited sample time points and sample locations (used vastus lateralis muscle only).
- May be affected by other variables that were not assessed such as diet, tobacco use, and other health issues such as asthma and psychological factors.
- Limited generalizability.

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