GEMs of the Week

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What's in this week's issue?

Week of January 18 - 22, 2021

SPOTLIGHT: Adverse Childhood Events - An Elephant Worth Addressing

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Adverse Childhood Events and Health: An Elephant worth Addressing

The Effect of Multiple Adverse Childhood Experiences on Health: A Systematic Review and Meta-Analysis

Hughes K, Bellis M, Hardcastle K, et al. The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis. *Lancet Public Health*. 2017 Aug; 2(8):e356–e366.

KEY TAKEAWAY: Adverse Childhood Event (ACE) score >3 portends significant risk for poor health outcomes.

STUDY DESIGN: Systematic review and meta-analysis

LEVEL OF EVIDENCE: STEP 2a (downgraded due to heterogeneity).

BRIEF BACKGROUND INFORMATION: Numerous studies demonstrate the negative long-term health effects of ACEs. No synthesis of studies evaluating the effects of multiple ACEs on long-term health outcomes has been published.

PATIENTS: N=253719; Worldwide, high, middle income countries; Males/females >17 years old.

INTERVENTION: Four or more ACEs

CONTROL: No ACEs

OUTCOME: pooled odds ratios of risk estimates between multiple ACEs and poor health outcomes.

METHODS (BRIEF DESCRIPTION): Five databases searched for cross-sectional, case-control, or cohort studies reporting health outcome risks (substance use, sexual health, mental health, weight, physical exercise, violence, & physical health status/conditions) associated with multiple ACEs. Studies with samples sizes >99 included. Studies focusing on high-risk or clinical populations excluded. Data extracted to calculate pooled odds ratios using a random-effects model.

INTERVENTION (# IN THE GROUP): 31,795

COMPARISON (# IN THE GROUP): 213,184

FOLLOW UP PERIOD: Variable; 1 day–63years

RESULTS: Odds ratios of health risks associated with 4 or more ACEs vs 0 ACEs:

Physical inactivity: 7 studies, n=32,760; OR 1.2; 95% CI, 1.0–1.5

Overweight/obesity: 8 studies, n=84,840; OR 1.3; 95% CI, 1.1–1.7

Diabetes: 8 studies, n=123,659; OR 1.5; 95% CI, 1.2–1.8

Cardiovascular disease: 8 studies, n=123,663; OR 2.0; 95% CI, 1.6–2.5

Heavy alcohol use: 9 studies, n=84,904; OR 2.2; 95% CI, 1.7–2.7

Poor self-rated health: 5 studies, n=74,005; OR 2.2; 95% CI, 1.9–2.5

Cancer: 4 studies, n=17,989; OR 2.3; 95% CI, 1.8–2.9

Liver or digestive disease: 6 studies, n=20,775; OR 2.7; 95% CI, 2.2–3.3

Smoking: 15 studies, n=152,830; OR 2.8; 95% CI, 2.3–3.3

Respiratory disease: 8 studies, n=72,050; OR 3.0; 95% CI, 2.4–3.7

Multiple sex partners: 3 studies, n=26,903; OR 3.6; 95% CI, 3.0–4.4

Anxiety: 7 studies, n=38,092; OR 3.7; 95% CI, 2.6–5.2

Early sexual initiation: 7 studies, n=38,259; OR 3.7; 95% CI, 2.8–4.8

Teenage pregnancy: 7 studies, n=29,715; OR 4.2; 95% CI, 2.9–5.9

Low life satisfaction: 5 studies, n=17,675; OR 4.3; 95% CI, 3.7–5.1

Depression: 13 studies, n=104,672; OR 4.4; 95% CI, 3.5–5.4

Illicit drug use: 10 studies, n=42, 816; OR 5.6; 95% CI, 4.4–7.0

Problem alcohol use: 5 studies, n=33,992; OR 5.8; 95% CI, 3.9–8.5

Sexually transmitted infections: 6 studies, n=28,014; OR 5.9; 95% CI, 3.2–10.9

Violence victimization: 6 studies, n=25,119; OR 7.5; 95% CI, 5.6–10.0

Violence perpetration: 8 studies, n=27,935; OR 8.1; 95% CI, 5.8–11.1

Problem drug use: 5 studies, n=30,101; OR 10.2; 95% CI, 7.6–13.7

Suicide attempt: OR 30.1; 7 studies, n=24,858; 95% CI, 14.7–61.6

LIMITATIONS:

- Comparing haloperidol to placebo, there was no difference in QT interval prolongation (3 RCTs, n=808; RR 1.1; 95% CI, 0.62–2.0)
- Comparing haloperidol to placebo, there was no increase in extrapyramidal symptoms (3 RCTs, n=808; RR 0.77; 95% CI, 0.29–2.0)

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Breastfeeding Initiation and Continuation

Factors Associated with Breastfeeding Initiation and Continuation: A Meta-Analysis

Cohen SS, Alexander DD, Krebs NF, et al. Factors Associated with Breastfeeding Initiation and Continuation: A Meta-Analysis. *J Pediatr*. 2018; 203:190-196.e21

KEY TAKEAWAY: Factors associated with successful breastfeeding initiation and continuation include: maternal nonsmoking, higher level of maternal education, vaginal delivery, breastfeeding education, and avoidance of dyad separation.

STUDY DESIGN: Meta-analysis

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Breastfeeding remains the "gold" standard for infant nutrition, conferring benefits for mother and infant. Exclusive breastfeeding for 12 months is universally recommended. In the United States from 2007 to 2014, only 36% of infants were exclusively breastfed. This meta-analysis explores factors affecting breastfeeding initiation and continuation.

PATIENTS: Maternal-infant dyads in developed countries

INTERVENTION: N/A

CONTROL: Breastfeeding initiation and continuation based on six high-impact factors: smoking, mode of delivery, parity, dyad separation, maternal education, and maternal breastfeeding education

OUTCOME: Initiation of early breastfeeding, exclusive breastfeeding for 6 months, continued breastfeeding for 12 months

METHODS (BRIEF DESCRIPTION): Authors followed Prisma guidelines for meta-analysis. Literature search conducted from January to May 2015 for factors impacting breastfeeding success, identifying 183 papers. Results reviewed by two authors independently and evidence score assigned for each factor demonstrating statistical significance. Six factors with highest impact identified. Second literature search conducted from January 2005 to March 2016 evaluated these six factors. Relative risks estimated for each factor and meta-analysis performed. Heterogeneity assessed; publication bias not assessed.

INTERVENTION (# IN THE GROUP): N/A

COMPARISON (# IN THE GROUP): 208 studies included in meta-analysis

FOLLOW UP PERIOD: 1 month–1 year

RESULTS:

- Smoking: Nonsmoking associated with increased breastfeeding initiation (17 trials, n=444,553, RR 1.7; 95% CI, 1.6–1.9) and continuation (25 trials, n=58,398, RR 1.9; 95% CI, 1.6–2.1) compared to smoking.
- Delivery mode: Vaginal delivery associated with increased breastfeeding initiation (31 studies, n=625,082, RR 1.3; 95% CI, 1.2–1.5) and continuation (16 studies, n=70,099, RR 1.2; 95% CI, 1.11.3) compared with caesarean delivery.
- Parity: No difference in initiation rates (20 studies, n=103,852, RR 1.0; 95% CI, 0.84–1.3); however, multiparous women more likely to continue breastfeeding (13 studies, n=60,264, RR 1.4; 95% CI 1.2–1.5).
- Dyad: Separation inversely related to breastfeeding initiation (10 studies, n=31,368, RR 2.0, 95% CI, 1.4–2.9) and continuation (8 studies, n=8,347, RR 1.2; 95% CI, 1.0–1.5).
- Maternal education: Higher education level associated with increased breastfeeding initiation (36 studies, n=161,745, RR 2.3; 95% CI, 1.9–2.7) and continuation (27 studies, n=129,529, RR 1.7; 95% CI, 1.3–2.1) compared to lower level.
- Breastfeeding education: Positively associated with breastfeeding initiation (19 studies, n=RR 1.4; 95% CI, 1.3–1.5) and continuation (14 studies, n=13,230, RR 1.34; 95% CI, 1.1–1.6).

LIMITATIONS:

- Study quality not assessed
- High heterogeneity
- Risk of publication bias, no gray literature search, English only studies included
- Other maternal factors (BMI, socioeconomic status, etc.) not considered
- Infant characteristics (hypoglycemia, jaundice, etc.) not considered

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Hospital Delirium: Haldol for All?

Antipsychotics for Treating Delirium in Hospitalized Adults: A Systematic Review

Nikooie R, Neufeld K, Oh E, et al. Antipsychotics for Treating Delirium in Hospitalized Adults: A Systematic Review. *Ann Intern Med*. 2019 Sep 3.

KEY TAKEAWAY: Antipsychotics for the treatment of inpatient delirium do not improve duration, hospital length of stay, sedation, and are associated with potentially harmful side-effects.

STUDY DESIGN: Systematic review and meta-analysis

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Antipsychotics are frequently used to treat delirium despite a lack of compelling evidence of efficacy. This study evaluated the impact of antipsychotics for the treatment of inpatient delirium and the potential harms.

PATIENTS: Inpatients with delirium

INTERVENTION: Haloperidol and second generation antipsychotics

CONTROL: Placebo or another antipsychotic

OUTCOME: Critical outcomes (cognitive functioning, hospital length of stay, delirium severity, sedation, and inappropriate continuation of antipsychotics), clinical outcomes (delirium duration and mortality), safety outcomes (cardiac and neurologic harms).

METHODS (BRIEF DESCRIPTION): Systematic review and meta-analysis of 16 RCTs and 10 observational studies (N=5607). Inclusion criteria: RCTs comparing haloperidol with placebo or with another antipsychotic in adults with delirium and prospective observational studies reporting adverse events. Literature search of multiple databases from inception to July 2019 without language restrictions. Studies assessed for strength of evidence and risk of bias. Meta-analysis performed for RCTs generating pooled odds ratios, relative risks, and mean-between group differences for RCTs with varied outcomes.

INTERVENTION (# IN THE GROUP): Patients received either haloperidol or a second generation antipsychotic (n not provided)

COMPARISON (# IN THE GROUP): Patients received placebo or another antipsychotic (n not provided)

FOLLOW UP PERIOD: Range of follow-up not indicated.

RESULTS:

Critical outcomes:

- Cognitive functioning: No evidence of change in mental status scores between second generation antipsychotics and placebo or haloperidol and second generation antipsychotics, or other second generation antipsychotics (3 RCTs, n=169; RR 0.36; 95% CI, -0.26 to 0.50).
- Hospital length of stay: No difference in length of stay in medical/surgical ICU patients between haloperidol and placebo (3 RCTs, n=808; RR 0.2; 95% CI, -1.7 to 2.1).
- Delirium severity: Compared to placebo, haloperidol had no significant impact on delirium severity (12 RCTs, n= 924; RR 0.4; 95% CI, -1.7 to 2.5).
- Sedation: Compared to placebo, haloperidol had no significant impact on over sedation (2 RCTs, n=707; RR 1.8; 95% CI, 0.71–4.6).
- Inappropriate continuation of antipsychotics: No study examined this outcome.

Clinical outcomes:

- Delirium duration: Compared to placebo, haloperidol had no effect on the length of delirium in critical patients (3 RCTs, n=808; RR –1.3; 95% CI, -1.9 to -0.7).
- Mortality: Compared with placebo, haloperidol was associated with decreased survival in palliative care patients (1 RCT, n= 545; hazard ratio (HR) 1.7; 95% CI, 1.2–2.5). Cardiovascular death rates between the two groups were 20 (11.2%) vs. 41 (22.3%) for catheter ablation and medical therapy, respectively (HR 0.49; 95% CI, 0.29–0.84; NNT=9).

Cardiac and Neurological outcomes:

- Comparing haloperidol to placebo, there was no difference in QT interval prolongation (3 RCTs, n=808; RR 1.1; 95% CI, 0.62–2.0).
- Comparing haloperidol to placebo, there was no increase in extrapyramidal symptoms (3 RCTs, n=808; RR 0.77; 95% CI, 0.29–2.0).

LIMITATIONS:

- Heterogeneity in dose/route of antipsychotics, measurement instruments, and outcomes assessed.
- Some RCTs excluded patients with cardiac and neurologic conditions limiting interpretation of side effects.
- Different classes of antipsychotics combined despite different mechanisms.

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Anticoagulation after non-cardiac postoperative atrial fibrillation; Just do it.

Risk of Thromboembolism Associated with Atrial Fibrillation Following Noncardiac Surgery

Butt JH, Olesen JB, Havers-Borgersen E, et al. Risk of thromboembolism associated with atrial fibrillation following noncardiac surgery. *J Am Coll Cardiol* 2018 72:2027–36.

KEY TAKEAWAY: Postoperative atrial fibrillation (POAF) has similar risk for thromboembolic events as non-surgical, non-valvular atrial fibrillation (NVAF). Anticoagulation for POAF is associated with lower risk for thromboembolic events, rehospitalization, and all-cause mortality compared to no anticoagulation.

STUDY DESIGN: Retrospective cohort

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Long-term risk of thromboembolic events in patients developing new onset POAF after noncardiac surgery is uncertain, and guidelines addressing the use of oral anticoagulation in this setting are lacking.

PATIENTS: Danish, older than 30 years of age, with POAF

INTERVENTION: Anticoagulation or no anticoagulation

CONTROL: Patients with NVAF with similar characteristics to those with POAF

OUTCOME: Long-term thromboembolic risk and effect of anticoagulation on risk in each cohort

METHODS (BRIEF DESCRIPTION): Using medical registries, Danish patients > 30 years of age born January 1st 1996 - June 30, 2015, with the following:

- noncardiac surgery
- no history of afib prior to surgery
- no history antiarrhythmic prior to surgery
- developed POAF
- no history of cancer 1 yr prior or during admission
- did not receive anticoagulation within 6 months of surgery
- alive at time of discharge compared to patients with similar clinical characteristics and demographics with NVAF in a 1:4 ratio

Long-term thromboembolic risk assessed and effect of oral anticoagulation on risk of thromboembolic events, rehospitalizations, and all-cause mortality.

INTERVENTION (# IN THE GROUP): 3,830

COMPARISON (# IN THE GROUP): 15,320

FOLLOW UP PERIOD: 19 years

RESULTS:

Primary outcomes:

- The rate of thromboembolism was not significantly greater in the POAF group compared to the NVAF group (31.7 vs. 29.9 events per 1,000 person-years; Hazard Ratio (HR): 0.95; 95% CI, 0.85–1.07).
- Anticoagulation compared to no anticoagulation was associated with lower risk of thromboembolism in both patients with POAF (HR: 0.52; 95% CI, 0.40–0.67) and NVAF (HR: 0.56; 95% CI, 0.51–0.62).

Secondary outcomes:

- The rate of rehospitalization was significantly lower in the POAF group compared to the NVAF group (48.2 vs. 89.8 per 1,000 person-years; HR: 0.58; 95% CI, 0.53–0.63).
- The rate of all-cause mortality was greater in the POAF group compared to the NVAF group (133.0 vs. 108.5 events per 1,000 person years). This was significantly higher in the first year post-op (HR 1.83; 95% CI, 1.6–2.0), but similar after 1 year (HR 1.0; 95% CI, 0.93–1.07).

LIMITATIONS:

- Observation study cannot prove causation.
- Short episodes of POAF may be dismissed by providers decreasing size of study population.
- Limitations to type/specificity of clinical data in registry.

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Hocus POCUS! Is ultrasound the stethoscope of the future?

Point-of-Care Ultrasound in General Practice: A Systematic Review

Andersen CA, Holden S, Vela J, Rathleff MS, Jensen MB. Point-of-Care Ultrasound in General Practice: A Systematic Review. *Ann Fam Med*. 2019 Jan; 17(1):61–69.

KEY TAKEAWAY: The implementation of bedside point-of-care-ultrasound (POCUS) has the potential to be a valuable resource for the primary care physician and requires further research.

STUDY DESIGN: Systematic Review

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: POCUS is increasingly used by general practitioners to gather diagnostic information. Evidence suggests POCUS may lead to earlier diagnosis and improved treatment outcomes. POCUS training is being integrated into medical school and resident training curricula. There is a lack of evidence regarding the use of POCUS among general practitioners.

PATIENTS: Patients in outpatient or inpatient settings undergoing POCUS by general practitioners

INTERVENTION: POCUS by general practitioners

CONTROL: N/A

OUTCOME: Use of ultrasonography, frequency of use, training in use, quality of scans, harms, patient perspective, and financial aspects

METHODS (BRIEF DESCRIPTION): A literature search via 5 medical databases was conducted in May 2016 and updated in August 2017.

Inclusion criteria: use of POCUS by general practitioners or general practitioners in training in inpatient or outpatient settings. Appropriate studies extracted and 51 articles included, all observational, 1 RCT. Cochrane and PRISMA guidelines followed by authors. No meta-analysis conducted.

INTERVENTION (# IN THE GROUP): 1–180 general practitioners, 1–90 clinics, and 3–9,959 patients.

COMPARISON (# IN THE GROUP): N/A

FOLLOW UP PERIOD: N/A

RESULTS:

- Use of POCUS (studies): diagnostic purposes (43), procedures (3), screening (16)
- Anatomic areas examined (studies): heart (23), lungs (8), abdomen (42), aorta (25), GYN-OB (54), musculoskeletal (10), other (22); specific POCUS (31) vs. full detailed exam (10)
- Frequency of POCUS use (5 studies): annual (131-601 exams): obstetric (72–133), abdominal (58), urinary tract (100), and broad screening exam (43).
- Training in use of POCUS (33 studies): training in multiple anatomic areas (4–320 hours), focused POCUS (2.3–31 hours)
- Quality of scans: diagnostic accuracy (sensitivity, specificity): lung (1 study, 92%, 95%), heart (2 studies, 73–77%, 75–78%), kidneys (1 study, 82%, 99%), aorta (2 studies, 100%, 100%), obstetrics (1 study, 97%, 98%), broad use (2 studies, 91–98%, 83–95%).
- Harms: percent of false positives: cardiac (3 studies, 4–33%), obstetric (3 studies, 0.7–3.2%), abdominal (3 studies, 0.5–9.9%). Percent of false negatives (7 studies): 0.02-2.3%; cardiac exams (1 study, 8.7%).
- Patient satisfaction (5 studies): 69% "satisfied with the procedure" (1 study), 56% "increased sense of security about their health" (1 study), 66% "exam should be performed during routine physical examination" (1 study), 29% "doctors overly emphasized technology" (1 study).
- Financial aspects: Health care costs lower with ultrasound use in general practice versus secondary care (3 studies); between 32-65% of scans eliminated the need for further testing (2 studies); 83% of patients were willing to pay extra for POCUS (1 study).

LIMITATIONS:

- Included studies of low quality with lack of detail on training.
- Most articles >10 years old, some languages excluded.
- No meta-analysis due to varied outcomes and quality indicators.

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