GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of December 18 - 22, 2023

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75 Minutes of Exercise a Week Makes a Big Difference

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Non-Occupational Physical Activity and Risk of Cardiovascular Disease, Cancer, and Mortality Outcomes: A Dose-Response Meta-Analysis of Large Prospective Studies

Garcia L, Pearce M, Abbas A, et al. Non-occupational physical activity and risk of cardiovascular disease, cancer and mortality outcomes: a dose-response meta-analysis of large prospective studies. *Br J Sports Med.* 2023;57(15):979-989. doi:10.1136/bjsports-2022-105669

KEY TAKEAWAY: 75 minutes or more of moderate-intensity exercise a week reduces heart disease, cancer incidence, and mortality in inactive adults.

STUDY DESIGN: Meta-analysis of 196 prospective cohort studies (N>30 million)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Higher physical activity levels are associated with lower rates of chronic disease morbidity and mortality. Few studies have examined whether smaller, incremental increases in physical activity also have the same benefit.

PATIENTS: Adults 18 years old and older

INTERVENTION: Non-occupational physical activity

CONTROL: No physical activity

PRIMARY OUTCOME: All-cause cardiovascular and cancer mortality, total incidence of cardiovascular disease and cancer

METHODS (BRIEF DESCRIPTION):

- A comprehensive literature review of prospective cohort studies examining outcomes related to three different levels of non-occupational physical activity was completed.
- Studies evaluating adult patients, 18 years old or older, without pre-existing conditions were included. Studies with less than 10,000 participants or had a follow up period of less than three years were excluded.
- The three different activity levels were 4.375 marginal metabolic equivalent task (mMET) hours per week which equated to 75 min/week of moderate-intensity exercise, 8.75 mMET-hours/week which equated to 150 min/week of moderate-intensity exercise, and 17.5 mMET-hours/week which equated to 300 min/week of moderate-intensity exercise.
- Because not all included studies used the same metric, non-occupational physical activity levels were converted to mMET-hours/week where MET was the ratio of a person's energy expenditure relative to their weight while performing certain activities. 0 mMET-hours/week was used as the control.
- Mortality, cardiovascular, and cancer incidence outcomes for the three different activity levels were examined.
- The incidence of site-specific cancers (e.g. head/neck, bladder, breast, colon, lung, and liver) and specific cardiovascular diseases (e.g. stroke, coronary artery disease, heart failure) were individually examined.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Three years or greater

RESULTS:

Primary Outcome –

- When compared to inactive individuals, 4.375 mMET-hours/week showed:
  - 23% lower risk of all-cause mortality (RR 0.77; 95% CI, 0.73–0.80)
  - 19% lower risk of cardiovascular disease mortality (RR 0.81; 95% CI, 0.77–0.85)
  - 10% lower risk of cancer mortality (RR 0.90; 95% CI, 0.88–0.93)
  - 17% lower risk of cardiovascular disease incidence (RR 0.83; 95% CI, 0.79–0.87)
  - 7% lower risk of cancer incidence (RR 0.93; 95% CI, 0.91–0.95)
- When compared with inactive individuals, 8.75 mMET-hours/week showed:
  - 31% lower risk of all-cause mortality (RR 0.69; 95% CI, 0.65–0.73)
  - 29% lower risk of cardiovascular disease mortality (RR 0.71; 95% CI, 0.66–0.77)
  - 15% lower risk of total cancer mortality (RR 0.85; 95% CI, 0.81–0.89)
  - 27% lower risk of total CVD incidence (RR 0.73; 95% CI, 0.69–0.79)

- 12% lower risk of total cancer incidence (RR 0.88; 95% CI, 0.85–0.92)
- When compared to inactive individuals, 17.5 mMET-hours/week showed lower risk of:
  - 24% lower risk of all-cause mortality (RR 0.66; 95% CI, 0.62–0.70)
  - 35% lower risk of cardiovascular disease mortality (RR 0.65; 95% CI, 0.60–0.71)
  - 18% lower risk of cancer mortality (RR 0.82; 95% CI, 0.78–0.86)
  - 33% lower risk of total cardiovascular disease incidence (RR 0.67; 95% CI, 0.63–0.72)
  - 15% lower risk of total cancer incidence (RR 0.85; 95% CI, 0.81–0.89)

LIMITATIONS:

- Although all studies reported all-cause, cardiovascular, and cancer mortality for each activity level, some studies did not report disease-specific cardiovascular or cancer incidence, which may affect results.
- Many of the included studies used self-reported questionnaires that lacked validation or calibration data.
- Some studies did not explicitly report physical activity details, so assumptions had to be made when standardizing the levels of physical activity.
- Physical activity levels were assumed to have remained constant during the entire follow-up period.

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The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Navy Medical Department, the Navy at large, or the Department of Defense.

Dupilumab Reduces COPD Exacerbations

Dupilumab for COPD with Type 2 Inflammation Indicated by Eosinophil Counts

Bhatt SP, Rabe KF, Hanania NA, et al. Dupilumab for COPD with Type 2 Inflammation Indicated by Eosinophil Counts. *N Engl J Med*. 2023;389(3):205-214. doi:10.1056/NEJMoa2303951

KEY TAKEAWAY: Dupilumab is a promising drug to reduce exacerbations, improve lung function, and quality of life in patients with type 2 inflammation chronic obstructive pulmonary disease (COPD).

STUDY DESIGN: Phase 3, multicenter, international, double-blind, randomized, placebo-controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Patients with Type 2 inflammation COPD are more susceptible to exacerbations and are shown to be more receptive to glucocorticoid treatments. Cytokines, such as IL-5, IL-4, and IL-13 drive inflammation. Previous studies have shown mixed results on the effect of drugs that target IL-5 receptors. Dupilumab is a fully human monoclonal antibody that blocks IL-4 and IL-13 receptors.

PATIENTS: Smokers with COPD

INTERVENTION: Dupilumab

CONTROL: Placebo

PRIMARY OUTCOME: Exacerbation rates

Secondary Outcome: Forced expiratory volume in one second (FEV1) improvement, quality of life

METHODS (BRIEF DESCRIPTION):

- Patients with the following characteristics were included:
  - Smokers with a pack-year history of at least 10, ages 40–80 years old with a diagnosis of COPD for 12 months.
  - FEV1/FVC ratio <0.70
  - Medical Research Council dyspnea score ≥2
  - >3 months of triple inhaler therapy with a stable dose for one month
  - >3 month duration of chronic bronchitis the year prior
  - Absolute eosinophil count of >300 per microliter
  - >2 moderate exacerbations (treated with systemic glucocorticoid, antibiotics, or both) and >1 severe exacerbation (hospitalization or emergency visit) the year prior.
- Patients with the following characteristics were excluded:
  - Current diagnosis or history of asthma
- Patients were randomly allocated in a 1:1 ratio.
- The intervention group received 300 mg dupilumab once every two weeks with triple inhaler therapy.
- The comparison group received a 300 mg placebo once every two weeks with triple inhaler therapy.
- Quality of life was measured using the St George's Respiratory Questionnaire (SGRQ):
  - Measures effects on daily health and overall quality of life in patients suffering from obstructive airway disease.
  - 50 items, two-part (symptoms and impact components) questionnaire with scores from 0–100, with higher scores signifying more limitations

INTERVENTION (# IN THE GROUP): 468

COMPARISON (# IN THE GROUP): 471

FOLLOW-UP PERIOD: 52 weeks

RESULTS:

Primary Outcome –

- Diplumab significantly decreased the annualized rate of exacerbation compared to placebo (rate ratio [RR] 0.70; 95% CI, 0.58–0.86).

Secondary Outcome –

- Dupilumab increased lung function (FEV1) compared to placebo (160 mL vs 77 mL, respectively; least-squares mean difference [LS MD] 83 mL; 95% CI, 42–125).
- Dupilumab increased quality of life compared to placebo (–9.7 vs –6.4, respectively; LS MD –3.4; 95% CI, –5.5 to –1.3).

LIMITATIONS:

- The trial was conducted during the coronavirus disease pandemic, which may have affected the exposures and thus, the rate of exacerbations of patients.
- The trial lacked diversity, with <1% of the participants identified as Black.

- Smoking status was not utilized as a criterion for randomization.

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Obesity Management with Daily Oral Semaglutide Along with Diet and Exercise

Oral Semaglutide 50 mg Taken Once Per Day in Adults with Overweight or Obesity (OASIS 1): A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial

Knop FK, Aroda VR, do Vale RD, et al. Oral semaglutide 50 mg taken once per day in adults with overweight or obesity (OASIS 1): a randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2023;402(10403):705-719. doi:10.1016/S0140-6736(23)01185-6

KEY TAKEAWAY: Semaglutide reduces body weight in overweight adults.

STUDY DESIGN: Randomized, double-blind, placebo-controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Obesity predisposes one to develop dyslipidemia, type 2 diabetes mellitus, nonalcoholic steatohepatitis, constructive sleep apnea, and hypertension. Treatment of obesity helps in reducing cardiovascular disease risk. In obese individuals, diet and exercise alone are inadequate to reduce body weight on a long-term basis so anti-obesity medication can help. Due to first-pass metabolism, the oral dose of semaglutide used in the trial is greater than subcutaneous formulations of semaglutide.

PATIENTS: Adults with BMI >30

INTERVENTION: Semaglutide

CONTROL: Placebo

PRIMARY OUTCOME: Percentage change in body weight after 68 weeks

METHODS (BRIEF DESCRIPTION):

- Participants were adults ≥18 years old with a BMI ≥30 or a BMI >27 with one or more comorbidities such as hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular disease, and at least one self-reported dietary weight loss effort.
- Participants were excluded if self-reported body weight changed more than 5 kgs in 90 days before screening, previous or planned surgery of body weight loss, A1C of 6.5% or more at screening, and history of type 1 or type 2 diabetes.
- 1:1 random allocation of semaglutide oral 50 mg or placebo.
- Semaglutide initial dose of 3 mg and escalated every four weeks to 50 mg by 16 weeks.
- All received counseling on diet and physical activity every four weeks.

INTERVENTION (# IN THE GROUP): 334

COMPARISON (# IN THE GROUP): 333

FOLLOW-UP PERIOD: 68 weeks

RESULTS:

Primary Outcome –

- Semaglutide 50 mg reduced weight more than placebo (–15% vs –2.4%; ETD –13; 95% CI, –14 to –11).
- Semaglutide resulted in more weight loss of 5% than placebo (85% vs. 26% of patients; OR 13; 95% CI, 8.5–19).

LIMITATIONS:

- The study does not reflect the general population, as participants were predominantly female and Caucasian.
- Strict eligibility criteria excluded adults with comorbid disorders closely associated with obesity.
- Adherence to the treatment regimen was not formally assessed.
- There was no strict monitoring of the timing of when it was taken.
- Flexibility and implementation of lifestyle intervention might have site-specific differences.

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Can Taking Vitamins Help Prevent Metabolic Syndrome?

Folate, Vitamin B6, and Vitamin B12 Status in Association with Metabolic Syndrome Incidence

Zhu J, Chen C, Lu L, Shikany JM, D'Alton ME, Kahe K. Folate, Vitamin B6, and Vitamin B12 Status in Association with Metabolic Syndrome Incidence. *JAMA Netw Open.* 2023;6(1):e2250621. Published 2023 Jan 3. doi:10.1001/jamanetworkopen.2022.50621

KEY TAKEAWAY: Among adults in the US intake and serum concentrations of folate, vitamin B6, and vitamin B12 were inversely associated with metabolic syndrome incidence.

STUDY DESIGN: Reanalysis of data from prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Metabolic syndrome, a highly prevalent condition in the US, is largely preventable through lifestyle changes and awareness of one's risk factors. Higher serum levels of folate and vitamin B vitamins have been associated with lower metabolic syndrome incidence, specifically in Black and White young adults in the US.

PATIENTS: Young adults living in the US

INTERVENTION: Higher levels of vitamin B6, vitamin B12, and folate

CONTROL: Lower levels of vitamin B6, vitamin B12, and folate

PRIMARY OUTCOME: Metabolic syndrome incidence with folate and B vitamin intake

Secondary Outcome: Correlation of serum homocysteine concentrations with folate and B vitamin concentrations

METHODS (BRIEF DESCRIPTION):

- The authors analyzed data from 4,414 participants from the CARDIA study, a population-based observational study of 5,115 black and white individuals from 1985–2016.
- The mean age of participants at the beginning of the study was 24.9 years old.
- Participants in the study were followed up at years two, five, seven, 10, 15, 20, 25, and 30.
- Participants were divided into quintiles based on their folate, vitamin B6, vitamin B12, or serum levels.
- Participants' mean serum homocysteine levels were compared to their mean folate, vitamin B6, and vitamin B12 levels using Spearman correlations.
- Metabolic syndrome components were defined in this study according to diagnostic criteria set forth by the American Heart Association and the National Heart, Lung, and Blood Institute.
- Participants with at least three of the following criteria were labeled as having metabolic syndrome: blood pressure, waist circumference, HDL, triglyceride, fasting glucose, and physical activity.

INTERVENTION (# IN THE GROUP): 4,414 total participants were divided into five quintiles ranging from lower to higher serum folate, B6, and B12 levels

COMPARISON (# IN THE GROUP): Not applicable

FOLLOW-UP PERIOD: Intervals of five years from 1985–2016

RESULTS:

Primary Outcome –

- Participants with higher levels of total folate intake had a 61% lower incidence of metabolic syndrome compared to those with the lowest folate intake (HR 0.39; 95% CI, 0.31–0.49).
- For vitamin B6, higher levels of intake corresponded with a 39% lower incidence of metabolic syndrome (HR 0.61; 95% CI, 0.46–0.81).
- For vitamin B12, higher levels of intake corresponded with a 26% lower incidence of metabolic syndrome (HR 0.74; 95% CI, 0.58–0.95).
- Overall, blood serum concentrations of folate, vitamin B6, and vitamin B12 were inversely associated with the incidence of metabolic syndrome.
  - Folate (HR 0.23; 95% CI, 0.17–0.33)
  - Vitamin B6 (HR 0.48; 95% CI, 0.34–0.67)
  - Vitamin B12 (HR 0.70; 95% CI, 0.51–0.96)
- The risk of developing a metabolic syndrome was significantly higher in those with low intake of folate, vitamin B6, and vitamin B12 when compared to those with higher intakes (HR 2.7; 95% CI, 2.0–3.5).

Secondary Outcome –

- Serum concentrations of folate, vitamin B6, and vitamin B12 were found to be inversely correlated

with serum homocysteine concentration (Spearman partial correlation coefficients –0.43, –0.22, –0.37, respectively).

- Higher homocysteine levels were associated with a higher incidence of metabolic syndrome (HR in quintile 5 vs 1, 2.0; 95% CI, 1.4–2.8).

LIMITATIONS:

- The results showed an association but not causation between vitamin intake and metabolic syndrome. For example, foods containing folate may have other nutrients that affect the development of metabolic syndrome.
- The participants studied were a mixture of Black and White people in the US, thus limiting the generalizability of results to other ethnic groups.

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