The Obesity Paradox Might Be Explained by Lean Body Mass

Mortality during 20 years was lowest in men with middle-quintile lean mass.

Many studies have shown a relation between body-mass index (BMI) and death that forms a J- or U-shaped curve — the so-called “obesity paradox.” However, BMI does not differentiate between fat and lean body mass. In this study, researchers used data from the U.S. Health Professionals Follow-up Study to determine associations between predicted fat and lean body mass and death in 38,000 men (age range, 40–75).

During mean follow-up of 21 years, 12,400 deaths occurred. A J-shaped curve was observed for BMI and all-cause death. However, when data were adjusted for multiple variables, a linear relation was observed.
between predicted fat mass and all-cause death and with deaths caused by cardiovascular disease, respiratory disease, and cancer. Compared with men in the lowest quintile of predicted fat mass, those in the highest quintile had 35% higher risk for all-cause death. In contrast, a U-shaped relation was noted between predicted lean body mass and all-cause death and deaths caused by cardiovascular disease and cancer. Compared with men in the lowest or highest quintiles of predicted lean body mass, men in the second to fourth quintiles had 8% to 10% lower risk for all-cause death.

COMMENT: In this study, the relation between predicted fat mass and all-cause death was linear, and the relation between predicted lean mass and death was U-shaped. These results suggest that low lean body mass, rather than fat mass, is the main factor driving the “obesity paradox” — the observation of excess risk for death in people with very low BMIs.


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Mol Psychiatry 2018 Jul 18

Eating Cured Meats May Increase Risk for Mania

A specific association between ingestion of nitrate-cured meat products and mania is bolstered by behavioral and genetic findings in animals.

Although there is a significant genetic contribution to bipolar illness, environmental factors, including diet, are thought to be important. These researchers surveyed the dietary history (foods “ever eaten”) of a broad group of psychiatric patients receiving hospital or outpatient care (bipolar mania, 217 individuals; bipolar depression, 91; major depression, 79; schizophrenia, 371) and 343 healthy controls.

A history of eating nitrate-cured meat products specifically was associated with being in the mania group. A subgroup of 42 patients with mania and 35 controls were asked about the type of cured meat products eaten; meat sticks, beef jerky, and turkey jerky were specifically implicated.

In follow-up experimental studies of rats, a meat diet with added nitrates produced both overall hyperactivity and hyperactivity to novel stimuli. The diet was also associated with expressed gene dysregulation involving serotonin, nuclear factor signaling, and sphingosine-1-phosphate signaling and with increases in small-bowel bacteria species previously linked to cognitive and behavioral alterations in animals.

COMMENT: The finding in people is strengthened by the experimental animal findings indicating both a possible mechanism for the clinically observed link of eating nitrated meat products to mania and the gene expression changes involving neurochemicals possibly involved in bipolar illness. The generalizability of the findings is limited by an absence of data on “dose” of ingested nitrates and degree of risk and by use of a brief survey, which likely limits the ability to control for multiple confounders, despite researchers’ adjustment for demographics, health factors, and other dietary habits. The link between eating nitrated meats and changes in intestinal bacterial flora is provocative in view of the increasing interest in the role of the microbiome in psychiatric illness.

EpiPen Expiration Dates Extended Amid Shortage

By Kristin J. Kelley, Edited by David G. Fairchild, MD, MPH

The FDA will be extending the expiration date of some lots of EpiPens and authorized generic versions by 4 months to mitigate the national shortage, the agency announced on Tuesday. The extension applies to the 0.3-mg dose of the epinephrine auto-injectors which are made by Pfizer for Mylan, and does not include EpiPen Jr.

A list of the affected lots, which have expiration dates from April 2018 to December 2018, can be seen in the FDA drug shortages link below. The products do not need to be relabeled with their new use dates, the agency notes, but they should be disposed of as soon as new devices are available. (Supplies are expected to be stabilized "in the fourth quarter of 2018," according to the manufacturer.)

Mylan has set up a customer service line for patients who are having trouble locating EpiPens (800-796-9526).

LINK(S): Manufacturer's news release (Free PDF), FDA drug shortages, FDA in brief, Background: Physician's First Watch coverage of generic EpiPen approval

JAMA 2018 Aug 21; 320:657

Does Cardiovascular Health Influence Risk for Dementia?

Two observational studies support improving cardiovascular health to lower dementia risk.

In two observational studies, researchers explored the relation between brain function and modifiable cardiovascular (CV) risk factors.

In a study from France, 6626 older adults (mean age, 74) without CV disease or dementia were assessed at baseline for optimal measures of CV health (American Heart Association's Life's Simple 7): smoking status, physical activity, diet, body-mass index, cholesterol level, blood pressure, and fasting glucose level. After mean follow-up of 8.5 years, dementia incidence, as assessed by structured instruments and physician assessments, was associated inversely with number of optimal CV risk factors at baseline. For example, the incidence of dementia in people with <2 factors at optimal levels was 1.56/100 person-years, compared with 0.83 for people who had 5 to 7 optimal factors. Controlling for demographic, clinical, and socioeconomic variables yielded similar results.
In a U.K. study, 125 young adults (mean age, 25) without known CV disease were assessed for similar measures of optimal CV health. Cerebral structure and vascular function were evaluated with magnetic resonance imaging. The number of risk factors at optimal levels was associated positively with several measures of cerebrovascular health as assessed by magnetic resonance imaging, including higher blood vessel density and caliber, more blood flow in the brain, and fewer white matter hyperintense lesions.

COMMENT: Despite being observational, these studies support promoting CV health to lower dementia risk in both younger and older adults.


Lancet 2018 Aug 26

Aspirin Was Not Beneficial in a Primary Prevention Trial

Among moderate-risk, nondiabetic patients, aspirin did not prevent cardiovascular events, and it raised risk slightly for gastrointestinal bleeding.

The effectiveness of aspirin for primary prevention of adverse cardiovascular (CV) events in contemporary patient populations remains unsettled. In the ARRIVE trial (funded by Bayer), 12,546 patients with no history of CV disease who were deemed to be at moderate risk were randomized to receive daily aspirin (100 mg) or placebo. Inclusion criteria were age 55 or older plus two to four risk factors for men, and age 60 or older plus three or more risk factors for women. Patients with diabetes or previous gastroduodenal ulceration or gastrointestinal bleeding were excluded. At baseline, 75% of participants were taking antihypertensive drugs, and 43% were taking statins.

During median follow-up of 5 years, the incidence of the primary endpoint (CV-related death, myocardial infarction, unstable angina, stroke, or transient ischemic event) was similar in the aspirin and placebo groups (4.3% and 4.5%; P=0.6), with no significant difference in time to first event and no differences for individual components of the primary endpoint. No subgroup (according to sex, age, smoking status, body-mass index [BMI], or baseline calculated 10-year risk) clearly benefited from aspirin. Gastrointestinal bleeding occurred more frequently with aspirin than with placebo (1.0% vs. 0.5%; P=0.0007), but only a few bleeding events in each group were “severe.”
COMMENT: This primary prevention study, conducted mainly in the U.K., Germany, and Poland, should influence practice: Aspirin did not add incremental benefit for moderate-risk, nondiabetic patients, many of whom were receiving treatment for hypertension and hyperlipidemia; results of a 2014 Japanese trial were similar (NEJM JW Gen Med Dec 15 2014 and JAMA 2014; 312:2510). Although a recent meta-analysis showed that low-dose aspirin was effective only in nonobese patients (NEJM JW Gen Med Aug 15 2018 and Lancet 2018; 392:387), this study's low dose (100 mg) showed no significant benefit in a subgroup with BMI <25 kg/m². Finally, in a recent 7-year primary prevention trial conducted in diabetic patients, aspirin prevented one vascular event but caused one serious hemorrhage for every 100 treated patients (NEJM JW Cardiol Oct 2018 and N Engl J Med 2018 Aug 26; [e-pub]).

COMMENT: The current study results demonstrate no overall increase in cardiovascular events with this weight loss medication. We need, however, to pay attention to the echocardiographic substudy, which found nonsignificantly higher rates of valvulopathy and pulmonary hypertension with lorcaserin at 1 year. Long-term studies of lorcaserin will be important to verify its safety.


A Weight Loss Drug Without Overall Increased Cardiovascular Events

But a numerical excess in valvulopathy indicates the need for longer-term studies of safety.

Lorcaserin is a selective serotonin 2C receptor agonist that modulates appetite and that has been demonstrated to facilitate modest long-term weight loss. Because other weight loss medications with similar mechanisms (e.g., fenfluramine) have had serious cardiovascular adverse effects, such as pulmonary hypertension and valvular abnormalities, proving the cardiovascular safety of lorcaserin is essential. Researchers examined the question in the manufacturer-funded CAMELLIA-TIMI 61 trial (NCT02019264), in which 12,000 obese or overweight patients with atherosclerotic cardiovascular disease or multiple risk factors were randomized to lorcaserin (10 mg twice daily) or placebo.

At a median follow-up of 3.3 years, the primary efficacy outcome (a composite of cardiovascular death, myocardial infarction, stroke, heart failure, coronary revascularization, or hospitalization for unstable angina) did not differ between lorcaserin and placebo (annual rates, 4.1% and 4.2%). An echocardiographic substudy involved 3270 patients with echocardiograms at baseline and at 1 year. FDA-defined valvulopathy occurred in 1.8% of the lorcaserin group and 1.3% of the placebo group — a numerical imbalance that was not statistically significant. The excess valvulopathy in the lorcaserin group was due to more cases of mild aortic insufficiency. At 1 year, new or worsening pulmonary hypertension occurred in 1.6% of the lorcaserin group and 1.0% in the placebo group — again a numerical but statistically nonsignificant imbalance.

COMMENT: The current study results demonstrate no overall increase in cardiovascular events with this weight loss medication. We need, however, to pay attention to the echocardiographic substudy, which found nonsignificantly higher rates of valvulopathy and pulmonary hypertension with lorcaserin at 1 year. Longer-term studies of lorcaserin will be important to verify its safety.

Parenteral Antibiotics Prior to Emergency Department Discharge for Children with UTI?

A single parenteral dose of antibiotics did not prevent ED revisits or eventual hospital admission.

Outpatient management of urinary tract infection (UTI) has become standard of care for uncomplicated cases, and oral antibiotics have been shown to be as effective as parenteral antibiotics. Despite this, many children with uncomplicated UTI receive a dose of either intravenous or intramuscular antibiotics prior to emergency department (ED) discharge, presumably to prevent return ED visits and subsequent hospital admission due to persistent symptoms.

To assess the effect of a single dose of parenteral antibiotics before ED discharge on rates of ED revisits with admission, researchers analyzed a national administrative database of ED visits at pediatric medical centers from 2010 to 2016. They reviewed records for nearly 30,000 children aged 29 days to 2 years (median age, 9 months; 75% girls) who were treated for UTI and then discharged from 36 different EDs.

Overall, 36% of patients received a single dose of parenteral antibiotics before ED discharge, and this percentage declined significantly over the study period. Rates of ED revisits within 3 days and ED revisits with admission were low (4.0% and 1.1%); in adjusted analyses, these rates did not differ significantly between children who received a dose of parenteral antibiotics and those who did not.

COMMENT: Administering a single dose of parenteral antibiotics to young children with UTI as they leave the ED does not reduce the chance that they will return and require admission. Administering such a dose may make clinicians feel better, but this study supports the likelihood that we are just treating ourselves. Children with uncomplicated UTIs treated exclusively with oral antibiotics fare just as well.

How Does Food Insecurity in Adolescence Affect BMI in Young Adulthood?

Addressing food insecurity at age 15 or later in adolescent girls could possibly prevent later obesity.

Food insecurity, a known social determinant of health, occurs in approximately 15% of teens in the U.S. To determine the relationship between food insecurity and obesity, researchers analyzed data from a longitudinal study of 559 teens (and their parents) surveyed from age 15 through age 31 at 1- to 2-year intervals. Families were white and lived in the rural Midwest. Food insecurity was assessed using two questions that asked whether respondents had enough money to buy food and if they altered food shopping or eating habits to save money. Results were as follows:

- A higher initial level of food insecurity (at age 15 years) predicted a faster rise in body-mass index (BMI) over the course of the study in girls but not boys.
- A faster rise in food insecurity scores over time predicted a faster BMI rise in girls.
- Initial BMI and initial food insecurity score were not related.
- Maternal BMI, but not paternal BMI, was positively associated with change in children's adolescent and young adult BMI during the study.
- Many other known behavioral and social determinants of BMI (e.g., socioeconomic status and exercise) were not related to change in BMI.

COMMENT: In girls especially, identifying and addressing food insecurity during mid-adolescence may help prevent the onset or worsening of obesity. The two survey questions utilized in this study are simple and could easily be implemented in practice. Of course, if you ask patients about food insecurity, it is imperative to be familiar with community resources for addressing it. The differences in the relationship between food insecurity and BMI in male versus female adolescents were not explained in this study but are consistent with other studies.

(https://doi.org/10.1016/j.jpeds.2018.05.052)

Botulinum Toxin for Neurogenic Bladder Due to Multiple Sclerosis

Improvements were seen for urgency, incontinence, and quality of life.

Neurogenic bladder is common in multiple sclerosis (MS) and can be refractory to pharmacologic and nonpharmacologic treatment. OnabotulinumtoxinA has been used to reduce urinary incontinence in patients with spinal cord disease, and was studied at a dose of 200 U. In the present study, researchers evaluated a lower dose — 100 U — to see if it has clinical benefit with less need for the transient complication of intermittent catheterization.
This multicenter, double-blind, placebo-controlled, manufacturer-sponsored study with 52 weeks' follow-up included 144 patients with MS, of whom 90% completed the study. Incontinence was reduced as early as week 2, from a mean 3 to 1 episodes per day. With treatment, 80% had at least 50% reduction in urinary incontinence (vs. 36% on placebo), and 53% had 100% reduction (vs. 10% on placebo). Median time to retreatment request was 52 weeks. Improvement was noted in quality-of-life questionnaires. Adverse effects included urinary tract infection (26% vs. 6%) and urinary retention (15% vs. 1%). For those 15% with retention, median time of intermittent catheterization was 2 months.

**COMMENT:** Botulinum toxin injections into the bladder result in greater bladder capacity and a clinically significant improvement in incontinence and urinary urgency. The effects seem to last beyond 3 months, and some patients appear to get a full year of improvement. Urinary retention requiring intermittent straight catheterization was noted in 15% (about half the proportion previously observed with the 200 U dose). The study supports the benefit of botulinum treatment for neurogenic bladder in MS with an acceptable safety profile.

(https://doi.org/10.1212/WNL.0000000000005991)

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**Direct-Acting Oral Anticoagulants vs. Warfarin in “Real-World” Patients**

*Although apixaban, compared with warfarin, was associated with lower risk for major bleeding, low-dose apixaban was associated with higher risk for death.*

Randomized trials have established the noninferiority of direct-acting oral anticoagulants (DOACs) compared with warfarin in patients with atrial fibrillation (AF). However, little is known about how these drugs compare in “real-world” patients, especially patients without AF. U.K. investigators used general practice databases and compared risks for bleeding, stroke, venous thromboembolism, and mortality among nearly 200,000 patients (about half with AF) who received first prescriptions for dabigatran (Pradaxa), rivaroxaban (Xarelto), apixaban (Eliquis), and warfarin between 2011 and 2016.

In patients with AF, the following statistically significant differences (for DOAC use, compared with warfarin use) were noted for bleeding and mortality:

- Both low-dose (<10 mg/day) and high-dose (≥10 mg/day) apixaban were associated with lower risks for major bleeding.
- Low-dose dabigatran (<300 mg/day) was associated with less risk for intracranial bleeding.
- Low-dose apixaban and low-dose rivaroxaban (<20 mg/day) were associated with higher mortality.

In patients without AF, the following significant differences were noted (for DOAC use, compared with warfarin use):
• High-dose apixaban was associated with lower risks for major and gastrointestinal bleeding.
• High-dose rivaroxaban (≥20 mg/day) was associated with less risk for intracranial bleeding.
• Low-dose apixaban, low-dose dabigatran, and high-dose rivaroxaban were associated with higher mortality.

No other significant differences were found in bleeding or mortality outcomes between warfarin and DOACs.

COMMENT: In this “real-world” study, which was subject to confounding, high-dose apixaban was associated with lower risk for major bleeding than was warfarin and had the best overall risk profile of the three DOACs studied. However, low-dose apixaban was associated with higher mortality. The reasons for this finding are unclear; perhaps low-dose apixaban is given preferentially to complex patients with the highest underlying risk for both bleeding and mortality.


Subcutaneous Apomorphine Infusions for Parkinson's Disease

A randomized trial showed a benefit compared with placebo infusions.

Subcutaneous apomorphine infusion for Parkinson disease (PD) has been tested only in open-label studies. Preliminary data suggested that it may be effective in improving dopaminergic “off” time. Now, researchers have conducted a randomized, placebo-controlled, multicenter, double-blind, manufacturer-funded study of 106 PD patients diagnosed at least 3 years previously who had persistent motor fluctuations despite medication optimization. Participants received either 3 to 8 mg/hour of apomorphine subcutaneously infused or a placebo saline infusion for 12 weeks. The flow rate as well as other PD medications could be adjusted for the first 4 weeks of therapy. The primary outcome variable was the change in daily dopaminergic “off” time, tracked by diary.

“Off” time was reduced significantly more from baseline with apomorphine than with placebo (−2.47 hours/day vs. −0.58 hours/day. There was no change in quality of life. Time in the on phase without troublesome dyskinesia improved significantly in the apomorphine group; however, dyskinesia scores were very low at baseline and the study was not powered for dyskinesia reduction. Only 71 participants completed the 12-week study. Six apomorphine recipients withdrew because of adverse events and 44% had nodules at the infusion site. More apomorphine recipients had erythema at the infusion site, nausea, and dyskinesia.

COMMENT: Apomorphine infusion improved “off” time by more than 2 hours a day, although a substantial proportion of patients withdrew from the study. An important limitation was the definition of optimization of therapy and the 4-week period wherein medications and apomorphine could be simultaneously adjusted. Despite these limitations, the study was randomized and showed a clear benefit
favoring apomorphine. The amount of benefit was significantly less than that observed previously with deep brain stimulation or dopamine pump (Duopa). Apomorphine infusion may therefore be an option for patients prior to deep brain stimulation or Duopa therapy but will unlikely be a viable treatment for moderate to severe dyskinesia.


Randomized Trial of Rasagiline Added to Riluzole for Amyotrophic Lateral Sclerosis

Rasagiline is the latest addition to a growing list of agents that show promise in preclinical and open-label ALS studies but subsequently fail to demonstrate efficacy in definitive phase 2/3 trials.

Rasagiline is a monoamine oxidase B inhibitor with established disease-modifying effects in Parkinson disease. Preclinical models of amyotrophic lateral sclerosis (ALS) have shown a benefit of rasagiline, and an open-label trial of 36 ALS patients showed encouraging changes in exploratory disease biomarkers.

To determine whether rasagiline, added to standard-dose riluzole, prolongs survival in ALS patients, researchers conducted an investigator initiated, industry sponsored, randomized, placebo-controlled, double-blind phase 2 trial of rasagiline (1 mg/day) in 251 ALS patients already taking 100 mg/day of riluzole. Exclusion criteria included use of numerous pertinent medications, including most antidepressants and dextromethorphan. Patients were randomized 1:1 and followed for 18 months. Baseline clinical characteristics were similar between groups, including bulbar onset in about 25% of each group.

Rasagiline was well tolerated. Adverse effects were primarily disease related. In the intention-to-treat analysis, rasagiline showed no survival benefit and there were no between-group differences in the secondary endpoints of rate of progression, change in vital capacity, and quality of life. An exploratory post hoc analysis suggested a benefit from rasagiline in normal to fast progressors, as determined by post hoc assessment of baseline monthly change in the ALS functional rating scale, revised.

COMMENT: The U.S. FDA has approved two therapies for ALS: riluzole and edaravone. The relatively small benefit of these agents on survival and disease progression have left patients, clinicians, and investigators in a desperate search for a more effective therapy for this devastating illness. To date, more than 50 randomized controlled trials of disease-modifying therapies for ALS have failed to meet their primary endpoints, and rasagiline can now be added to that list. The reasons underlying these repeated failures have been debated, but a common conclusion is that our lack of understanding of the pathogenesis of this heterogeneous illness plays a major role. In keeping with expert recommendations, and similar to the approach taken with edaravone, the post hoc analysis suggest that another phase 2 study limited to fast progressors may be warranted.
Dr. Bucelli is Associate Professor of Neurology, Washington University School of Medicine, St. Louis.


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Obstet Gynecol 2018 Sep; 132:605

**Is Sexual Orientation Linked to Risk for Experiencing Sexual Violence?**

*Nonheterosexual women seeking abortions were more often victims of sexual violence than their heterosexual counterparts.*

Poor-quality data suggest that sexual minority women (i.e., bisexual, lesbian, and other nonheterosexual) are more likely to have unintended pregnancies resulting in abortion than heterosexual women. To expand this limited knowledge, investigators conducted an observational study using data from the Guttmacher Institute's 2014 Abortion Patient Survey, a random sample of 8380 respondents nationally representative of women undergoing nonhospital abortions in the U.S.

The vast majority of respondents provided information on their sexual identity, with 4.1% identifying as bisexual, 1.1% as “something else” (an open-ended response), and 0.4% as lesbian. Exposure to sexual violence was significantly more common in the three sexual minority groups than in heterosexuals; furthermore, lesbian (33.3%) and bisexual (8.7%) respondents were significantly more likely than heterosexual women (3.6%) to report exposure to physical violence by the man causing the pregnancy. Lesbians (34.6%), bisexuals (7.1%), and those identifying as something else (5.1%) were more likely than heterosexuals (1.9%) to report that the men involved in their pregnancies had sexually abused them. Fully 14.8% of lesbian respondents indicated that the pregnancy was the result of forced sex, and all three sexual minorities were more likely than heterosexual women to indicate that the pregnancy might have resulted from forced sex.

**COMMENT:** The authors emphasize that no pregnant patient should be presumed to be heterosexual. They also suggest that acknowledging the disproportionate percentage of sexual minorities who may be victims of sexual violence may help develop guidelines and interventions addressing the needs of these individuals.


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