**Selected by
Andreas Michalsen
Berlin**

Latest Publications You Should Not Miss

Chowdhury R, Kunutsor S, Vitezova Oliver-Williams C, Chowdhury S, Kieft-de-Jong JC, Khan H, Baena CP, Prabhakaran D, Hoshen MB, Feldman BS, Pan A, Johnson L, Crowe F, Hu FB, Franco OH: Vitamin D and risk of cause specific death: systematic review and meta-analysis of observational cohort and randomised intervention studies. BMJ 2014;348: g1903.

Objective: To evaluate the extent to which circulating biomarker and supplements of vitamin D are associated with mortality from cardiovascular, cancer, or other conditions, under various circumstances.

Design: Systematic review and meta-analysis of observational studies and randomised controlled trials.

Data Sources: Medline, Embase, Cochrane Library, and reference lists of relevant studies to August 2013; correspondence with investigators.

Study Selection: Observational cohort studies and randomised controlled trials in adults, which reported associations between vitamin D (measured as circulating 25-hydroxyvitamin D concentration or vitamin D supplement given singly) and cause specific mortality outcomes.

Data Extraction: Data were extracted by two independent investigators, and a consensus was reached with involvement of a third. Study specific relative risks from 73 cohort studies (849,412 participants) and 22 randomised controlled trials (vitamin D given alone versus placebo or no treatment; 30,716 participants) were meta-analysed using random effects models and were grouped by study and population characteristics.

Results: In the primary prevention observational studies, comparing bottom versus top thirds of baseline circulating 25-hydroxyvitamin D distribution, pooled relative risks were 1.35 (95% confidence interval 1.13 to 1.61) for death from cardiovascular disease, 1.14 (1.01 to 1.29) for death from cancer, 1.30 (1.07 to 1.59) for non-vascular, non-cancer death, and 1.35 (1.22 to 1.49) for all cause mortality. Subgroup analyses in the observational studies indicated that risk of mortality was significantly higher in studies with lower baseline use of vitamin D supplements. In randomised

controlled trials, relative risks for all cause mortality were 0.89 (0.80 to 0.99) for vitamin D3 supplementation and 1.04 (0.97 to 1.11) for vitamin D2 supplementation. The effects observed for vitamin D3 supplementation remained unchanged when grouped by various characteristics. However, for vitamin D2 supplementation, increased risks of mortality were observed in studies with lower intervention doses and shorter average intervention periods.

Conclusions: Evidence from observational studies indicates inverse associations of circulating 25-hydroxyvitamin D with risks of death due to cardiovascular disease, cancer, and other causes. Supplementation with vitamin D3 significantly reduces overall mortality among older adults; however, before any widespread supplementation, further investigations will be required to establish the optimal dose and duration.

Emond JA, Pierce JP, Natarajan L, Gapuz LR, Nguyen J, Parker BA, Varki NM, Patterson RE: Risk of breast cancer recurrence associated with carbohydrate intake and tissue expression of IGF-1 receptor. Cancer Epidemiol Biomarkers Prev 2014;22:epub ahead of print.

Background: The insulin-like growth factor-1 (IGF-1) receptor is a potential target for breast cancer treatment and may be influenced by dietary intake.

Methods: Nested, case-control study of 265 postmenopausal breast cancer survivors; primary breast cancer tissue was stained to determine IGF-1 receptor status. Change in carbohydrate intake from baseline to year 1 of study was estimated from 24-hour dietary recalls. Breast cancer recurrence cases (91) were matched to 2 controls (n = 174) on disease and study characteristics and counter-matched on change in carbohydrate intake. Weighted conditional logistic regression models fit the risk of recurrence on IGF-1 receptor status and dietary change.

Results: Half of tumors were IGF-1 receptor positive. Increased risk of recurrence was associated with IGF-1 receptor positive status (HR 1.7; 95% CI: 1.2–2.5) and, separately, with a stable/increased intake of carbohydrates (HR 2.0; 95% CI: 1.3–5.0). There was a borderline significant interaction between those two variables ($p = 0.11$). Specifically, carbohydrate intake had no significant impact on risk of recurrence among women who were receptor negative, yet increased the risk of recurrence by over 5-fold among women who were receptor positive (HR 5.5; 95% CI 1.8–16.3).

Conclusions: Among women whose tumor tissue is positive for the IGF-1 receptor, reducing carbohydrate intake after diagnosis could reduce the risk of breast cancer recurrence. These findings need replication in a larger sample.

Impact: This is the first study to suggest that it may be possible to personalize dietary recommendations for breast cancer survivors based on molecular characteristics of their primary tumor tissue.

Fontana L, Hu FB: Optimal body weight for health and longevity: bridging basic, clinical, and population research. *Aging Cell* 2014;13:391–400.

Excess body weight and adiposity cause insulin resistance, inflammation, and numerous other alterations in metabolic and hormonal factors that promote atherosclerosis, tumorigenesis, neurodegeneration, and aging. Studies in both animals and humans have demonstrated a beneficial role of dietary restriction and leanness in promoting health and longevity. Epidemiological studies have found strong direct associations between increasing body mass index (BMI) and risks of developing type 2 diabetes, cardiovascular disease, and several types of cancer, beginning from BMI of 20–21 kg m². Although a recent meta-analysis suggests that overweight individuals have significantly lower overall mortality than normal-weight individuals, these data are likely to be an artifact produced by serious methodological problems, especially confounding by smoking, reverse causation due to existing chronic disease, and nonspecific loss of lean mass and function in the frail elderly. From a clinical and public health point of view, maintaining a healthy weight through diet and physical activity should remain the cornerstone in the prevention of chronic diseases and the promotion of healthy aging.

Morgan E, Levine ME, Suarez JA, Brandhorst S, Balasubramanian P, Cheng C-W, Madia F, Fontana L, Mirisola MG, Guevara-Aguirre J, Wan J, Passarino G, Kennedy BK, Wei M, Cohen P, Crimmins EM, Longo VD: Low protein intake is associated with a major reduction in IGF-1, cancer, and overall mortality in the 65 and younger but not older population. *Cell Metab* 2014;19:407–417.

Mice and humans with growth hormone receptor/IGF-1 deficiencies display major reductions in age-related diseases. Because protein restriction reduces GHR-IGF-1 activity, we examined links between protein intake and mortality. Respondents aged 50–65 reporting high protein intake had a 75% increase in overall mortality and a 4-fold increase in cancer death risk during the following 18 years. These associations were either abolished or attenuated if the proteins were plant derived. Conversely, high protein intake was associated with reduced cancer and overall mortality in respondents over 65, but a 5-fold increase in diabetes mortality across all ages. Mouse studies confirmed the effect of high protein intake and GHR-IGF-1 signaling on the incidence and progression of

breast and melanoma tumors, but also the detrimental effects of a low protein diet in the very old. These results suggest that low protein intake during middle age followed by moderate to high protein consumption in old adults may optimize healthspan and longevity.

Solon-Biet SM, McMahon AC, Ballard WO, Ruohonen K, Wu LE, Cogger VC, Warren A, Huang X, Pichaud N, Melvin RG, Gokarn R, Khalil M, Turner N, Cooney GJ, Sinclair DA, Raubenheimer D, Le Couteur DG, Simpson SJ: The ratio of macronutrients, not caloric intake, dictates cardio-metabolic health, aging, and longevity in ad libitum-fed mice. *Cell Metab* 2014;19:418–430.

The fundamental questions of what represents a macronutritionally balanced diet and how this maintains health and longevity remain unanswered. Here, the Geometric Framework, a state-space nutritional modeling method, was used to measure interactive effects of dietary energy, protein, fat, and carbohydrate on food intake, cardiometabolic phenotype, and longevity in mice fed one of 25 diets ad libitum. Food intake was regulated primarily by protein and carbohydrate content. Longevity and health were optimized when protein was replaced with carbohydrate to limit compensatory feeding for protein and suppress protein intake. These consequences are associated with hepatic mammalian target of rapamycin (mTOR) activation and mitochondrial function and, in turn, related to circulating branched-chain amino acids and glucose. Calorie restriction achieved by high-protein diets or dietary dilution had no beneficial effects on lifespan. The results suggest that longevity can be extended in ad libitum-fed animals by manipulating the ratio of macronutrients to inhibit mTOR activation.

Bao Y, Han J, Hu FB, Giovannucci EL, Stampfer MJ, Willett WC, Fuchs CS: Association of nut consumption with total and cause-specific mortality. *N Engl J Med* 2013;369:2001–2011.

Background: Increased nut consumption has been associated with a reduced risk of major chronic diseases, including cardiovascular disease and type 2 diabetes mellitus. However, the association between nut consumption and mortality remains unclear.

Methods: We examined the association between nut consumption and subsequent total and cause-specific mortality among 76,464 women in the Nurses' Health Study (1980–2010) and 42,498 men in the Health Professionals Follow-up Study (1986–2010). Participants with a history of cancer, heart disease, or stroke were excluded. Nut consumption was assessed at baseline and updated every 2 to 4 years.

Results: During 3,038,853 person-years of follow-up, 16,200 women and 11,229 men died. Nut consumption was inversely associated with total mortality among both women and men, after adjustment for other known or suspected risk factors. The pooled multivariate hazard ratios for death among participants who ate nuts, as compared with those who did not, were 0.93 (95% confidence interval (CI), 0.90 to 0.96) for the consumption of nuts less than once per week, 0.89 (95% CI, 0.86 to 0.93) for once per week, 0.87 (95% CI, 0.83 to 0.90) for two to four times per week, 0.85 (95% CI, 0.79 to 0.91) for five or six times per week, and 0.80 (95% CI, 0.73 to 0.86) for seven or more times per week ($P < 0.001$ for trend). Significant inverse associations were also observed between nut consumption and deaths due to cancer, heart disease, and respiratory disease.

Conclusions: In two large, independent cohorts of nurses and other health professionals, the frequency of nut consumption was inversely associated with total and cause-specific mortality, independently of other predictors of death. (Funded by the National Institutes of Health and the International Tree Nut Council Nutrition Research and Education Foundation).

Quanhe Yang Q, Zhang Z, Gregg EW, Flanders D, Merritt R, Hu FB: Added sugar intake and cardiovascular diseases mortality among US adults. JAMA Intern Med 2014;174:516–524.

Importance: Epidemiologic studies have suggested that higher intake of added sugar is associated with cardiovascular disease (CVD) risk factors. Few prospective studies have examined the association of added sugar intake with CVD mortality.

Objective: To examine time trends of added sugar consumption as percentage of daily calories in the United States and investigate the association of this consumption with CVD mortality.

Design, Setting, and Participants: National Health and Nutrition Examination Survey (NHANES, 1988–1994 (III), 1999–2004, and 2005–2010 (n = 31 147)) for the time trend analysis and NHANES III Linked Mortality cohort (1988–2006 (n = 11 733)), a prospective cohort of a nationally representative sample of US adults for the association study.

Main Outcomes and Measures: Cardiovascular disease mortality.

Results: Among US adults, the adjusted mean percentage of daily calories from added sugar increased from 15.7% (95% CI, 15.0%–16.4%) in 1988–1994 to 16.8% (16.0%–17.7%; $P = 0.02$) in 1999–2004 and decreased to 14.9% (14.2%–15.5%; $P < 0.001$) in 2005–2010. Most adults consumed 10% or more of calories from added sugar (71.4%) and approximately 10% consumed 25% or more in 2005–2010. During a median follow-up period of 14.6 years, we documented 831 CVD deaths during 163,039 person-years. Age-, sex-, and race/ethnicity-adjusted hazard ratios (HRs) of CVD mortality across quintiles of the percentage of daily calories consumed from added sugar were 1.00 (reference), 1.09 (95% CI, 1.05–1.13), 1.23 (1.12–1.34), 1.49 (1.24–1.78), and 2.43 (1.63–3.62; $P < 0.001$), respectively. After additional adjustment for sociodemographic, behavioral, and clinical characteristics, HRs were 1.00 (reference), 1.07 (1.02–1.12), 1.18 (1.06–1.31), 1.38 (1.11–1.70), and 2.03 (1.26–3.27; $P = 0.004$), respectively. Adjusted HRs were 1.30 (95% CI, 1.09–1.55) and 2.75 (1.40–5.42; $P = 0.004$), respectively, comparing participants who consumed 10.0% to 24.9% or 25.0% or more calories from added sugar with those who consumed less than 10.0% of calories from added sugar. These findings were largely consistent across age group, sex, race/ethnicity (except among non-Hispanic blacks), educational attainment, physical activity, health eating index, and body mass index.

Conclusions and Relevance: Most US adults consume more added sugar than is recommended for a healthy diet. We observed a significant relationship between added sugar consumption and increased risk for CVD mortality.

Longo VD, Mattson MP: Fasting: molecular mechanisms and clinical applications. Cell Metab 2014;19:181–192.

Fasting has been practiced for millennia, but, only recently, studies have shed light on its role in adaptive cellular responses that reduce oxidative damage and inflammation, optimize energy metabolism, and bolster cellular protection. In lower eukaryotes, chronic fasting extends longevity, in part, by reprogramming metabolic and stress resistance path-

ways. In rodents intermittent or periodic fasting protects against diabetes, cancers, heart disease, and neurodegeneration, while in humans it helps reduce obesity, hypertension, asthma, and rheumatoid arthritis. Thus, fasting has the potential to delay aging and help prevent and treat diseases while minimizing the side effects caused by chronic dietary interventions.

Yokoyama Y, Nishimura K, Barnard ND, Takegami M, Watanabe M, Sekikawa A, Okamura T, Miyamoto Y: Vegetarian diets and blood pressure: a meta-analysis. JAMA Intern Med 2014;174:577–587.

Importance: Previous studies have suggested an association between vegetarian diets and lower blood pressure (BP), but the relationship is not well established.

Objective: To conduct a systematic review and meta-analysis of controlled clinical trials and observational studies that have examined the association between vegetarian diets and BP.

Data Sources: MEDLINE and Web of Science were searched for articles published in English from 1946 to October 2013 and from 1900 to November 2013, respectively.

Study Selection: All studies met the inclusion criteria of the use of (1) participants older than 20 years, (2) vegetarian diets as an exposure or intervention, (3) mean difference in BP as an outcome, and (4) a controlled trial or observational study design. In addition, none met the exclusion criteria of (1) use of twin participants, (2) use of multiple interventions, (3) reporting only categorical BP data, or (4) reliance on case series or case reports.

Data Extraction and Synthesis: Data collected included study design, baseline characteristics of the study population, dietary data, and outcomes. The data were pooled using a random-effects model.

Main Outcomes and Measures: Net differences in systolic and diastolic BP associated with the consumption of vegetarian diets were assessed.

Results: Of the 258 studies identified, 7 clinical trials and 32 observational studies met the inclusion criteria. In the 7 controlled trials (a total of 311 participants; mean age, 44.5 years), consumption of vegetarian diets was associated with a reduction in mean systolic BP (–4.8 mm Hg; 95% CI, –6.6 to –3.1; $P < 0.001$; $I^2 = 0$; $P = 0.45$ for heterogeneity) and diastolic BP (–2.2 mm Hg; 95% CI, –3.5 to –1.0; $P < 0.001$; $I^2 = 0$; $P = 0.43$ for heterogeneity) compared with the consumption of omnivorous diets. In the 32 observational studies (a total of 21,604 participants; mean age, 46.6 years), consumption of vegetarian diets was associated with lower mean systolic BP (–6.9 mm Hg; 95% CI, –9.1 to –4.7; $P < 0.001$; $I^2 = 91.4$; $P < 0.001$ for heterogeneity) and diastolic BP (–4.7 mm Hg; 95% CI, –6.3 to –3.1; $P < 0.001$; $I^2 = 92.6$; $P < 0.001$ for heterogeneity) compared with the consumption of omnivorous diets.

Conclusions and Relevance: Consumption of vegetarian diets is associated with lower BP. Such diets could be a useful nonpharmacologic means for reducing BP.

Petersen GL, Finnerup NB, Colloca L, Amanzio M, Price DD, Jensen S, Vase L: The magnitude of nocebo effects in pain: a meta-analysis. Pain 2014; 26pii:S0304–3959.

The investigation of nocebo effects is evolving, and a few literature reviews have emerged, although so far without quantifying such effects. This meta-analysis investigated nocebo effects in pain. We searched the databases PubMed, EMBASE, Scopus, and the Cochrane Controlled Trial Register with the term ‘nocebo.’ Only studies that investigated no-

cebo effects as the effects that followed the administration of an inert treatment along with verbal suggestions of symptom worsening and that included a no-treatment control condition were eligible. Ten studies fulfilled the selection criteria. The effect sizes were calculated using Cohen's d and Hedges' g . The overall magnitude of the placebo effect was moderate to large (lowest $g = 0.62$ (0.24–1.01) and highest $g = 1.03$ (0.63–1.43)) and highly variable (range of $g = -0.43$ to 4.05). The magnitudes and range of effect sizes was similar to those of placebo effects ($d = 0.81$) in mechanistic studies. In studies in which placebo effects were induced by a combination of verbal suggestions and conditioning, the effect size was larger (lowest $g = 0.76$ (0.39–1.14) and highest $g = 1.17$ (0.52–1.81)) than in studies in which placebo effects were induced by verbal suggestions alone (lowest $g = 0.64$ (–0.25 to 1.53) and highest $g = 0.87$ (0.40–1.34)). These findings are similar to those in the placebo literature. As the magnitude of the placebo effect is variable and sometimes large, this meta-analysis demonstrates the importance of minimizing placebo effects in clinical practice.

Goyal M, Singh S, Sibinga EMS, Gould NF, Rowland-Seymour A, Sharma S, Berger Z, Sleicher D, Maron DD, Shihab HM, Ranasinghe PD, Linn S, Saha S, Bass EB, Haythornthwaite JA: Meditation programs for psychological stress and well-being: a systematic review and meta-analysis. JAMA Intern Med 2014;174:357–368.

Importance: Many people meditate to reduce psychological stress and stress-related health problems. To counsel people appropriately, clinicians need to know what the evidence says about the health benefits of meditation.

Objective: To determine the efficacy of meditation programs in improving stress-related outcomes (anxiety, depression, stress/distress, positive mood, mental health-related quality of life, attention, substance use, eating habits, sleep, pain, and weight) in diverse adult clinical populations.

Evidence Review: We identified randomized clinical trials with active controls for placebo effects through November 2012 from MEDLINE, PsycINFO, EMBASE, PsycArticles, Scopus, CINAHL, AMED, the Cochrane Library, and hand searches. Two independent reviewers screened citations and extracted data. We graded the strength of evidence using 4 domains (risk of bias, precision, directness, and consistency) and determined the magnitude and direction of effect by calculating the relative difference between groups in change from baseline. When possible, we conducted meta-analyses using standardized mean differences to obtain aggregate estimates of effect size with 95% confidence intervals. *Findings:* After reviewing 18,753 citations, we included 47 trials with 3,515 participants. Mindfulness meditation programs had moderate evidence of improved anxiety (effect size, 0.38 (95% CI, 0.12–0.64) at 8 weeks and 0.22 (0.02–0.43) at 3–6 months), depression (0.30 (0.00–0.59) at 8 weeks and 0.23 (0.05–0.42) at 3–6 months), and pain (0.33 (0.03–0.62)) and low evidence of improved stress/distress and mental health-related quality of life. We found low evidence of no effect or insufficient evidence of any effect of meditation programs on positive mood, attention, substance use, eating habits, sleep, and weight. We found no evidence that meditation programs were better than any active treatment (i.e. drugs, exercise, and other behavioral therapies).

Conclusions and Relevance: Clinicians should be aware that meditation programs can result in small to moderate reductions of multiple negative dimensions of psychological stress. Thus, clinicians should be prepared to talk with their patients about the role that a meditation program could have in addressing psychological stress. Stronger study designs are needed to determine the effects of meditation programs in improving the positive dimensions of mental health and stress-related behavior.