N Engl J Med. 2013 Aug 8;369(6):540-8. doi: 10.1056/NEJMoa1215740.

Glucose levels and risk of dementia.

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BACKGROUND: Diabetes is a risk factor for dementia. It is unknown whether higher glucose levels increase the risk of dementia in people without diabetes. METHODS: We used 35,264 clinical measurements of glucose levels and 10,208 measurements of glycated hemoglobin levels from 2067 participants without dementia to examine the relationship between glucose levels and the risk of dementia. Participants were from the Adult Changes in Thought study and included 839 men and 1228 women whose mean age at baseline was 76 years; 232 participants had diabetes, and 1835 did not. We fit Cox regression models, stratified according to diabetes status and adjusted for age, sex, study cohort, educational level, level of exercise, blood pressure, and status with respect to coronary and cerebrovascular diseases, atrial fibrillation, smoking, and treatment for hypertension. RESULTS: During a median follow-up of 6.8 years, dementia developed in 524 participants (74 with diabetes and 450 without). Among participants without diabetes, higher average glucose levels within the preceding 5 years were related to an increased risk of dementia (P=0.01); with a glucose level of 115 mg per deciliter (6.4 mmol per liter) as compared with 100 mg per deciliter (5.5 mmol per liter), the adjusted hazard ratio for dementia was 1.18 (95% confidence interval [CI], 1.04 to 1.33). Among participants with diabetes, higher average glucose levels were also related to an increased risk of dementia (P=0.002); with a glucose level of 190 mg per deciliter (10.5 mmol per liter) as compared with 160 mg per deciliter (8.9 mmol per liter), the adjusted hazard ratio was 1.40 (95% CI, 1.12 to 1.76). CONCLUSIONS: Our results suggest that higher glucose levels may be a risk factor for dementia, even among persons without diabetes. (Funded by the National Institutes of Health.)

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Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes.

Look AHEAD Research Group, Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, Coday M, Crow RS, Curtis JM, Egan CM, Espeland MA, Evans M, Foreyt JP, Ghazarian S, Gregg EW,

Harrison B, Hazuda HP, Hill JO, Horton ES, Hubbard VS, Jakicic JM, Jeffery RW, Johnson KC, Kahn SE, Kitabchi AE, Knowler WC, Lewis CE, Maschak-Carey BJ, Montez MG, Murillo A, Nathan DM, Patricio J, Peters A, Pi-Sunyer X, Pownall H, Reboussin D, Regensteiner JG, Rickman AD, Ryan DH, Safford M, Wadden TA, Wagenknecht LE, West DS, Williamson DF, Yanovski SZ.
Comment in N Engl J Med. 2013 Jul 11;369(2):189-90.

BACKGROUND: Weight loss is recommended for overweight or obese patients with type 2 diabetes on the basis of short-term studies, but long-term effects on cardiovascular disease remain unknown. We examined whether an intensive lifestyle intervention for weight loss would decrease cardiovascular morbidity and mortality among such patients. METHODS: In 16 study centers in the United States, we randomly assigned 5145 overweight or obese patients with type 2 diabetes to participate in an intensive lifestyle intervention that promoted weight loss through decreased caloric intake and increased physical activity (intervention group) or to receive diabetes support and education (control group). The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for angina during a maximum follow-up of 13.5 years. RESULTS: The trial was stopped early on the basis of a futility analysis when the median follow-up was 9.6 years. Weight loss was greater in the intervention group than in the control group throughout the study (8.6% vs. 0.7% at 1 year; 6.0% vs. 3.5% at study end). The intensive lifestyle intervention also produced greater reductions in glycated hemoglobin and greater initial improvements in fitness and all cardiovascular risk factors, except for low-density-lipoprotein cholesterol levels. The primary outcome occurred in 403 patients in the intervention group and in 418 in the control group (1.83 and 1.92 events per 100 person-years, respectively; hazard ratio in the intervention group, 0.95; 95% confidence interval, 0.83 to 1.09; P=0.51). CONCLUSIONS: An intensive lifestyle intervention focusing on weight loss did not reduce the rate of cardiovascular events in overweight or obese adults with type 2 diabetes. (Funded by the National Institutes of Health and others; Look AHEAD ClinicalTrials.gov number, NCT00017953.).

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Br J Surg. 2013 Jul;100(8):1030-6. doi: 10.1002/bjs.9176.

Raised haematocrit concentration and the risk of death and vascular complications after major surgery.

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BACKGROUND: Preoperative anaemia is associated with adverse postoperative outcomes. Data on raised preoperative haematocrit concentration are limited. This study aimed to evaluate the effect of raised haematocrit on 30-day postoperative mortality and vascular events in patients undergoing major surgery. METHODS: This was a cohort study using the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database. Thirty-day mortality and vascular events, demographics and perioperative risk factors were obtained for adults undergoing major surgery. The adjusted effect of raised (over 0·50) compared with normal (0·41-0·50, American Medical Association reference range) preoperative haematocrit concentration on postoperative outcomes was assessed. Separate sex-specific analyses were also conducted, using haematocrit concentration thresholds commonly used in the diagnosis and management of apparent or absolute erythrocytosis. RESULTS: Some 3961 (2·0 per cent) of 197469 patients had a raised haematocrit concentration before surgery. After adjustment, the 30-day postoperative mortality rate was higher in patients with raised haematocrit than in those without (odds ratio (OR) 2·23, 95 per cent confidence interval 1·77 to 2·80). Thirty-day rates of deep vein thrombosis (OR 1·95, 1·44 to 2·64) and pulmonary embolism (OR 1·79, 1·17 to 2·73), but not myocardial infarction or stroke, were also higher in patients with a raised haematocrit concentration. The effect on mortality was noted beyond the haematocrit thresholds of 0·48 in women and 0·52 in men; the effect estimates were considerably higher for values exceeding 0·54. Values between 0·41 and 0·45 were not associated with increased mortality risk. Similar observations were noted for venous thrombosis, although with apparent sex differences. CONCLUSION: A raised haematocrit concentration was associated with an increased risk of 30-day mortality and venous thrombosis following major surgery.

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Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention.

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Since the first description of the association between chronic kidney disease and heart disease, many epidemiological studies have confirmed and extended this finding. As chronic kidney disease progresses, kidney-specific risk factors for cardiovascular events and disease come

into play. As a result, the risk for cardiovascular disease is notably increased in individuals with chronic kidney disease. When adjusted for traditional cardiovascular risk factors, impaired kidney function and raised concentrations of albumin in urine increase the risk of cardiovascular disease by two to four times. Yet, cardiovascular disease is frequently underdiagnosed and undertreated in patients with chronic kidney disease. This group of patients should, therefore, be acknowledged as having high cardiovascular risk that needs particular medical attention at an individual level. This view should be incorporated in the development of guidelines and when defining research priorities. Here, we discuss the epidemiology and pathophysiological mechanisms of cardiovascular risk in patients with chronic kidney disease, and discuss methods of prevention.

PMID: 23727170 [PubMed - indexed for MEDLINE]

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Chronic kidney disease: global dimension and perspectives.

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Erratum in Lancet. 2013 Jul 20;382(9888):208.

Chronic kidney disease is defined as a reduced glomerular filtration rate, increased urinary albumin excretion, or both, and is an increasing public health issue. Prevalence is estimated to be 8-16% worldwide. Complications include increased all-cause and cardiovascular mortality, kidney-disease progression, acute kidney injury, cognitive decline, anaemia, mineral and bone disorders, and fractures. Worldwide, diabetes mellitus is the most common cause of chronic kidney disease, but in some regions other causes, such as herbal and environmental toxins, are more common. The poorest populations are at the highest risk. Screening and intervention can prevent chronic kidney disease, and where management strategies have been implemented the incidence of end-stage kidney disease has been reduced. Awareness of the disorder, however, remains low in many communities and among many physicians. Strategies to reduce burden and costs related to chronic kidney disease need to be included in national programmes for non-communicable diseases.

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Effect of fetal and child health on kidney development and long-term risk of hypertension and kidney disease.

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Developmental programming of non-communicable diseases is now an established paradigm. With respect to hypertension and chronic kidney disease, adverse events experienced in utero can affect development of the fetal kidney and reduce final nephron number. Low birthweight and prematurity are the most consistent clinical surrogates for a low nephron number and are associated with increased risk of hypertension, proteinuria, and kidney disease in later life. Rapid weight gain in childhood or adolescence further compounds these risks. Low birthweight, prematurity, and rapid childhood weight gain should alert clinicians to an individual's lifelong risk of hypertension and kidney disease, prompting education to minimise additional risk factors and ensuring follow-up. Birthweight and prematurity are affected substantially by maternal nutrition and health during pregnancy. Optimisation of maternal health and early childhood nutrition could, therefore, attenuate this programming cycle and reduce the global burden of hypertension and kidney disease in the future.

PMID: 23727166 [PubMed - indexed for MEDLINE]

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Promoting health and wellness in the workplace: a unique opportunity to establish primary and extended secondary cardiovascular risk reduction programs.

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Given the burden of cardiovascular disease (CVD), increasing the prevalence of healthy lifestyle choices is a global imperative. Currently, cardiac rehabilitation programs are a primary way that modifiable risk factors are addressed in the secondary prevention setting after a cardiovascular (CV) event/diagnosis. Even so, there is wide consensus that primary prevention of CVD is an

effective and worthwhile pursuit. Moreover, continual engagement with individuals who have already been diagnosed as having CVD would be beneficial. Implementing health and wellness programs in the workplace allows for the opportunity to continually engage a group of individuals with the intent of effecting a positive and sustainable change in lifestyle choices. Current evidence indicates that health and wellness programs in the workplace provide numerous benefits with respect to altering CV risk factor profiles in apparently healthy individuals and in those at high risk for or already diagnosed as having CVD. This review presents the current body of evidence demonstrating the efficacy of worksite health and wellness programs and discusses key considerations for the development and implementation of such programs, whose primary intent is to reduce the incidence and prevalence of CVD and to prevent subsequent CV events. Supporting evidence for this review was obtained from PubMed, with no date limitations, using the following search terms: worksite health and wellness, employee health and wellness, employee health risk assessments, and return on investment. The choice of references to include in this review was based on study quality and relevance.

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Am J Clin Nutr. 2013 Jul;98(1):197-208. doi: 10.3945/ajcn.112.056101. Epub 2013 May 29.

Association between circulating vitamin K1 and coronary calcium progression in community-dwelling adults: the Multi-Ethnic Study of Atherosclerosis.

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BACKGROUND: Animal studies have shown that vitamin K treatment reduced vascular calcification, but human data are limited. OBJECTIVE: We determined the association between vitamin K status and coronary artery calcium (CAC) progression in the Multi-Ethnic Study of Atherosclerosis by using a case-cohort design. DESIGN: Serum phylloquinone (vitamin K1) was measured in 296 participants with extreme CAC progression and 561 randomly selected participants without extreme CAC progression; all subjects had baseline and follow-up CAC measures (mean follow-up: 2.5 y). A serum vitamin K1 concentration was considered low at <1.0 nmol/L (the distribution median). Outcomes were replicated by using post hoc per-protocol analyses of a vitamin K1 supplementation trial. RESULTS: The OR (95% CI) for extreme CAC progression for subjects with low serum vitamin K1 compared with subjects without extreme CAC progression was 1.34 (0.94, 1.90; NS) when adjusted for demographics and confounders. A significant interaction between low vitamin K1 and antihypertension medication use was

detected (P = 0.016). Hypertension medication users with low serum vitamin K1 were more likely to have extreme CAC progression than were medication users without extreme CAC progression [OR (95% CI): 2.37 (1.38, 4.09)]. In replication, baseline antihypertensive medication users in the supplementation group had less CAC progression than did those in the control group [adjusted mean ± SEM of the 3-y CAC change was +5 ± 20 Agatston units (AU) in the vitamin K1 group (n = 40) and +44 ± 13 AU in the placebo group (n = 49); P < 0.01]. CONCLUSIONS: Although the point estimate of our primary analysis suggests low serum vitamin K1 is associated with greater CAC progression, the difference was NS. Low serum vitamin K1 was significantly associated with CAC progression in antihypertension medication users, which, to our knowledge, is a novel finding conditionally replicated by using an independent sample. Intervention trials are needed to determine whether improving serum vitamin K1 reduces CAC progression, especially in hypertensive individuals. This trial was registered at clinicaltrials.gov as NCT00183001.

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PMID: 23719555 [PubMed - indexed for MEDLINE]

Am J Clin Nutr. 2013 Jul;98(1):160-73. doi: 10.3945/ajcn.112.053132. Epub 2013 May 29.

Circulating and dietary magnesium and risk of cardiovascular disease: a systematic review and meta-analysis of prospective studies.

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BACKGROUND: Clinical hypomagnesemia and experimental restriction of dietary magnesium increase cardiac arrhythmias. However, whether or not circulating or dietary magnesium at usual concentrations or intakes influences the risk of cardiovascular disease (CVD), including fatal ischemic heart disease (IHD), is unclear. OBJECTIVE: We performed a systematic review and meta-analysis to investigate prospective associations of circulating and dietary magnesium with incidence of CVD, IHD, and fatal IHD. DESIGN: Multiple literature databases were systematically searched without language restriction through May 2012. Inclusion decisions and data extraction were performed in duplicate. Linear dose-response associations were assessed by using random-effects meta-regression. Potential nonlinear associations were evaluated by using restricted cubic splines. RESULTS: Of 2303 articles, 16 studies met the eligibility criteria; these studies comprised 313,041 individuals and 11,995 CVD, 7534 IHD, and 2686 fatal IHD events. Circulating magnesium (per 0.2 mmol/L increment) was associated with a 30% lower risk of CVD (RR: 0.70; 95% CI: 0.56, 0.88 per 0.2 mmol/L) and trends toward lower risks of IHD

(RR: 0.83; 95% CI: 0.75, 1.05) and fatal IHD (RR: 0.61; 95% CI: 0.37, 1.00). Dietary magnesium (per 200-mg/d increment) was not significantly associated with CVD (RR: 0.89; 95% CI: 0.75, 1.05) but was associated with a 22% lower risk of IHD (RR: 0.78; 95% CI: 0.67, 0.92). The association of dietary magnesium with fatal IHD was nonlinear (P < 0.001), with an inverse association observed up to a threshold of ~250 mg/d (RR: 0.73; 95% CI: 0.62, 0.86), compared with lower intakes. CONCLUSION: Circulating and dietary magnesium are inversely associated with CVD risk, which supports the need for clinical trials to evaluate the potential role of magnesium in the prevention of CVD and IHD.

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PMID: 23719551 [PubMed - indexed for MEDLINE]

Pediatrics. 2013 Jun;131(6):e1821-8. doi: 10.1542/peds.2012-2789. Epub 2013 May 27.

Weight gain in infancy and vascular risk factors in later childhood.

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OBJECTIVE: We hypothesized that early weight gain would be associated with incident obesity, higher blood pressure, systemic inflammation, and arterial wall thickening in later childhood. METHODS: A longitudinal birth cohort was recruited antenatally from 2 maternity hospitals in Sydney, Australia, between September 1997 and December 1999. Three hundred ninety-five nondiabetic children who were followed to age 8 years had complete data for early weight gain and arterial wall thickness. RESULTS: Independent predictors of excess early weight gain (age 0-18 months; adjusted for height gain) included male gender (0.411 kg [SE: 0.103], P < .001), fewer weeks' gestation (-0.121 kg [SE: 0.044] per week, P = .006), birth length (0.156 kg [SE: 0.024] per cm, P < .001), and failure to breastfeed to 6 months of age (0.498 kg [SE: 0.108], P < .001). Early height-adjusted weight gain was significantly associated with later childhood overweight (odds ratio [OR]: 1.67 [95% confidence interval (CI): 1.26 to 2.20] per kg) and obesity (OR: 2.07 [95% CI: 1.53 to 2.79] per kg), excess central adiposity (OR: 1.54 [95% CI: 1.20 to 1.98] per kg), higher systolic blood pressure (1.24 mmHg [SE: 0.33] per kg, P < .001), higher C-reactive protein (0.17 mg/dL [SE: 0.06] per 100% increase in weight gain, P = .006), and greater carotid intima-media thickness (0.012 mm [SE: 0.004] per kg, P = .002). CONCLUSIONS: Early postnatal weight gain from birth to age 18 months is significantly associated with later childhood overweight and obesity, excess central adiposity, and greater arterial wall thickness.

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Gender differences in clinical outcomes among diabetic patients hospitalized for cardiovascular disease.

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BACKGROUND: The risk of incident cardiovascular disease (CVD) has been shown to be greater among diabetic women than men, but gender differences in clinical outcomes among diabetic patients hospitalized with CVD are not established. We aimed to determine if hemoglobin A1c (HbA1c) was associated with 30-day and 1-year CVD rehospitalization and total mortality among diabetic patients hospitalized for CVD, overall and by gender. METHODS: This was a prospective analysis of diabetic patients hospitalized for CVD, enrolled in an National Heart, Lung and Blood Institute-sponsored observational clinical outcomes study (N = 902, 39% female, 53% racial/ethnic minority, mean age 67 ± 12 years). Laboratory, rehospitalization, and mortality data were determined by hospital-based electronic medical record. Poor glycemic control was defined as HbA1c ≥7%. The association between HbA1c and clinical outcomes was evaluated using logistic regression; gender modification was evaluated by interaction terms and stratified models. RESULTS: Hemoglobin A1c ≥7% prevalence was 63% (n = 566) and was similar by gender. Hemoglobin A1c ≥7% vs <7% was associated with increased 30-day CVD rehospitalization in univariate (odds ratio [OR] = 1.63, 95% CI 1.05-2.54) and multivariable-adjusted models (OR 1.74, 95% CI 1.06-2.84). There was an interaction between glycemic control and gender for 30-day CVD rehospitalization risk (P = .005). In stratified univariate models, the association was significant among women (OR 4.83, 95% CI 1.84-12.71) but not among men (OR 1.02, 95% CI 0.60-1.71). The multivariate-adjusted risk for HbA1c ≥7% versus <7% among women was 8.50 (95% CI 2.31-31.27) and 1.02 (95% CI 0.57-1.80) for men. A trend toward increased 30-day/1-year mortality risk was observed for HbA1c <6% vs ≥6% for men and women. CONCLUSIONS: Risk of 30-day CVD rehospitalization was 8.5-fold higher among diabetic women hospitalized for CVD with HbA1c ≥7% vs <7%; no association was observed among men. A trend for increased 30-day/1-year mortality risk with HbA1c <6% deserves further study.

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PMID: 23708169 [PubMed - indexed for MEDLINE]

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Temporal trends in sudden unexpected death in a general population: the Hisayama study.

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BACKGROUND: Studies addressing the temporal trends in the prevalence of sudden unexpected death (SUD) and its underlying causes in the general population are limited. METHODS: Among a total of 1934 residents aged ≥20 years of the town of Hisayama, Japan, who died of endogenous causes of death and underwent autopsy examination (autopsy rate 78.5%) from 1962 to 2009, 204 were determined to be cases of SUD within 24 hours. RESULTS: The trend in the age- and sex-adjusted prevalence of SUD among all autopsy subjects was stable over four 12-year periods (13.1% in 1962-1973, 13.4% in 1974-1985, 15.0% in 1986-1997, and 14.6% in 1998-2009; P for trend = .80). Regarding causes of death, the prevalence of SUD from stroke significantly declined with time (8.0%, 5.0%, 2.3%, and 2.1%, respectively; P for trend < .001), whereas significant increments were observed in the prevalence of SUD from heart disease (4.0%, 6.2%, 8.6%, and 9.7%; P for trend = .02) and from aortic aneurysm and dissection (0.2%, 1.2%, 2.9%, and 2.8%; P for trend = .01). In particular, the prevalence of ischemic heart disease increased 3-fold from 2.1% in 1962-1973 to 6.6% in 1998-2009 (P = .04). Reflecting the increment of ischemic heart disease, SUD within 1 hour increased significantly from 2.5% to 7.6% during this period (P = .01). CONCLUSIONS: The trend in the prevalence of SUD was stable across a half century in a general Japanese population. Despite the decrement in the prevalence of SUD from stroke, that from heart disease, especially ischemic heart disease, increased significantly with time.

PMID: 23708164 [PubMed - indexed for MEDLINE]

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Risk of stroke with percutaneous coronary intervention compared with on-pump and off-pump coronary artery bypass graft surgery: Evidence from a comprehensive network meta-analysis.

Palmerini T, Biondi-Zoccai G, Riva DD, Mariani A, Savini C, Di Eusanio M, Genereux P, Frati G, Marullo AG, Landoni G, Greco T, Branzi A, De Servi S, Di Credico G, Taglieri N, Williams MR, Stone GW.

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BACKGROUND: Although some trials have reported that on-pump coronary artery bypass graft (CABG) surgery may be associated with higher rates of stroke than percutaneous coronary intervention (PCI), whether stroke is more common after off-pump CABG compared with PCI is unknown. We therefore sought to determine whether off-pump CABG is associated with an increased risk of stroke compared with PCI by means of network meta-analysis. METHODS: Randomized controlled trials (RCTs) comparing CABG vs PCI were searched through MEDLINE, EMBASE, Cochrane databases, and proceedings of international meetings. RESULTS: Eighty-three RCTs with 22,729 patients randomized to on-pump CABG (n = 10,957), off-pump CABG (n = 7,119), or PCI (n = 4,653) were analyzed. Thirty-day rates of stroke were significantly lower in patients treated with PCI compared with either off-pump CABG (odds ratio [OR]; 0.39, 95% CI, 0.19-0.83) or on-pump CABG (OR, 0.26; 95% CI, 0.12-0.47). Compared with on-pump CABG, off-pump CABG was associated with significantly lower 30-day risk of stroke (OR, 0.67; 95% CI, 0.41-0.95). However, in sensitivity analyses restricted to high-quality studies, studies with more than either 100 or 1,000 patients, or studies with protocol definition or adjudication of stroke by a clinical events committee, the precision of the point estimate for the 30-day risk of stroke between off-pump vs on-pump CABG was markedly reduced. CONCLUSIONS: Percutaneous coronary intervention is associated with lower 30-day rates of stroke than both off-pump and on-pump CABG. Further studies are required to determine whether the risk of stroke is reduced with off-pump CABG compared with on-pump CABG.

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Prevalence and clinical outcomes of undiagnosed diabetes mellitus and prediabetes among patients with high-risk non-ST-segment elevation acute coronary syndrome.

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BACKGROUND: We examined the prevalence of undiagnosed diabetes or prediabetes and associations with ischemic outcomes among non-ST-segment elevation acute coronary syndrome (ACS) patients. METHODS: We categorized 8795 EARLY ACS trial patients into one of the following groups: "known diabetes" (n = 2860 [32.5%]; reported on the case report form), "undiagnosed diabetes" (n = 1069 [12.2%]; no diabetes history and fasting glucose ≥126 mg/dL

or hemoglobin A1c ≥6.5%), "prediabetes" (n = 947 [10.8%]; fasting glucose ≥110 to <126 mg/dL, or "normal" (n = 3919 [44.5%]). Adjusted associations of known diabetes, undiagnosed diabetes, and prediabetes (versus normal) with 30-day and 1-year outcomes were determined. RESULTS: Undiagnosed diabetes was associated with greater 30-day death or myocardial infarction (MI) (ORadj 1.28, 95% CI 1.05-1.57), driven primarily by greater 30-day mortality (ORadj 1.65, 95% CI 1.09-2.48). Known diabetic patients had 30-day death or MI outcomes similar to those of normal patients, but 30-day mortality was higher (ORadj 1.40, 95% CI 1.01-1.93). Prediabetic patients had 30-day death or MI outcomes similar to those of normal patients. One-year mortality was greater among known diabetic patients (HRadj 1.38, 95% CI 1.13-1.67) but not among those with undiagnosed diabetes or prediabetes. CONCLUSIONS: Undiagnosed diabetes and prediabetes were common among high-risk non-ST-segment elevation ACS patients. Routine screening for undiagnosed diabetes may be useful since these patients seem to have worse short-term outcomes and deserve consideration of alternative management strategies.

PMID: 23708162 [PubMed - indexed for MEDLINE]

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Urinary flavonoid excretion and risk of acute coronary syndrome in a nested case-control study.

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BACKGROUND: Epidemiologic studies have suggested that a higher intake of flavonoids may be associated with lower risk of ischemic heart disease. However, the traditional estimation of flavonoid intake by using dietary assessment methods is affected by subjective measures. OBJECTIVE: We examined whether the objective measurement of dietary flavonoids excreted in urine is associated with lower risk of acute coronary syndrome (ACS). DESIGN: A case-control study was nested in the Danish Diet, Cancer and Health cohort study. Cases were identified in participants who had received a first-time ACS diagnosis in the Danish National Patient Registry after the time of enrollment into the Diet, Cancer and Health study. The excretion of 10 flavonoids, which represent 5 subclasses, was measured in spot urine samples by using liquid chromatography-mass spectrometry. RESULTS: A total of 393 eligible cases with ACS were identified and matched to 393 noncases by using incidence density sampling. For kaempferol, most of the individual ORs were statistically significant and from 42% to 61% lower when the higher 4 quintiles were compared with the lowest quintile. The P-trend was not significant. For daidzein, individual ORs were 5-38% lower. None of the individual ORs were significant, but the P-trend was 0.041. For the remaining flavonoids, there were no significant

relations between urinary excretion and risk of ACS. CONCLUSIONS: Except for kaempferol and daidzein, there were no significant associations between the urinary excretion of flavonoids and risk of ACS. A lack of relations may be a result of the use of short-term exposure measures.

PMID: 23697704 [PubMed - indexed for MEDLINE]

Am J Clin Nutr. 2013 Jul;98(1):146-59. doi: 10.3945/ajcn.112.051318. Epub 2013 May 15.

Egg consumption in relation to risk of cardiovascular disease and diabetes: a systematic review and meta-analysis.

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BACKGROUND: The associations of egg consumption with cardiovascular disease (CVD) and diabetes are still unclear. OBJECTIVE: We aimed to quantitatively summarize the literature on egg consumption and risk of CVD, cardiac mortality, and type 2 diabetes by conducting a meta-analysis of prospective cohort studies. DESIGN: A systematic literature review was conducted for published studies in PubMed and EMBASE through March 2012. Additional information was retrieved through Google or a hand review of the reference from relevant articles. Studies were included if they had a prospective study design, were published in English-language journals, and provided HRs and 95% CIs for the associations of interest. Data were independently extracted by 2 investigators, and the weighted HRs and 95% CIs for the associations of interest were estimated by using a random-effects model. RESULTS: A total of 22 independent cohorts from 16 studies were identified, including participants ranging in number from 1600 to 90,735 and in follow-up time from 5.8 to 20.0 y. Comparison of the highest category (≥1 egg/d) of egg consumption with the lowest (<1 egg/wk or never) resulted in a pooled HR (95% CI) of 0.96 (0.88, 1.05) for overall CVD, 0.97 (0.86, 1.09) for ischemic heart disease, 0.93 (0.81, 1.07) for stroke, 0.98 (0.77, 1.24) for ischemic heart disease mortality, 0.92 (0.56, 1.50) for stroke mortality, and 1.42 (1.09, 1.86) for type 2 diabetes. Of the studies conducted in diabetic patients, the pooled HR (95% CI) was 1.69 (1.09, 2.62) for overall CVD. CONCLUSIONS: This meta-analysis suggests that egg consumption is not associated with the risk of CVD and cardiac mortality in the general population. However, egg consumption may be associated with an increased incidence of type 2 diabetes among the general population and CVD comorbidity among diabetic patients.

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Prevalence and prognostic role of resistant hypertension in chronic kidney disease patients.

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Comment in J Am Coll Cardiol. 2013 Jun 18;61(24):2468-70.

OBJECTIVES: This study sought to evaluate in chronic kidney disease (CKD) prevalence and prognosis of true resistant hypertension (RH) (i.e., confirmed by ambulatory blood pressure [ABP] monitoring). BACKGROUND: In CKD, uncontrolled hypertension is a major risk factor, but no study has properly investigated the role of RH. METHODS: We prospectively studied 436 hypertensive CKD patients under nephrology care. Four groups were constituted by combining 24-h ABP with diagnosis of RH (office blood pressure ≥130/80 mm Hg, despite adherence to ≥3 full-dose antihypertensive drugs including a diuretic agent or ≥4 drugs): control (ABP <125/75 mm Hg without RH); pseudoresistance (ABP <125/75 mm Hg with RH); sustained hypertension (ABP ≥125/75 mm Hg without RH); and true resistance (ABP ≥125/75 mm Hg with RH). Endpoints of survival analysis were renal (end-stage renal disease or death) and cardiovascular events (fatal and nonfatal cardiovascular event). RESULTS: Age was 65 ± 14 years, men 58%, diabetes 36%, cardiovascular disease 30%, median proteinuria 0.24 (interquartile range 0.09 to 0.83) g/day, estimated glomerular filtration rate 43 ± 20 ml/min/1.73 m(2), office blood pressure 146 ± 19/82 ± 12 mm Hg, and 24-h ABP 129 ± 17/72 ± 10 mm Hg. True resistant patients were 22.9%, and pseudoresistant patients were 7.1%, whereas patients with sustained hypertension were 42.9%, and control subjects were 27.1%. Over 57 months of follow-up, 109 cardiovascular events and 165 renal events occurred. Cardiovascular risk (hazard ratio [95% confidence interval]) was 1.24 (0.55 to 2.78) in pseudoresistance, 1.11 (0.67 to 1.84) in sustained hypertension, and 1.98 (1.14 to 3.43) in true resistance, compared with control subjects. Corresponding hazards for renal events were 1.18 (0.45 to 3.13), 2.14 (1.35 to 3.40), and 2.66 (1.62 to 4.37). CONCLUSIONS: In CKD, pseudoresistance is not associated with an increased cardio-renal risk, and sustained hypertension predicts only renal outcome. True resistance is prevalent and identifies patients carrying the highest cardiovascular risk.

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Long-term alcohol and caffeine intake and risk of sudden cardiac death in women.

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BACKGROUND: Alcohol and caffeine intakes may play a role in the development of sudden cardiac death (SCD) because of their effects on cholesterol, blood pressure, heart rate variability, and inflammation. OBJECTIVE: Our objective was to examine the association between long-term alcohol and caffeine intakes and risk of SCD in women. DESIGN: We examined 93,676 postmenopausal women who participated in the Women's Health Initiative Observational Study. Women were enrolled between 1993 and 1998 and were followed until August 2009. Women completed a food-frequency questionnaire at baseline and again at year 3. We modeled exposure to alcohol 3 ways: by using baseline intake only, a cumulative average of baseline and year 3 intake, and the most recent reported intake (a simple time-varying analysis). RESULTS: Intake of 5-15 g alcohol/d (about one drink) was associated with a nonsignificantly reduced risk of SCD compared with 0.1-5 g/d of baseline intake (HR: 0.64; 95% CI: 0.40, 1.02), of cumulative average intake (HR: 0.69; 95% CI: 0.43, 1.11), and of most recent intake (HR: 0.58; 95% CI: 0.35, 0.96), with adjustment for age, race, income, smoking, body mass index, physical activity, hormone use, and total energy. No association was found between SCD and total caffeine intake (mg/d) or cups of caffeinated coffee, decaffeinated coffee, and caffeinated tea.CONCLUSIONS: Our results suggest that about one drink per day (or 5.1-15 g/d) may be associated with a reduced risk of SCD in this population; however, this association was only statistically significant for a model using the most recent alcohol intake. Total caffeine, regular coffee, decaffeinated coffee, and regular tea intake were not associated with the risk of SCD. This trial was registered at clinicaltrials.gov as NCT00000611.

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Relationship between 25-hydroxyvitamin D and all-cause and cardiovascular disease mortality.

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BACKGROUND: Observational studies have suggested a strong relationship between 25(OH)D and all-cause and cardiovascular disease mortality. A few studies also have described a nonlinear trend for this relationship in population subgroups, but less is known about this relationship in healthy adults. We examined the presence of a nonlinear relationship between 25(OH)D and all-cause and cardiovascular disease mortality among healthy adults. METHODS: We examined 10,170 participants (≥18 years of age) using National Health and Nutrition Examination Survey data (2001-2004) combined with National Death Index for vital status information through December 2006. Cox proportional hazard models with spline (single knot at population median of 25[OH]D) were fit to estimate hazard ratios (HRs) for all-cause and cardiovascular disease mortality for each 10-unit increase in serum 25(OH)D. Models were adjusted for demographic and conventional cardiovascular disease risk factors. RESULTS: Mean age of study participants was 46.6 (20.5) years, while median (interquartile range) 25(OH)D was 21 (15-27) ng/mL. After a median follow-up of 3.8 years (range 2.8-4.9), 509 all-cause and 184 cardiovascular diseases-related deaths were observed. In univariate analysis, 25(OH)D decreased hazards of all-cause (HR 0.59; 95% confidence interval [CI], 0.45-0.77) and cardiovascular disease (HR 0.56; 95% CI, 0.38-0.82) mortality below but not above its population median. In adjusted models, 25(OH)D retained the inverse association for all-cause (HR 0.54; 95% CI, 0.35-0.84) and cardiovascular disease (HR 0.50; 95% CI, 0.26-0.98) mortality below but not above its population median. CONCLUSIONS: We found an inverse association between 25(OH)D and all-cause and cardiovascular disease mortality in healthy adults with serum 25(OH)D levels of ≤21 ng/mL. Clinical trials for the primary prevention of cardiovascular disease with 25(OH)D supplementation may target healthy adults with serum 25(OH)D levels of ≤21 ng/mL to validate these findings.

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Prevalence, extent, and independent predictors of silent myocardial infarction.

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BACKGROUND: The phenomenon of silent myocardial infarction is poorly understood. METHODS: We aimed to evaluate the prevalence, extent, and independent predictors of silent myocardial infarction in 2 large independent cohorts of consecutive patients without a history of myocardial infarction referred for rest/stress myocardial perfusion single photon emission

computed tomography. There were 1621 patients enrolled in the derivation cohort and 338 patients in the validation cohort. Silent myocardial infarction was diagnosed in patients with a myocardial scar ≥5% of the left ventricle. RESULTS: In the derivation cohort, the prevalence of silent myocardial infarction was 23.3% (n = 377). The median infarct size was 10% (interquartile range [IQR] 5%-15%) of the left ventricle. The prevalence of silent myocardial infarction was 28.5% in diabetics and 21.5% in nondiabetics (P = .004). Diabetes mellitus was an independent predictor for the presence of silent myocardial infarction (odds ratio 1.5; 95% confidence interval, 1.1-1.9; P = .004). These findings were confirmed in the independent validation cohort. In the validation cohort, the prevalence of silent myocardial infarction was 26.3% (n = 89), while the prevalence was higher in diabetics (35.8%) than in nondiabetics (24%; P = .049). The median infarct size was 11.8% (IQR 5.9%-17.6%) of the left ventricle. Again, in logistic regression analysis, diabetes mellitus was a significant predictor of the presence of silent myocardial infarction. CONCLUSION: Silent myocardial infarctions are more common than previously thought. One of 4 patients with suspected coronary artery disease had experienced a silent myocardial infarction; the extent in average is 10% of the left ventricle, and it is more common in diabetics.

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Elevated resting heart rate, physical fitness and all-cause mortality: a 16-year follow-up in the Copenhagen Male Study.

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OBJECTIVE: To examine whether elevated resting heart rate (RHR) is an independent risk factor for mortality or a mere marker of physical fitness (VO2Max). METHODS: This was a prospective cohort study: the Copenhagen Male Study, a longitudinal study of healthy middle-aged employed men. Subjects with sinus rhythm and without known cardiovascular disease or diabetes were included. RHR was assessed from a resting ECG at study visit in 1985-1986. VO2Max was determined by the Åstrand bicycle ergometer test in 1970-1971. Subjects were classified into categories according to level of RHR. Associations with mortality were studied in multivariate Cox models adjusted for physical fitness, leisure-time physical activity and conventional cardiovascular risk factors. RESULTS: 2798 subjects were followed for 16 years. 1082 deaths occurred. RHR was inversely related to physical fitness ($p < 0.001$). Overall, increasing RHR was highly associated with mortality in a graded manner after adjusting for

physical fitness, leisure-time physical activity and other cardiovascular risk factors. Compared to men with RHR ≤ 50, those with RHR > 90 had an HR (95% CI) of 3.06 (1.97 to 4.75). With RHR as a continuous variable, risk of mortality increased with 16% (10-22) per 10 beats per minute (bpm). There was a borderline interaction with smoking (p = 0.07); risk per 10 bpm increase in RHR was 20% (12-27) in smokers, and 14% (4-24) in non-smokers. CONCLUSIONS: Elevated RHR is a risk factor for mortality independent of physical fitness, leisure-time physical activity and other major cardiovascular risk factors.

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PMID: 23595657 [PubMed - indexed for MEDLINE]

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Association between obstructive sleep apnea and pulmonary embolism.

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OBJECTIVES: To compare the prevalence of obstructive sleep apnea (OSA) in patients with pulmonary embolism (PE) with a sex-, age-, and body mass index (BMI)-matched, population-based control group and to assess the association between OSA and PE. METHODS: We performed a case-control study from October 1, 2006, through November 30, 2009. We included 107 patients with PE and a control group (n=102) without PE in University Hospitals Son Espases and La Paz in Spain. Variables included in the analysis were medical history, anthropometric variables (weight, height, BMI, and neck circumference), Epworth Sleepiness Scale score, home respiratory polygraphy, basic biochemical profile and hemogram, spirometry, and physical activity. RESULTS: The mean ± SD apnea-hypopnea index (AHI) was significantly higher in patients with PE than population controls (21.2±20.6 vs 11.5±15.9 h(-1); P<.001). The presence of an AHI greater than 5 h(-1) and hypersomnolence (Epworth Sleepiness Scale score ≥11) was more frequent in PE patients than in controls (14.0% vs 4.9%; P=.0002). A crude model analysis by several cutoffs revealed that the AHI was significantly associated with PE. After adjustment for age, sex, smoking, BMI, lung function, and all known PE risk factors, the odds ratio for PE was 3.7 (95% CI, 1.3-10.5; P=.01). CONCLUSION: A higher prevalence of OSA was detected in patients diagnosed as having acute PE than controls. This study identified a significant and independent association between OSA and PE.

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Am J Cardiol. 2013 Jul 1;112(1):14-20. doi: 10.1016/j.amjcard.2013.02.047. Epub 2013 Apr 8.

Exercise stress tests for detecting myocardial ischemia in asymptomatic patients with diabetes mellitus.

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The predominant cause of death in diabetes mellitus (DM) is coronary artery disease (CAD). Little is known about prevalence of silent ischemia in developing nations. We compared prevalence of silent ischemia in DM to a control group by exercise myocardial perfusion imaging (MPI) and electrocardiogram (ECG) in developing nations. The prospective multinational Ischemia Assessment with Exercise imaging in Asymptomatic Diabetes study recruited participants at 12 sites in Asia, Africa, and Latin America. DM participants were age- and gender-matched 2:1 to non-DM individuals with ≥1 CAD risk factor. Subjects underwent exercise tests that were interpreted in core labs in blinded fashion. The study included 392 DM and 205 control participants. Among participants with diagnostic ECGs, a similar proportion of DM and controls had ischemic ECG (15% vs 12%, p = 0.5). A significantly higher proportion of DM group had MPI abnormalities compared with controls (26% vs 14%, p <0.001). In participants with ischemia on MPI, only 17% had ischemic ECG, whereas in those without ischemia on MPI, 10% had ischemic ECG. In a multivariable model, DM was independently associated with abnormal MPI (odds ratio 2.1, 95% confidence interval 1.3-3.5, p = 0.004). Women were less likely to have ischemia by MPI than men (10% vs 30%, p <0.001) and concordance between ECG and MPI was much worse in women. In conclusion, in this large prospective study, asymptomatic DM participants had (1) more ischemia by exercise MPI than ECG, (2) more ischemia by MPI but not ECG than control group, and (3) ischemia by MPI was less in women than men.

PMID: 23578350 [PubMed - indexed for MEDLINE]

Heart. 2013 Jun;99(12):866-72. doi: 10.1136/heartjnl-2013-303640. Epub 2013 Apr 10.

Development and validation of a prediction rule for recurrent vascular events based on a cohort study of patients with arterial disease: the SMART risk score.

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OBJECTIVES: To enable risk stratification of patients with various types of arterial disease by the development and validation of models for prediction of recurrent vascular event risk based on vascular risk factors, imaging or both. DESIGN: Prospective cohort study. SETTING: University Medical Centre. PATIENTS: 5788 patients referred with various clinical manifestations of arterial disease between January 1996 and February 2010. MAIN OUTCOME MEASURES: 788 recurrent vascular events (ie, myocardial infarction, stroke or vascular death) that were observed during 4.7 (IQR 2.3 to 7.7) years' follow-up. RESULTS: Three Cox proportional hazards models for prediction of 10-year recurrent vascular event risk were developed based on age and sex in addition to clinical parameters (model A), carotid ultrasound findings (model B) or both (model C). Clinical parameters were medical history, current smoking, systolic blood pressure and laboratory biomarkers. In a separate part of the dataset, the concordance statistic of model A was 0.68 (95% CI 0.64 to 0.71), compared to 0.64 (0.61 to 0.68) for model B and 0.68 (0.65 to 0.72) for model C. Goodness-of-fit and calibration of model A were adequate, also in separate subgroups of patients having coronary, cerebrovascular, peripheral artery or aneurysmal disease. Model A predicted < 20% risk in 59% of patients, 20-30% risk in 19% and > 30% risk in 23%. CONCLUSIONS: Patients at high risk for recurrent vascular events can be identified based on readily available clinical characteristics.

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Is subclinical hypothyroidism a cardiovascular risk factor in the elderly?

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CONTEXT: The negative impact of subclinical hypothyroidism (sHT) on cardiovascular risk, widely recognized in young adults (aged <55-60 y), is still debated in the elderly (>65 y), especially in the oldest olds (>80 y). EVIDENCE ACQUISITION: We searched Medline for reports published with the following search terms: "hypothyroidism," "subclinical

hypothyroidism," "ageing," "elderly," "L-thyroxin," "thyroid," "guidelines," "treatment," "quality of life," "cardiovascular risk," "heart failure," "coronary heart disease" (CHD), "atherosclerosis," and "endothelial dysfunction." We limited our search to reports in English published after 1980, although we incorporated some reports published before 1980. We supplemented the search with records from personal files, textbooks, and relevant articles. Analyzed parameters included the epidemiology of thyroid failure, the effect of thyroid hormone on the aging process, cardiovascular function, and CHD risk factors. We also included the potential benefits of L-T4 therapy on the quality of life, cardiovascular events, and survival. EVIDENCE SYNTHESIS: TSH levels increase with age, even in older people without thyroid disease. Most longitudinal studies show an increased risk for CHD events and mortality in sHT participants. This increase is less evident in the elderly, mainly in cases of serum TSH values above 10 mIU/L. Lower mortality rate in a cohort of the oldest olds (>85 y) has been reported. CONCLUSIONS: sHT in older people should be not regarded as a unique condition, and moderately old patients (aged <70-75 y) could be considered clinically similar to the adult population, albeit with a higher optimal TSH target value. Conversely, the oldest old subjects should be carefully followed with a wait-and-see strategy, generally avoiding hormonal treatment. The decision to treat elderly people is still an unresolved clinical challenge--first, due to a lack of appropriately powered randomized controlled trials of L-T4 in sHT patients, examining cardiovascular hard endpoints in various classes of age; and second, because of the negative effects of possible overtreatment.

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Development and validation of a cardiovascular risk assessment model in patients with established coronary artery disease.

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Appropriate risk stratification of patients with established, stable coronary artery disease could contribute to the prevention of recurrent cardiovascular events. The purpose of the present study was to develop and validate risk prediction models for various cardiovascular end points in the EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) database, consisting of 12,218 patients with established coronary artery disease, with a median follow-up of 4.1 years. Cox proportional hazards models were used for model development. The end points examined were cardiovascular mortality, noncardiovascular

mortality, nonfatal myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, resuscitated cardiac arrest, and combinations of these end points. The performance measures included Nagelkerke's R^2, time-dependent area under the receiver operating characteristic curves, and calibration plots. Backward selection resulted in a prediction model for cardiovascular mortality (464 events) containing age, current smoking, diabetes mellitus, total cholesterol, body mass index, previous myocardial infarction, history of congestive heart failure, peripheral vessel disease, previous revascularization, and previous stroke. The model performance was adequate for this end point, with a Nagelkerke R^2 of 12%, and an area under the receiver operating characteristic curve of 0.73. However, the performance of models constructed for nonfatal and combined end points was considerably worse, with an area under the receiver operating characteristic curve of about 0.6. In conclusion, in patients with established coronary artery disease, the risk of cardiovascular mortality during longer term follow-up can be adequately predicted using the clinical characteristics available at baseline. However, the prediction of nonfatal outcomes, both separately and combined with fatal outcomes, poses major challenges for clinicians and model developers.

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Relation between transient or persistent acute kidney injury and long-term mortality in patients with myocardial infarction.

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Limited information is available regarding the impact of acute kidney injury (AKI) during hospitalization on clinical outcomes after myocardial infarction (MI), and the effect of transient kidney injury (KI) on long-term mortality has not been validated. We retrospectively analyzed 2,289 patients diagnosed with MI. AKI patients were classified into a transient KI group and a persistent KI group based on serum creatinine levels at discharge. The end point of the study was 3-year mortality after MI. We included 2,110 patients of whom 237 patients (11%) developed AKI during hospitalization. Of these 237 patients, 154 (65%) had transient KI, and 83 (35%) had persistent KI. Multivariate analysis showed that age, left ventricular ejection fraction, estimated glomerular filtration rate on admission, and Killip class were significantly associated with developing AKI during hospitalization. The adjusted hazard ratios for 3-year mortality were 1.71 (95% confidence interval: 1.08-2.70) for AKI patients with transient KI and 2.21 (95%

confidence interval: 1.34-3.64) for AKI patients with persistent KI, compared with no AKI. In conclusion, AKI was associated with an increased risk of death for patients who experienced MIs and survived during hospitalization. Although renal function had completely recovered in many AKI patients at discharge, these transient KI patients are also at a great risk of death after MI.

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Systolic blood pressure and cardiovascular outcomes during treatment of hypertension.

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OBJECTIVE: Randomized controlled trials in hypertension demonstrate cardiovascular benefits when systolic blood pressures are reduced from higher values to<160 mm Hg. The value of lower targets has not been fully defined, although major guidelines recommend achieving systolic blood pressures of<140 mm Hg. This study was conducted to explore cardiovascular outcomes at differing on-treatment blood pressure levels. METHODS: On the basis of a prespecified plan to explore relationships between clinical outcomes and systolic blood pressures, the pooled cohort of high-risk hypertensive patients (N=10,705) in the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension trial were divided into 4 strata of systolic blood pressure levels: >140 mm Hg, 130 to <140 mm Hg, 120 to <130 mm Hg, and 110 to <120 mm Hg. The primary end point was cardiovascular death or nonfatal myocardial infarction or stroke. Outcomes comparisons between the blood pressure groups were by Cox regression. RESULTS: The mean patient age was 68 years, and the study duration was 35.7 months. The primary end point occurred in 171 of 3429 patients (5.0%) with systolic blood pressure in the 10 mm Hg range<140 and in 179 of 2354 patients (7.6%) with systolic blood pressure≥140 mm Hg (hazard ratio [HR], 0.62; 95% CI, 0.50-0.77; P=.0001). Likewise, cardiovascular death decreased by 36% (P=.0147), total myocardial infarction (fatal+nonfatal) decreased by 37% (P=.0028), and stroke decreased by 47% (P=.0002). Cardiovascular event rates in those with systolic blood pressure<130 mm Hg were not different from those with systolic blood pressure<140 mm Hg. However, compared with systolic blood pressure<130 mm Hg, stroke incidence in those with systolic blood pressure<120 mm Hg was lower (HR, 0.60; 95% CI, 0.35-1.01; P=.0529), but myocardial function was higher (HR, 1.52; 95% CI, 1.00-2.29; P=.0437), as were composite coronary events (myocardial infarction, hospitalized angina, or sudden death) (HR, 1.63; 95% CI, 1.18-

2.24; P=.0023). The renal end point of a sustained>50% increase in serum creatinine was significantly lower in those with systolic blood pressure<140 mm Hg than in any of the other higher or lower blood pressure ranges. CONCLUSIONS: In high-risk hypertensive patients, major cardiovascular events are significantly lower in those with systolic blood pressures<140 mm Hg and<130 mm Hg than in those with levels>140 mm Hg. There are stroke benefits at levels<120 mm Hg, but they are offset by increased coronary events. Renal function is best protected in the 130 to 139 mm Hg range.

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Competing cardiovascular outcomes associated with subclinical atherosclerosis (from the Multi-Ethnic Study of Atherosclerosis).

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Subclinical atherosclerosis measured by coronary artery calcium (CAC) is associated with increased risk for multiple cardiovascular disease (CVD) outcomes and non-CVD death simultaneously. The aim of this study was to determine the competing risks of specific CVD events and non-CVD death associated with varying burdens of subclinical atherosclerosis. A total of 3,095 men and 3,486 women from the Multi-Ethnic Study of Atherosclerosis (MESA), aged 45 to 84 years, from 4 ethnic groups were included. Participants were stratified by CAC score (0, 1 to 99, and ≥100). Competing Cox models were used to determine competing cumulative incidences and hazard ratios within a group (e.g., those with CAC scores ≥100) and hazard ratios for specific events between groups (e.g., CAC score ≥100 vs 0). Risks were compared for specific CVD events and also against non-CVD death. In women, during a mean follow-up period of 7.1 years, the hazard ratios for any CVD event compared with a non-CVD death occurring first for CAC score 0 and CAC score ≥100 were 1.40 (95% confidence interval 0.97 to 2.04) and 3.07 (95% confidence interval 2.02 to 4.67), respectively. Coronary heart disease was the most common first CVD event type at all levels of CAC, and coronary heart disease rates were 9.5% versus 1.6% (hazard ratio 6.24, 95% confidence interval 3.99 to 9.75) for women with CAC scores ≥100 compared with CAC scores of 0. Similar results were observed in men. In conclusion, at all levels of CAC, coronary heart disease was the most common first CVD event, and this analysis represents a novel approach to understanding the temporal sequence of cardiovascular events associated with atherosclerosis.

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Urinary and plasma magnesium and risk of ischemic heart disease.

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BACKGROUND: Previous studies on dietary magnesium and risk of ischemic heart disease (IHD) have yielded inconsistent results, in part because of a lack of direct measures of actual magnesium uptake. Urinary excretion of magnesium, an indicator of dietary magnesium uptake, might provide more consistent results. OBJECTIVE: The objective was to investigate whether urinary magnesium excretion and plasma magnesium are associated with IHD risk. DESIGN: We examined 7664 adult participants free of known cardiovascular disease in the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study-a prospective population-based cohort study. Urinary magnesium excretion was measured in 2 baseline 24-h urine collections. RESULTS: Mean ± SD urinary magnesium excretion was 4.24 ± 1.65 mmol/24 h for men and 3.54 ± 1.40 mmol/24 h for women. During a median follow-up of 10.5 y (IQR: 9.9-10.8 y), 462 fatal and nonfatal IHD events occurred. After multivariable adjustment, urinary magnesium excretion had a nonlinear relation with IHD risk (P-curvature = 0.01). The lowest sex-specific quintile (men: <2.93 mmol/24 h; women: <2.45 mmol/24 h) had an increased risk of fatal and nonfatal IHD (multivariable HR: 1.60; 95% CI: 1.28, 2.00) compared with the upper 4 quintiles of urinary magnesium excretion. A similar increase in risk of the lowest quintile was observed for mortality related to IHD (HR: 1.70; 95% CI: 1.10, 2.61). No associations were observed between circulating magnesium and risk of IHD. CONCLUSIONS: Low urinary magnesium excretion was independently associated with a higher risk of IHD incidence. An increased dietary intake of magnesium, particularly in those with the lowest urinary magnesium, could reduce the risk of IHD.

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Cardiovascular risk among stable individuals suspected of having coronary artery disease with no modifiable risk factors: results from an international multicenter study of 5262 patients.

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PURPOSE: To assess the prevalence, extent, severity, and risk of coronary artery disease (CAD) in patients suspected of having CAD but with no medically modifiable risk factors. MATERIALS AND METHODS: Institutional review board approval or waiver of consent was obtained at each center. This study was HIPAA compliant. From an international multicenter cohort study of 27 125 subjects undergoing coronary computed tomographic (CT) angiography from 12 centers, 5262 patients without known CAD and without modifiable risk factors were identified. CAD severity was defined as none (0%), mild (1%-49%), or obstructive (≥ 50%) on a per-patient, per-vessel, and per-segment basis. CAD presence, extent, and severity were related to incidence of major adverse cardiovascular event (MACE) by using Cox proportional hazards models. RESULTS: At a mean follow-up of 2.3 years ± 1.2 (standard deviation), MACE occurred in 106 patients. CAD was common for nonobstructive (n = 1452, 27%) and obstructive (n = 629, 12%) CAD. In risk-adjusted analysis, per-patient obstructive CAD (hazard ratio [HR], 6.64; 95% confidence interval [CI]: 3.68, 12.00; P ≤ .001) was related to MACE. MACE was associated with a dose-response relationship to the number of vessels exhibiting obstructive CAD, increasing risk for obstructive one-vessel (HR, 6.11; 95% CI: 3.22, 11.6; P ≤ .001), two-vessel (HR, 5.86; 95% CI: 2.75, 12.5; P ≤ .0001), or three-vessel or left main (HR, 11.69; 95% CI: 5.38, 25.4; P ≤ .001) CAD. The increased hazard for MACE of obstructive disease holds true for symptomatic (HR, 11.9; 95% CI: 4.81, 29.6; P ≤ .001) and asymptomatic (HR, 6.3; 95% CI: 2.4, 16.7; P ≤ .001) patients. No CAD at coronary CT angiography was associated with a low annualized MACE rate: 0.31% versus 2.06% with obstructive disease. CONCLUSION: Among individuals suspected of having CAD but without modifiable risk factors, CAD is common, with significantly increased hazards for MACE and mortality.

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Cardiovascular risk factors in women who had hypertensive disorders late in pregnancy: a cohort study.

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OBJECTIVE: The purpose of this study was to determine cardiovascular risk factors in women with a history of hypertensive pregnancy disorders at term (HTP) 2.5 years after pregnancy. STUDY DESIGN: In a multicenter cohort study in The Netherlands from June 2008 through November 2010, cardiovascular risk factors were compared between women with a history of HTP (HTP cohort, n = 306) and women with a history of normotensive pregnancies at term (NTP cohort, n = 99). HTP women had participated in a randomized, longitudinal trial assessing the effectiveness of induction of labor in women with hypertensive pregnancy disorders at term. All women were assessed 2.5 years after pregnancy for blood pressure, anthropometrics, glucose, glycosylated hemoglobin, insulin, homeostatic model assessment score, total cholesterol, high-density lipoprotein cholesterol, triglycerides, high-sensitivity C-reactive protein, and microalbumin and metabolic syndrome. RESULTS: After a mean follow-up period of 2.5 years, hypertension (HTP, 34%; NTP, 1%; P < .001) and metabolic syndrome (HTP, 25%; NTP, 5%; P < .001) were more prevalent in HTP women compared with NTP women. HTP women had significantly higher systolic and diastolic blood pressure, higher body mass index, and higher waist circumference. Glucose, glycosylated hemoglobin, insulin, homeostatic model assessment score, total cholesterol, triglycerides, and high-sensitivity C-reactive protein levels were significantly higher and high-density lipoprotein cholesterol was significantly lower in HTP women. CONCLUSION: In women with a history of HTP, hypertension and metabolic syndrome are more common, and they have higher levels of biochemical cardiovascular risk factors 2.5 years after pregnancy.

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sRAGE and risk of diabetes, cardiovascular disease, and death.

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Advanced glycation end products (AGEs) and their receptors are strongly implicated in the development of diabetes complications. When stimulated by AGEs, the receptors for AGEs (RAGEs) induce inflammation and are thought to fuel disease progression. Soluble circulating RAGE (sRAGE) may counteract the detrimental effects of RAGE. We measured sRAGE in stored plasma from a random sample of 1,201 participants in the Atherosclerosis Risk in Communities (ARIC) Study who were aged 47-68 years, had normal kidney function, and had no history of cardiovascular disease. In cross-sectional analyses, black race, male sex, higher BMI, and higher C-reactive protein were independently associated with low sRAGE. The racial difference was striking, with blacks approximately three times more likely to have low sRAGE compared with whites even after adjustment. During ~18 years of follow-up, there were 192 incident coronary heart disease events, 53 ischemic strokes, 213 deaths, and 253 cases of diabetes (among the 1,057 persons without diabetes at baseline). In multivariable Cox models comparing risk in the first quartile with that in the fourth quartile of baseline sRAGE, low levels of sRAGE were significantly associated with risk of diabetes (hazard ratio 1.64 [95% CI 1.10-2.44]), coronary heart disease (1.82 [1.17-2.84]), and mortality (1.72 [1.11-2.64]) but not ischemic stroke (0.78 [0.34-1.79]). In conclusion, we found that low levels of sRAGE were a marker of future chronic disease risk and mortality in the community and may represent an inflammatory state. Racial differences in sRAGE deserve further examination.

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White matter hyperintensities: use of aortic arch pulse wave velocity to predict volume independent of other cardiovascular risk factors.

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PURPOSE: To evaluate the relationship between pulse wave velocity (PWV) from the aortic arch and subsequent cerebral microvascular disease independent of other baseline cardiovascular risk factors among the participants in the multiethnic Dallas Heart Study. MATERIALS AND METHODS: Each subject gave written consent to participate in this HIPAA-compliant, institutional review board-approved prospective study. Aortic arch PWV was measured with phase-contrast magnetic resonance (MR) imaging in a population sample (n = 1270) drawn from the probability-based Dallas Heart Study. Seven years later, the volume of white matter hyperintensities (WMHs) was determined from brain MR images. Linear regression was conducted with aortic arch PWV, 15 other cardiovascular risk factors, and age, sex, and ethnicity included as predictors of WMH. The authors implemented a smoothly clipped absolute deviation-penalized variable selection method to evaluate an optimal predictive risk factor model. RESULTS: Aortic arch PWV helped predict WMH volume independent of the other demographic and cardiovascular risk factors (regression coefficient: 0.29; standard error: 0.06; 95% confidence interval: 0.17, 0.42; P < .0001). The optimal predictor variables of subsequent WMH volume adjusted for sex and ethnicity included aortic arch PWV, age, systolic blood pressure, hypertension treatment, and congestive heart failure. The authors estimated that a 1% increase in aortic arch PWV (in meters per second) is related to a 0.3% increase in subsequent WMH volume (in milliliters) when all other variables in the model are held constant. CONCLUSION: Aortic arch PWV measured with phase-contrast MR imaging is a highly significant independent predictor of subsequent WMH volume, with a higher standardized effect than any other cardiovascular risk factor assessed except for age. In an optimal predictive model of subsequent WMH burden, aortic arch PWV provides a distinct contribution along with systolic blood pressure, hypertension treatment, congestive heart failure, and age.

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A model for predicting the risk of carotid artery disease.

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OBJECTIVE: To develop a model for the identification of individuals at risk for carotid stenosis (CS) that could be useful in a clinical setting when trying to decide whether screening is worthwhile. BACKGROUND: Evidence that aggressive medical therapy and life style changes reduce the risk of stroke in individuals with CS is increasing and has led to a renewed interest in screening for CS. METHODS: Data on demographics and risk factors were obtained from 2,885,257 individuals who had carotid Duplex scans by Life Line Screening between 2003 and 2008. Multivariable logistic regression analysis was used to identify independent risk factors for CS (>50% stenosis). A scoring system was developed where risk factors were assigned a weighted score. Predictive ability was assessed by calculating C statistics and r2. RESULTS: In the screened cohort, 71,004 patients (2.4%) had CS. Independent risk factors include advanced age, smoking, peripheral arterial disease, high blood pressure, coronary artery disease, diabetes, cholesterol, and abdominal aortic aneurysm. African Americans, Asians, and Hispanics had reduced risk than whites. Exercise and consumption of fruit, vegetables, and nuts had a modest protective effect. A predictive scoring system was created that identifies individuals with CS more efficiently (C statistic = 0.753) than previously published models. CONCLUSIONS: We provide a model that enables identification of individuals who have a high probability of having CS. This model can be helpful in designing targeted screening programs that are cost-effective.

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Cardiometabolic risk after weight loss and subsequent weight regain in overweight and obese postmenopausal women.

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BACKGROUND: Little is known about the effect of intentional weight loss and subsequent weight regain on cardiometabolic risk factors in older adults. The objective of this study was to determine how cardiometabolic risk factors change in the year following significant intentional weight loss in postmenopausal women, and if observed changes were affected by weight and fat regain. METHODS: Eighty, overweight and obese, older women (age = 58.8±5.1 years) were followed through a 5-month weight loss intervention and a subsequent 12-month nonintervention period. Body weight/composition and cardiometabolic risk factors (blood pressure; total, high-density lipoprotein, and low-density lipoprotein cholesterol; triglycerides;

fasting glucose and insulin; and Homeostatic Model Assessment of Insulin Resistance) were analyzed at baseline, immediately postintervention, and 6- and 12-months postintervention. RESULTS: Average weight loss during the 5-month intervention was 11.4±4.1kg and 31.4% of lost weight was regained during the 12-month follow-up. On average, all risk factor variables were significantly improved with weight loss but regressed toward baseline values during the year subsequent to weight loss. Increases in total cholesterol, triglycerides, glucose, insulin, and Homeostatic Model Assessment of Insulin Resistance during the postintervention follow-up were significantly ($p < .05$) associated with weight and fat mass regain. Among women who regained weight, model-adjusted total cholesterol (205.8±4.0 vs 199.7±2.9mg/dL), low-density lipoprotein cholesterol (128.4±3.4 vs 122.7±2.4mg/dL), insulin (12.6±0.7 vs 11.4±0.7mg/dL), and Homeostatic Model Assessment of Insulin Resistance (55.8±3.5 vs 50.9±3.7mg/dL) were higher at follow-up compared with baseline. CONCLUSIONS: For postmenopausal women, even partial weight regain following intentional weight loss is associated with increased cardiometabolic risk. Conversely, maintenance of or continued weight loss is associated with sustained improvement in the cardiometabolic profile.

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The association between the body mass index and 4-year all-cause mortality in older hospitalized patients.

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BACKGROUND: Association between body mass index (BMI) and long-term mortality is poorly studied in older hospitalized populations. METHODS: The researchers prospectively studied the impact of the BMI, comorbidities, and malnutrition on long-term mortality in 444 patients (mean age 85.3±6.7 years; 74.0% women) receiving geriatric inpatient care. All-cause mortality was determined using simple and multiple Cox proportional hazard models. RESULTS: Higher BMI was associated with a higher prevalence of diabetes, hypertension, and heart failure, but with a lower prevalence of malignancies. Four-year all-cause mortality was inversely associated with a BMI greater than or equal to 30kg/m(2) (hazard ratio = 0.59, $p = .037$) and positively associated with age, male gender, several individual comorbidities, and the global disease load determined by the Cumulative Illness Rating scale. The inverse association between a BMI greater than or

equal to 30 and mortality remained significant after adjustment for age, gender, smoking, individual comorbidities (including heart failure and malignancies), Cumulative Illness Rating scale scores, and malnutrition parameters (hazard ratio = 0.52, p = .015). One-year mortality was associated with the Cumulative Illness Rating scale score but not with BMI categories. There were no survival differences between patients in low (<20.0) and intermediate (20.0-24.9 and 25.0-29.9) BMI categories. CONCLUSIONS: A BMI greater than or equal to 30 is associated with better long-term survival in hospitalized older patients, even after extensive adjustment for comorbidities, malnutrition, and smoking. Conversely, a low BMI (<20-25) is not associated with excess mortality, likely due to the overriding impact of multiple comorbidities. The researchers' observations have important implications for the mortality risk stratification in older high-risk patients.

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The impact of CHADS2 score on late stroke after the Cox maze procedure.

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OBJECTIVE: The Heart Rhythm Society, European Heart Rhythm Association, and European Cardiac Arrhythmia Society jointly recommend indefinite warfarin anticoagulation in patients with CHADS2 (congestive heart failure, hypertension, age, diabetes, and stroke) score of at least 2 who have undergone ablation for atrial fibrillation. This study determined the impact of CHADS2 score on risk of late stroke or transient ischemic attack after the performance of a surgical Cox maze procedure. METHODS: A retrospective review of 433 patients who underwent a Cox maze procedure at our institution was conducted. Three months after surgery, warfarin was discontinued regardless of CHADS2 score if the patient showed no evidence of atrial fibrillation, was off antiarrhythmic medications, and had no other indication for anticoagulation. A follow-up questionnaire was used to determine whether any neurologic event had occurred since surgery. RESULTS: Follow-up was obtained for 90% of the study group (389/433) at a mean of 6.6 ± 5.0 years. Among these patients, 32% (125/389) had a CHADS2 score of at least 2, of whom only 40% (51/125) remained on long-term warfarin after surgery. Six patients had late neurologic events (annualized risk of 0.2%). Neither CHADS2 score nor warfarin anticoagulation was significantly associated with the occurrence of late neurologic

events. Among the individual CHADS2 criteria, both diabetes mellitus and previous stroke or transient ischemic attack were predictive of late neurologic events. CONCLUSIONS: The risk of stroke or transient ischemic attack in patients after a surgical Cox maze procedure was low and not associated with CHADS2 score or warfarin use. Given the known risks of warfarin, we recommend discontinuation of anticoagulation 3 months after the procedure if the patient has no evidence of atrial fibrillation, has discontinued antiarrhythmic medications, and is without any other indication for systemic anticoagulation.

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