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Hormones (Athens). 2016 Apr;15(2):170-85.

Cardiovascular safety of type 2 diabetes medications: Review of existing literature and clinical implications.

Paredes S, Matta-Coelho C, Monteiro AM, Brás A, Marques O, Alves M, Ribeiro L.

Type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD) and the cardiovascular effect of antidiabetic drugs are today critical medical issues, with the prevalence of T2DM in particular showing a steep increase worldwide, mainly due to unhealthy lifestyle habits. T2DM in association with obesity and other cardiovascular risk factors, results in the development of CVD, the leading cause of morbidity and mortality in patients with T2DM. Thus, treatment of T2DM is an individualized and complex challenge in which targeting cardiovascular risk factors is an important component in the decision making. Given the cardiovascular adverse events associated with rosiglitazone, both the Food and Drug Administration and the European Medicines Agency currently require the demonstration of cardiovascular safety of new antidiabetic drugs. Consequently, clinical trials to guarantee their cardiovascular safety are now obligatory. This review aims to summarize the available evidence on the cardiovascular effects and safety of the major drugs used in T2DM treatment and also to provide an overview of upcoming and ongoing clinical trials in this field. Our belief is that this review will be of substantial assistance to all medical doctors who are treating diabetic patients, namely primary care physicians, internal medicine doctors, endocrinologists, diabetologists and less well experienced personnel such as young doctors in training.

Atherosclerosis. 2016 Jun 23; 251:206-212.

Impact of adipose tissue composition on cardiovascular risk assessment in patients with stable coronary artery disease.

Kunimura A, Ishii H, Uetani T, Harada K, Hirayama K, Harata S, Shibata Y, Kawashima K, Shimbo Y, Takayama Y, Tatami Y, Kawamiya T, Osugi N, Ota T, Yamamoto D, Okumura N, Suzuki S, Amano T, Murohara T.

BACKGROUND AND AIMS: Visceral adipose tissue (VAT), unlike subcutaneous adipose tissue (SAT), is highly correlated with cardiovascular risk factors. This study aimed to evaluate the predictive value of adipose tissue composition, as measured by computed tomography, for cardiovascular events in patients with stable coronary artery disease.

METHODS: 357 consecutive patients who underwent 64-slice computed tomography and elective percutaneous coronary intervention (PCI) were recruited. The ratio of visceral to subcutaneous adipose tissue (VAT/SAT) was calculated. Patients were divided into three groups in accordance with VAT/SAT (low VAT/SAT, <0.55 [<25th percentile]; moderate VAT/SAT, 0.55-1.03 [25th-75th percentile]; high VAT/SAT, ≥1.03 [≥75th percentile]). The investigated risk factors were hypertension, hyperglycaemia, and dyslipidaemia. We analysed the incidence of major adverse cardiovascular events (MACE), defined as the composite of cardiac death, myocardial infarction, and any revascularization.

RESULTS: The rate of patients with two or more concomitant risk factors was significantly higher in the high VAT/SAT group (p = 0.006). During 1480 person-years, 109 events were documented. There was a significant association between the incidence of MACE and VAT/SAT, with the worst event-free survival rate in the high VAT/SAT group (log-rank, p = 0.01). In Cox analysis, the hazard ratio of high VAT/SAT for MACE was 2.72 (95% confidence interval 1.04-7.09, p = 0.04) compared with the low VAT/SAT after adjustment for confounding factors.

CONCLUSIONS: Increased VAT/SAT is independently associated with the incidence of MACE, indicating that adipose tissue composition is a useful predictor of cardiovascular outcome, after elective PCI.

JAMA Intern Med. 2016 Jun 27.

Association Between Socioeconomic Status and Mortality, Cardiovascular Disease, and Cancer in Patients With Type 2 Diabetes.

Rawshani A, Svensson AM, Zethelius B, Eliasson B, Rosengren A, Gudbjörnsdottir S.

Importance: The association between socioeconomic status and survival based on all-cause, cardiovascular (CV), diabetes-related, and cancer mortality in type 2 diabetes has not been examined in a setting of persons with equitable access to health care with adjustment for important confounders. Objective: To determine whether income, educational level, marital status, and country of birth are independently associated with all-cause, CV, diabetes-related, and cancer mortality in persons with type 2 diabetes. Design, Setting, and Participants: A study including all 217 364 individuals younger than 70 years with type 2 diabetes in the Sweden National Diabetes Register (January 1, 2003, to December 31, 2010) who were monitored through December 31, 2012, was conducted. A Cox proportional hazards regression model with up to 17 covariates was used for analysis. Main Outcomes and Measures: All-cause, CV, diabetes-related, and cancer mortality. Results: Of the 217 364 persons included in the study, mean (SD) age was 58.3 (9.3) years and 130 839 of the population (60.2%) was male. There were a total of 19 105 all-cause deaths with 11 423 (59.8%), 6984 (36.6%), and 6438 (33.7%) CV, diabetes-related, or cancer deaths, respectively. Compared with being single, hazard ratios (HRs) for married individuals, determined using fully adjusted models, for all-cause, CV, and diabetes-related mortality were 0.73 (95% CI, 0.70-0.77), 0.67 (95% CI, 0.63-0.71), and 0.62 (95% CI, 0.57-0.67), respectively. Marital status was not associated with overall cancer mortality, but married men had a 33% lower risk of prostate cancer mortality compared with single men, with an HR of 0.67 (95% CI, 0.50-0.90). Comparison of HRs for the lowest vs highest income quintiles for all-cause, CV, diabetes-related, and cancer mortality were 1.71 (95% CI, 1.60-1.83), 1.87 (95% CI, 1.72-2.05), 1.80 (95% CI, 1.61-2.01), and 1.28 (95% CI, 1.14-1.44), respectively. Compared with native Swedes, HRs for all-cause, CV, diabetes-related, and cancer mortality for non-Western immigrants were 0.55 (95% CI, 0.48-0.63), 0.46 (95% CI, 0.38-0.56), 0.38 (95% CI, 0.29-0.49), and 0.72 (95% CI, 0.58-0.88), respectively, and these HRs were virtually unaffected by covariate adjustment. Hazard ratios for those with a college/university degree compared with 9 years or less of education were 0.85 (95% CI, 0.80-0.90), 0.84 (95% CI, 0.78-0.91), and 0.84 (95% CI, 0.76-0.93) for all-cause, CV, and cancer mortality, respectively. Conclusions and Relevance: Independent of risk factors, access to health care, and use of health care, socioeconomic status is a powerful predictor of all-cause and CV mortality but was not as strong as a predictor of death from cancer.

Arch Toxicol. 2016 Jun 29. [Epub ahead of print]

Phtalates: new cardiovascular health disruptors?

Muscogiuri G, Colao A.

Phtalates are commonly found in several household products such as food packaging, furniture and toys. Humans are exposed to phtalates through different ways such as inhalation, ingestion and dermal contact. Due to the abundance of plastic in our society, the exposure to phtalates is ubiquitous. A growing body of evidence investigated the association of phtalate exposure with cardiovascular risk factors, i.e., obesity, type 2 diabetes and hypertension. Phtalates are thought to contribute to obesity through their binding and activation of PPARγ receptor that in turn results in the upregulation of adipocyte production. Phtalates are also known to interfere with insulin signaling and to increase oxidative stress. All these mechanisms contribute to the onset of insulin resistance. Recent evidences support a role of phtalates in the pathogenesis of atherosclerosis and hypertension. Thus, the aim of this communication was to summarize the current evidences dealing with the association of phtalates and cardiovascular risk factors.

Curr Vasc Pharmacol. 2016 Jun 24. [Epub ahead of print]

The Role of Inflammatory Biomarkers in the Detection and Therapy of Atherosclerotic Disease.

Poredos P, Jezovnik MK.

The estimation of risk for atherosclerotic cardiovascular (CV) events based only on the presence of classical risk factors is often insufficient. Therefore, efforts have been made to find markers that indicate the presence of preclinical or clinical disease. Inflammation mediates all stages of the disease, from initiation to the thrombotic complications of atherosclerosis. Raised levels of several circulating markers, particularly inflammatory mediators, have been reported in subjects with atherosclerosis. Increased risk for CV events is associated with increased levels of cytokines, cell-adhesion molecules, P-selectin and E-selectin, and acute phase reactants, such a high-sensitivity C-reactive protein and serum amyloid-A. Elevation of some of these markers predicts the outcomes of patients with acute coronary syndromes. However, because of their non-specificity, these biomarkers represent only a moderate added predicting value after considering conventional CV risk factors. Consequently, recent research has focused on the detection of vulnerable plaque, using vascular bed-specific biomarkers that can help identify individuals at highest risk and help guide how to intervene to prevent CV events. Considerable progress in the understanding of the role of the inflammation in atherogenesis has opened new possibilities for the management of atherosclerosis. Recently new drugs mediating the direct inhibition of circulating markers of inflammation were developed. These drugs could provide a novel therapeutic approach and further enhance the understanding of the role of inflammation in atherosclerosis.

J Am Heart Assoc. 2016 Jun 29;5(7).

Lifetime Risk for Sudden Cardiac Death in the Community.

Bogle BM(1), Ning H, Mehrotra S, Goldberger JJ, Lloyd-Jones DM.

BACKGROUND: Sudden cardiac death (SCD) is a leading cause of death in the United States and often occurs without previous cardiac symptoms. Lifetime risk for SCD and the influence of established risk factors on lifetime risks for SCD have not been estimated previously.
METHODS AND RESULTS: We followed Framingham Heart Study participants who were free of cardiovascular disease before their earliest examination. SCD was defined as death attributed to coronary heart disease within 1 hour of symptom onset without another probable cause of death, as adjudicated by a panel of 3 physicians. Lifetime risk for SCD was estimated to 85 years of age for men and women, with death attributed to other causes as the competing risk, and stratified by risk factor levels. We followed 2294 men and 2785 women for 160 396 person-years; 375 experienced SCD. At 45 years of age, lifetime risks were 10.9% (95% CI, 9.4-12.5) for men and 2.8% (95% CI, 2.1-3.5) for women. Greater aggregate burden of established risk factors was associated with a higher lifetime risk for SCD. Categorizing men and women solely by blood pressure levels resulted in a clear stratification of lifetime risk curves.
CONCLUSIONS: We present the first lifetime risk estimates for SCD. Greater aggregate risk factor burden, or blood pressure level alone, is associated with higher lifetime risks for SCD. This high risk of premature death attributed to SCD (approximately 1 in 9 men and 1 in 30 women) should serve as a motivator of public health efforts in preventing and responding to SCD.

Hypertension. 2016 Jun 27. [Epub ahead of print]

Prehypertension During Normotensive Pregnancy and Postpartum Clustering of Cardiometabolic Risk Factors: A Prospective Cohort Study.

Lei Q, Zhou X, Zhou YH, Mai CY, Hou MM, Lv LJ, Duan DM, Wen JY, Lin XH, Wang PP, Ling XB, Li YM, Niu JM.

The nonstratification of blood pressure (BP) levels may underestimate future cardiovascular risk in pregnant women who present with BP levels in the range of prehypertension (120-139/80-89 mm Hg). We prospectively evaluated the relationship between multiple antepartum BP measurements (from 11(+0) to 13(+6) weeks' gestation to term) and the occurrence of postpartum metabolic syndrome in 507 normotensive pregnant women after a live birth. By using latent class growth modeling, we identified the following 3 distinctive diastolic BP (DBP) trajectory groups: the low-J-shaped group (34.2%; DBP from 62.5±5.8 to 65.0±6.8 mm Hg), the moderate-U-shaped group (52.6%; DBP from 71.0±5.9 to 69.8±6.2 mm Hg), and the elevated-J-shaped group (13.2%; DBP from 76.2±6.7 to 81.8±4.8 mm Hg). Notably, the elevated-J-shaped trajectory group had mean DBP and systolic BP levels within the range of prehypertension from 37(+0) and 26(+0) weeks of pregnancy, respectively. Among the 309 women who completed the ≈1.6 years of postpartum follow-up, the women in the elevated-J-shaped group had greater odds of developing postpartum metabolic syndrome (adjusted odds ratio, 6.55; 95% confidence interval, 1.79-23.92; P=0.004) than the low-J-shaped group. Moreover, a parsimonious model incorporating DBP (membership in the elevated-J-shaped group but not in the DBP prehypertension group as identified by a single measurement) and elevated levels of fasting glucose (>4.99 mmol/L) and triglycerides (>3.14 mmol/L) at term was developed, with good discrimination and calibration for postpartum metabolic syndrome (c-statistic, 0.764; 95% confidence interval, 0.674-0.855; P<0.001). Therefore, prehypertension identified by DBP trajectories throughout pregnancy is an independent risk factor for predicting postpartum metabolic syndrome in normotensive pregnant women.

Heart. 2016 Jun 27. pii: heartjnl-2015-309155.

Circulating vascular endothelial growth factor and the risk of cardiovascular events.

Kaess BM, Preis SR, Beiser A, Sawyer DB, Chen TC, Seshadri S, Vasan RS.

OBJECTIVE: To investigate the relation of circulating concentrations of vascular endothelial growth factor (VEGF) for the risk of developing cardiovascular disease (CVD) in a large community-based sample.

METHODS: We prospectively assessed the relation of circulating VEGF concentrations with the incidence of CVD among 3041 Framingham Heart Study participants (mean age 63.4±11.1 years, 59% women). Multivariable Cox proportional hazards models were estimated adjusting for standard risk factors to VEGF quartiles to incident CVD. Restricted cubic splines were used to examine the linearity of the association.

RESULTS: After a mean follow-up of 8.8 (±2.8) years, 527 individuals experienced a first CVD event. Compared with participants in the first VEGF quartile, individuals in the second VEGF quartile had a 34% increased risk for future CVD (HR 1.34, 95% CI 1.03 to 1.74; p value=0.03) and individuals in third quartile had a 59% higher risk (HR 1.59; 95% CI 1.23 to 2.05, p value=0.0003). Individuals

in the highest VEGF quartile had a similar cardiovascular risk as compared with those in the lowest VEGF quartile (HR 1.18, 95% CI 0.91 to 1.53, p value=0.21). Evaluation of restricted cubic splines confirmed the nonlinear, inverted U-shaped relation of serum VEGF and CVD events ($p<0.0001$ for model fit, $p=0.006$ for non-linearity).

CONCLUSIONS: Circulating VEGF concentrations exhibit a complex non-linear (inverted U-shaped) relation with the risk of developing CVD events, with the lowest risk experienced at the lower and upper end of the distribution. The underlying pathophysiological mechanisms remain to be elucidated.

Br J Radiol. 2016 Jun 28:20160342. [Epub ahead of print]

Whole body cardiovascular MRI for the comparison of atherosclerotic burden and cardiac remodelling in healthy South Asian and European adults.

Weir-McCall J, Cassidy DB, Belch JJ, Gandy SJ, Houston JG, Lambert MA, Littleford RC, Rowland J, Struthers AD, Khan F.

OBJECTIVES: To determine the feasibility of using whole body cardiovascular MRI (WB-CVMR) to compare South Asians (SA) - a population known to have a higher risk of cardiovascular disease (CVD) but paradoxically lower prevalence of peripheral arterial disease (PAD) - and Western Europeans (WE).

METHODS: 19 SA and 38 age, gender and BMI matched WE were recruited. All were ≥40 years, free from CVD and with a 10-year risk of CVD <20% as assessed by the ATPIII risk score. WB-CVMR was performed, comprising a whole body angiogram (WBA) and cardiac MR (CMR), on a 3T MRI scanner following dual phase injection of gadolinium based contrast agent. A standardized atherosclerotic score (SAS) was calculated from the WBA, while indexed left ventricular mass and volumes were calculated from the CMR.

RESULTS: SAs exhibited a significantly lower iliofemoral atheroma burden (regional SAS 0.0±0.0 vs 1.9±6.9, p=0.048) and a trend towards lower overall atheroma burden (WB SAS 0.7±0.8 vs 1.8±2.3, p=0.1). They had significantly lower indexed left ventricular mass (46.9±11.8 vs 56.9±13.4ml/m(2), p=0.008), end diastolic volume (63.9±10.4 vs 75.2±11.4ml/m(2), p=0.001), end systolic volume (20.5±6.1 vs 24.6±6.8ml/m(2), p=0.03) and stroke volume (43.4±6.6 vs 50.6±7.9ml/m(2), p=0.001), but with no significant difference in ejection fraction, mass-volume ratio or global functioning index. These differences persisted after accounting for CVD risk factors.

CONCLUSIONS: Whole body cardiovascular MRI (WB-CVMR) can quantify cardiac and atheroma burden, and can detect differences in these metrics between ethnic groups that, if validated, may suggest that the paradoxical high risk of CVD compared with PVD risk may be due to an adverse cardiac haemodynamic status incurred by the smaller heart rather than atherosclerosis.

ADVANCES IN KNOWLEDGE: WB-CVMR can be used to stratify and compare disease between ethnicities.

Endocr Res. 2016 Jun 28:1-10. [Epub ahead of print]

Effects of visceral adipose tissue reduction on CVD risk factors independent of weight loss: The Look AHEAD study.

Sanguankeo A, Lazo M, Upala S, Brancati FL, Bonekamp S, Pownall HJ, Balasubramanyam A, Clark JM; Fatty Liver Subgroup of the Look AHEAD Research Group.

OBJECTIVES: To determine if the reduction of visceral adipose tissue (VAT) volume by lifestyle intervention improved risk factors for cardiovascular disease (CVD) independent of weight loss amount.
DESIGN: Ancillary study of randomized-controlled trial.
SETTING: Data analysis using multivariable regression models.
PARTICIPANTS: Participants of the Look AHEAD (Action for HEAlth in Diabetes) Fatty Liver Ancillary Study.
MAIN OUTCOME MEASURES: Correlations between changes in VAT and in CVD risk factors, while adjusting for weight loss and treatment (intensive lifestyle intervention [ILI] vs. diabetes support and education [DSE]).
RESULTS: Of 100 participants analyzed, 52% were women, and 36% were black, with a mean age of 61.1 years. In the DSE group, mean weight and VAT changed by 0.1 % (p=0.90) and 4.3% (p=0.39), respectively. In the ILI group, mean weight and VAT decreased by 8.0% (p<0.001) and 7.7% (p=0.01), respectively. Across both groups, mean weight decreased by 3.6% (p<0.001), and mean VAT decreased by 1.2% (p=0.22); the decrease in VAT was correlated with the increase in HDL-cholesterol (HDL-C; R=-0.37; p=0.03). There were no correlations between changes in VAT and blood pressure, triglycerides, LDL-C, glucose, or HbA1c. After adjusting for age, race, gender, baseline metabolic values, fitness, and treatment group, changes in HDL-C were not associated with changes in VAT, while weight changes were independently associated with decrease in glucose, HbA1c, and increase in HDL-C.
CONCLUSIONS: VAT reduction was not correlated with improvements of CVD risk factors in a sample of overweight and obese adults with type 2 diabetes after adjusting for weight loss.

Asian Nurs Res (Korean Soc Nurs Sci). 2016 Jun;10(2):150-7.

Difficulties of Portuguese Patients Following Acute Myocardial Infarction: Predictors of Readmissions and Unchanged Lifestyles.

Nunes S, Rego G, Nunes R.

PURPOSE: Myocardial infarction can occur due to known risk factors and lifestyle choices. The difficulties that patients experience after discharge can lead to readmission and nonadherence to lifestyle change. The purpose of this study was to analyze the difficulties experienced by patients after hospitalization due to myocardial infarction and to identify the predictors of readmission and unchanged lifestyles.

METHODS: The study used a mixed-methods design across 106 patients who had experienced a first episode of acute myocardial infarction. The data were collected from two patient interviews and the patients' medical records. A logistic regression was used to predict unchanged lifestyle and readmission.

RESULTS: In the first interview, 74.5% of the patients reported receiving information prior to discharge. Six months after discharge, 80.2% mentioned that they had changed their lifestyles, but only 59.4% reported that their health had improved, and 75.5% continued to have concerns regarding their health. Patients described difficulties with regard to psychological problems, family dynamics, professional issues, problems with managing cardiovascular symptoms, and complications associated with hospital interventions. A follow-up assessment revealed that 12.3% of patients had been readmitted for cardiovascular disease.

CONCLUSIONS: The analysis revealed significant predictors of readmission amongst patients with hypertension and three-vessel disease. Specifically, the number of people in the household, per capita income, and a lack of information/education provided at discharge as well as problems related to mental health after discharge predicted unchanged lifestyle. An educational program might be advantageous to clarify doubts and involve patients in their own disease management.

Can J Cardiol. 2016 Jul;32(7):900-7.

Shared Risk Factors for Cardiovascular Disease and Cancer: Implications for Preventive Health and Clinical Care in Oncology Patients.

Johnson CB, Davis MK, Law A, Sulpher J.

The cardiovascular toxicity of cancer therapy has raised awareness of the importance of heart disease in cancer care among oncologists and cardiologists, leading to the new interdisciplinary field of cardio-oncology. Evidence is accumulating to suggest that risk factors associated with cardiovascular disease are also related to an increased incidence of cancer and excess cancer mortality. We review the epidemiologic evidence that smoking, obesity, poor diet, and inactivity can cause both heart disease and cancer. The importance of cardiovascular disease and cardiovascular risk factors in adversely affecting oncological outcomes and leading to increased cancer mortality is discussed. Cardiotoxicity prediction tools that incorporate cardiac disease and risk factors are described. Raising awareness about shared risk factors for cancer and heart disease may result in more effective advocacy to promote healthy lifestyle changes through the combined efforts of the historically separate specialties of cardiology and oncology.

J Pediatr (Rio J). 2016 Jun 22. pii: S0021-7557(16)30063-8.

Serum TSH levels are associated with cardiovascular risk factors in overweight and obese adolescents.

Souza LL, Guedes EP, Teixeira PF, Moreira RO, Godoy-Matos AF, Vaisman M.

OBJECTIVE: To investigate the relationship between serum thyrotropin (TSH), insulin resistance (IR), and cardiovascular risk factors (CRF) in a sample of overweight and obese Brazilian adolescents. METHODS: A retrospective, longitudinal analysis of 199 overweight and obese pubescent adolescents was performed. The TSH and free T4 (fT4) levels, anthropometric measurements, and laboratory test results of these patients were analyzed.
RESULTS: 27 individuals (13.56%) presented with TSH levels above the normal level (subclinical hypothyroidism [SCH]). Their waist circumference (WC) was significantly higher than those of euthyroid individuals. Serum TSH was positively correlated with the homeostasis model assessment of insulin resistance (HOMA-IR) index, triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C). Using TSH and BMI as independent variables, TSH levels were shown to be independently related to HOMA-IR (p=0.001) and TG (p=0.007). Among euthyroid subjects, individuals with TSH values <2.5mIU/mL exhibited statistically significant decreases in waist-to-hip ratio, HDL-C levels, and HOMA-IR scores and a tendency toward lower WC values.
CONCLUSION: SCH in overweight and obese adolescents appears to be associated with excess weight, especially visceral weight. In euthyroid adolescents, there appears to be a direct relationship between TSH and some CRF. In conclusion, in the present sample of overweight and obese adolescents, TSH levels appear to be associated with IR and CRF.

J Hypertens. 2016 Jun 23. [Epub ahead of print]

Abdominal fat and blood pressure in healthy young children.

Jansen MA, Uiterwaal CS, Visseren FL, van der Ent CK, Grobbee DE, Dalmeijer GW.

OBJECTIVES: High blood pressure (BP) and obesity are well known risk factors for cardiovascular diseases. Both risk factors exert an influence early in life, and BP is related to body weight. However, the effect of abdominal fat accumulation on BP in childhood is still unclear. We aimed to determine the relation between visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT) and BP in young children.

METHODS: In 862 healthy 5-year-old children of the Wheezing-Illnesses-Study-Leidsche-Rijn birth cohort, VAT and SAT were measured ultrasonographically. SBP and DBP were measured in sitting and supine postures using a semi-automatic oscillometric device. General linear regression analyses were performed to assess associations between abdominal fat and BP adjusted for confounders. Further explanatory models were run to explore if associations with localized abdominal fat distributions were independent of measures of overall body adiposity.

RESULTS: Each millimeter increase in VAT was related to 0.17mmHg (95% confidence interval: 0.08; 0.3) and 0.11mmHg (0.02; 0.2) higher sitting SBP and DBP, respectively. These associations remained after additional adjustment for BMI (SBP: 0.14mmHg/mm, 0.05; 0.2; DBP: 0.11mmHg/mm, 0.02; 0.2), waist circumference (SBP: 0.16mmHg/mm, 0.06; 0.3; DBP: 0.12mmHg/mm, 0.03; 0.2) or early life growth (SBP: 0.16mmHg/mm, 0.07; 0.3; DBP: 0.115mmHg/mm, 0.03; 0.2). Associations between VAT and supine SBP and DBP were, respectively, 0.14mmHg/mm (0.06; 0.2) and 0.08mmHg/mm (0.004; 0.2), which remained after further explanatory analyses. SAT was not associated to SBP or DBP.

CONCLUSION: Independent of body size, children with more VAT have higher BP, especially when measured in sitting posture.

Public Health Nutr. 2016 Jun 24:1-9. [Epub ahead of print]

Childhood dietary patterns and cardiovascular risk factors in adolescence: results from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort.

Bull CJ, Northstone K.

OBJECTIVE: To investigate the prospective associations between dietary patterns in childhood and CVD risk in adolescence.
DESIGN: Prospective cohort study. Exposures were dietary patterns at age 7, 10 and 13 years derived by cluster analysis. Outcomes were physiological and biochemical cardiovascular risk markers.
SETTING: Avon Longitudinal Study of Parents and Children (ALSPAC), UK. SUBJECTS: Children (n 2311, 44.1 % male) with complete data available.
RESULTS: After adjustment for known confounders, we observed an association between being in the 'Processed' and 'Packed lunch' dietary pattern clusters at age 7 and BMI at age 17. Compared with the 'healthy' cluster, the OR (95 % CI) for being in the top 10 % for BMI was 1·60 (1·01, 2·55; P=0·05) for the 'Processed' cluster and 1·96 (1·22, 3·13; P=0·005) for the 'Packed lunch' cluster. However, no association was observed between BMI and dietary patterns at age 10 and 13. Longitudinal analyses showed that being in either the 'Processed' or 'Packed lunch' cluster at age 7 was associated with increased risk of being in the top 10 % for BMI regardless of subsequent cluster membership. No associations between other cardiovascular risk measures and dietary patterns were robust to adjustment for confounders.
CONCLUSIONS: We did not find any consistent evidence to support an association between dietary patterns in childhood and cardiovascular risk factors in adolescence, with the exception of BMI and dietary pattern at age 7 only. However, the importance of dietary intake in childhood upon health later in life requires further investigation and we would encourage the adoption of a healthy diet as early in life as possible.

Mar Drugs. 2016 Jun 8;14(6). pii: E113. doi: 10.3390/md14060113.

Nutraceuticals and Bioactive Components from Fish for Dyslipidemia and Cardiovascular Risk Reduction.

Chiesa G, Busnelli M, Manzini S, Parolini C.

Cardiovascular disease remains the most common health problem in developed countries, and residual risk after implementing all current therapies is still high. Permanent changes in lifestyle may be hard to achieve and people may not always be motivated enough to make the recommended modifications. Emerging research has explored the application of natural food-based strategies in disease management. In recent years, much focus has been placed on the beneficial effects of fish consumption. Many of the positive effects of fish consumption on dyslipidemia and heart diseases have been attributed to n-3 polyunsaturated fatty acids (n-3 PUFAs, i.e., EPA and DHA); however, fish is also an excellent source of protein and, recently, fish protein hydrolysates containing bioactive peptides have shown promising activities for the prevention/management of cardiovascular disease and associated health complications. The present review will focus on n-3 PUFAs and bioactive peptides effects on cardiovascular disease risk factors. Moreover, since considerable controversy exists regarding the association between n-3 PUFAs and major cardiovascular endpoints, we have also reviewed the main clinical trials supporting or not this association.

Eur J Prev Cardiol. 2016 Jun 21.. [Epub ahead of print]

Primary prevention of cardiovascular disease: More patient gender-based differences in risk evaluation among male general practitioners.

Delpech R, Ringa V, Falcoff H, Rigal L.

OBJECTIVE: Our objective was to analyse general practitioner (GP) cardiovascular risk assessment of patients for primary prevention while considering the gender of both the GP and the patient.
METHODS: This study consisted of an observational survey of GPs who were internship supervisors in the Paris metropolitan area. Each of 52 volunteer GPs completed a self-administered questionnaire regarding their own characteristics and randomly selected 70 patients from their patient list. Dependent variables from the patient files included the presence of information about risk factors necessary to assess the patient's cardiovascular risk according to the French scale and the Systematic COronary Risk Evaluation (SCORE) scale. Analyses used mixed logistic models with a random intercept and adjusted for patient and physician characteristics.
RESULTS: Both cardiovascular risk scales could be assessed less frequently in women than in men (odds ratio (OR)=0.64 (95% confidence interval (CI): 0.5-0.8) for the French scale and OR=0.63 (95% CI: 0.5-0.8) for the SCORE scale). These gender differences were less substantial when the patients were seen by female (for the SCORE scale OR=0.72 (95% CI: 0.5-1.01)) compared with male physicians (OR=0.56 (95% CI: 0.4-0.7)). The patients who were least well assessed for cardiovascular risk were women seen by male physicians.
CONCLUSION: Even before the onset of cardiovascular disease, women patients receive less satisfactory preventative management than men do, and these differences are even more marked when the physician is a man. More attention to the influence of gender stereotypes is needed in medical training in order to combat the inequalities that they cause.

Climacteric. 2016 Aug;19(4):329-36.

Cardiovascular risk assessment in women - an update.

Collins P(1), Webb CM(1), de Villiers TJ(2), Stevenson JC(1), Panay N(3), Baber RJ(4).

Cardiovascular disease is the leading cause of morbidity and mortality in postmenopausal women. Although it is a disease of aging, vascular disease initiates much earlier in life. Thus, there is a need to be aware of the potential to prevent the development of the disease from an early age and continue this surveillance throughout life. The menopausal period and early menopause present an ideal opportunity to assess cardiovascular risk and plan accordingly. Generally in this period, women will be seen by primary health-care professionals and non-cardiovascular specialists. This review addresses female-specific risk factors that may contribute to the potential development of cardiovascular disease. It is important for all health-care professionals dealing with women in midlife and beyond to be cognisant of these risk factors and to initiate female-specific preventative measures or to refer to a cardiovascular specialist.

Proc Nutr Soc. 2016 Jun 22:1-12. [Epub ahead of print]

Meal irregularity and cardiometabolic consequences: results from observational and intervention studies.

Pot GK, Almoosawi S, Stephen AM.

Studying irregular meal patterns fits in with the latest research focusing not only on what people eat but also when they eat, also called chrono-nutrition. Chrono-nutrition involves studying the impact of nutrition on metabolism via circadian patterns, including three aspects of time: (ir)regularity, frequency and clock time. The present paper aimed to narratively review research on irregular meal patterns and cardiometabolic consequences. Only few cross-sectional studies and prospective cohort studies were identified, and most of these suggested that eating meals irregularly is associated with a higher risk of the metabolic syndrome and cardiometabolic risk factors, including BMI and blood pressure. This was supported by two randomised controlled intervention studies showing that consuming meals regularly for 2 weeks v. an irregular meal pattern, led to beneficial impact on cardiometabolic risk factors as lower peak insulin, lower fasting total and LDL-cholesterol, both in lean and obese women. In conclusion, the limited evidence on meal regularity and cardiometabolic consequences supports the hypothesis that consuming meals irregularly is adversely associated with cardiometabolic risk. However, it also highlights the need for more large-scale studies, including detailed dietary assessment to further advance the understanding of the impact of chrono-nutrition on public health.

Obes Rev. 2016 Jun 21. [Epub ahead of print]

Interventions that cause weight loss and the impact on cardiovascular risk factors: a systematic review and meta-analysis.

Zomer E, Gurusamy K, Leach R, Trimmer C, Lobstein T, Morris S, James WP, Finer N.

Overweight and obesity increase the risks of diabetes and cardiovascular disease (CVD). This has been shown to be reversed with weight loss. A systematic review and meta-analysis were performed to determine the effect of weight loss in the primary prevention of CVD. PubMed, Embase and the Cochrane Library databases were searched electronically through to May 2013. Randomized controlled trials assessing weight loss and cardiovascular risk factors and outcomes were included. A random effects meta-analysis, with sub-group analyses for degree of weight loss, and age were performed. Because few studies reported clinical outcomes of CVD, analyses were limited to cardiovascular risk factors (83 studies). Interventions that caused any weight loss significantly reduced systolic blood pressure (-2.68 mmHg, 95% CI -3.37, -2.11), diastolic blood pressure (-1.34 mmHg, 95% CI -1.71, -0.97), low-density lipoprotein cholesterol (-0.20 mmol L(-1) , 95% CI -0.29, -0.10), triglycerides (-0.13 mmol L(-1) , 95% CI -0.22, -0.03), fasting plasma glucose (-0.32 mmol L(-1) , 95% CI -0.43, -0.22) and haemoglobin A1c(-0.40%, 95% CI -0.52, -0.28) over 6-12 months. Significant changes remained after 2 years for several risk factors. Similar results were seen in sub-group analyses. Interventions that cause weight loss are effective at improving cardiovascular risk factors at least for 2 years.

AIDS Care. 2016 Jun 20:1-8. [Epub ahead of print]

Incidence of cardiovascular events in HIV-positive patients compared to general population over the last decade: a population-based study from 2000 to 2012.

Quiros-Roldan E(1), Raffetti E(2), Focà E(1), Brianese N(1), Ferraresi A(1), Paraninfo G(1), Pezzoli MC(1), Bonito A(1), Magoni M(3), Scarcella C(3), Castelli F(1).

Cardiovascular diseases are currently a main cause of death among people living with HIV. This population-based study aimed to investigate the incidence of cardiovascular events (CVEs) in HIV-positive people and factors associated with CVEs. We performed a retrospective cohort study of the HIV-infected patients residing in the Local Health Authority of Brescia, northern Italy, from 2000 to 2012. Incidence of CVEs events in HIV-positive patients was compared with that expected in general population living in the same area, computing standardized incidence ratios (SIRs). CVEs-associated risk factors were assessed using Cox regression analysis and competing risk model of death. About 3766 HIV-infected patients were included in the study. Over the 12-year-period, we recorded 134 CVEs: 83 (61.9%) acute myocardial infarctions (CVE type-1), and 51 (38.1%) strokes (CVE type-2). A twofold increased risk (SIR = 2.02) of CVEs was found in HIV-infected patients compared to the general population. Notably, within male patients: for CVE type-1, SIR = 1.89, for CVE type-2 SIR = 2.25; within female patients: for CVE type-1, SIR = 2.91, for CVE type-2 SIR = 2.07. Age >45 years, male gender, diabetes, and total blood cholesterol >200 mg/dl were significantly associated with CVEs incidence (for all, $p < .05$). These results were confirmed using the competing risk model. Our cohort study confirmed the higher incidence of CVEs in HIV-positive patients, and put emphasis on the importance of traditional cardiovascular risk factors. Overall CVE risk in HIV-positive patients was twice as high as CVE risk in general population. We found a peculiar gender distribution, with a relative risk for CVE type-1 higher in HIV-positive females, and a higher CVE type-2 risk in male patients. More studies are needed in order to support these findings and to further highlight possible gender differences in the risk of developing CVEs in HIV-positive patients.

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PLoS One. 2016 Jun 17;11(6):e0157417.

Association of Vasomotor and Other Menopausal Symptoms with Risk of Cardiovascular Disease: A Systematic Review and Meta-Analysis.

Muka T, Oliver-Williams C, Colpani V, Kunutsor S, Chowdhury S, Chowdhury R, Kavousi M(1), Franco OH(1).

IMPORTANCE: Vasomotor symptoms (hot flushes and night sweats) and other symptoms, including depression, anxiety and panic attacks, are commonly experienced by menopausal women and have been associated with an unfavourable cardiovascular risk profile.
OBJECTIVE: To investigate whether presence of menopausal symptoms is associated with the development of cardiovascular disease (CVD).
METHODS: Five electronic databases (Medline, EMBASE and Web of Science) were search until February 17th, 2015 to identify relevant studies. Observational cohort studies or randomised intervention studies were eligible for inclusion if they followed participants prospectively (at least 1 year of follow-up), and reported relevant estimates on the association of any vasomotor symptoms, or other menopausal symptoms, with risk of CVD, coronary heart disease (CHD), or stroke in perimenopausal, menopausal, or postmenopausal women. Data were extracted by two independent reviewers using a pre-designed data collection form. Separate pooled relative risks (RRs) for age and non-established cardiovascular risk factors (e.g., education, ethnicity) adjusted data and for established cardiovascular risk factors and potential mediators-adjusted data (e.g., smoking, body mass index, and hypertension) were calculated.
RESULTS: Out of 9,987 initially identified references, ten studies were selected, including 213,976 women with a total of 10,037 cardiovascular disease outcomes. The age and non-established cardiovascular risk factors adjusted RRs) [95% confidence intervals] for development of CHD, Stroke and CVD comparing women with and without any menopausal symptoms were 1.34 [1.13-1.58], 1.30 [0.99-1.70], 1.48 [1.21-1.80] respectively, and the corresponding RRs adjusted for cardiovascular risk factors and potential mediators were 1.18 [1.03-1.35], 1.08 [0.89-1.32], 1.29 [0.98-1.71]. However, these analyses were limited by potential unmeasured confounding and the small number of studies on this topic.
CONCLUSION: Presence of vasomotor symptoms and other menopausal symptoms are generally associated with an increased risk of cardiovascular disease, which is mainly explained by cardiovascular risk factors.

J Am Coll Nutr. 2016 Jun 17:1-13. [Epub ahead of print]

Influence of a Mediterranean Dietary Pattern on Body Fat Distribution: Results of the PREDIMED-Canarias Intervention Randomized Trial.

Álvarez-Pérez J, Sánchez-Villegas A, Díaz-Benítez EM, Ruano-Rodríguez C, Corella D, Martínez-González MÁ, Estruch R, Salas-Salvadó J, Serra-Majem L; PREDIMED Study Investigators.

OBJECTIVE: To assess the influence of a Mediterranean dietary pattern (MeDiet) on anthropometric and body composition parameters in one of the centers of the
PREDIMED randomized dietary trial.
SUBJECTS/SETTINGS: 351 Canarian free-living subjects aged 55 to 80 years, with type 2 diabetes or ≥3 cardiovascular risk factors.
INTERVENTION: Participants were randomly assigned to one of 3 different dietary interventions: MeDiet + extra-virgin olive oil (EVOO), MeDiet + nuts (walnuts, almonds, and hazelnuts), or a control low-fat diet. Total energy intake was ad libitum.
OUTCOME MEASURES: Measures included changes in anthropometric measures (weight, body mass index [BMI] and waist circumference [WC]), body fat distribution, energy, and nutrient intake after 1 year. Body composition (percentage of total body fat [%TBF], total fat mass [TFM], free fat mass [FFM], percentage of truncal fat [%TrF], truncal fat mass [TrFM]) and total body water (TBW) were estimated by octapolar electrical impedance analysis.
STATISTICAL ANALYSES: Paired t tests were conducted to assess within-group changes. Analyses of variance (ANOVAs) were used to assess the effect of the dietary intervention on the percentage change in anthropometric variables, body composition, and dietary intake profile. All pairwise comparisons that were statistically significant in ANOVA were subsequently adjusted using the Benjamini-Hochberg test, which penalizes for multiple comparisons.
RESULTS: After 1 year of intervention, significant within-group reductions in all anthropometric variables were observed for the MeDiet + EVOO and the control group. The MeDiet + nuts group exhibited a significant reduction in WC and TBW. The control group showed a significant increase in %TBF and a reduction in TBW. The control group showed a significant increase in the percentage of total body fat and a reduction in TBW. However, we did not find any between-group significant difference in anthropometric or body composition changes.
CONCLUSIONS: Mediterranean diets enriched with EVOO or specific mixed nuts (walnuts, almonds, hazelnuts) that contain approximately 40% total fat can be alternative options to low-fat diets for weight maintenance regimes in older overweight or obese adults.

Rev Clin Esp. 2016 Jun 10. pii: S0014-2565(16)30081-9.

Stroke in young adults: Incidence rate, risk factors, treatment and prognosis.

[Article in English, Spanish]

González-Gómez FJ, Pérez-Torre P, DeFelipe A Vera R, Matute C, Cruz-Culebras A, Álvarez-Velasco R, Masjuan J.

OBJECTIVES: To analyse the incidence, risk factors, aetiology, treatment and clinical evolution of young patients with stroke.
PATIENTS AND METHODS: Retrospective registry of patients aged 55 years or younger hospitalised in a stroke unit during 2014. We recorded the incidence rate for all strokes and analysed demographic data, risk factors, degree of stress, stroke type and aetiology, reperfusion treatments and clinical evolution.
RESULTS: The study included 110 patients, the majority of whom were men (60.9%, 1.6:1 ratio). The incidence rate was 13.3% (110 of 830 strokes). Most of the patients had cardiovascular risk factors. Smoking was the most common risk factor (56.4%), followed by arterial hypertension (50%), dyslipidaemia (42.7%), obesity (33%), diabetes (18.2%) and emboligenic heart disease (12.7%). Some 64.3% of the heart disease cases and 51.1% of the dyslipidaemia cases were discovered during hospitalisation. Some 57.2% of the patients experienced psychosocial stress in the stage prior to the stroke. Some 83.6% of the stroke cases were ischaemic, 12.7% were haemorrhagic and 3.6% were venous sinus thrombosis. Of the ischaemic stroke cases, 30.4% were cryptogenic, 23.9% were lacunar, 16.3% were from uncommon causes, 15.2% were atherothrombotic and 14.1% were cardioembolic. Some 78.6% of the cerebral haemorrhage cases were hypertensive. Some 23.3% of the ischaemic stroke cases underwent reperfusion treatments in the acute phase, achieving levels of functional independence at 3 months of 62.5%.
CONCLUSIONS: The majority of stroke events in patients 55 years of age or younger appear to be related to a high prevalence of classical cardiovascular risk factors and possibly to psychosocial stress.

BMC Med. 2016 Jun 14;14(1):87.

Modifiable causes of premature death in middle-age in Western Europe: results from the EPIC cohort study.

Muller DC, Murphy N, Johansson M, Ferrari P, Tsilidis KK, Boutron-Ruault MC), Clavel F, Dartois L, Li K, Kaaks R(9), Weikert C, Bergmann M, Boeing H, Tjønneland A, Overvad K, Redondo ML, Agudo A, Molina-Portillo E, Altzibar JM, Cirera L, Ardanaz E, Khaw KT, Wareham NJ, Key TJ, Travis RC, Bamia C, Orfanos P, Trichopoulou A, Palli D, Pala V, Tumino R, Vineis P, Panico S, Bueno-de-Mesquita HB, Verschuren WM, Struijk EA, Peeters PH Engström G, Melander O, Sund M, Weiderpass E, Skeie G, Lund E, Norat T, Gunter M, Riboli E, Brennan P.

BACKGROUND: Life expectancy is increasing in Europe, yet a substantial proportion of adults still die prematurely before the age of 70 years. We sought to estimate the joint and relative contributions of tobacco smoking, hypertension, obesity, physical inactivity, alcohol and poor diet towards risk of premature death. METHODS: We analysed data from 264,906 European adults from the EPIC prospective cohort study, aged between 40 and 70 years at the time of recruitment. Flexible parametric survival models were used to model risk of death conditional on risk factors, and survival functions and attributable fractions (AF) for deaths prior to age 70 years were calculated based on the fitted models. RESULTS: We identified 11,930 deaths which occurred before the age of 70. The AF for premature mortality for smoking was 31 % (95 % confidence interval (CI), 31-32 %) and 14 % (95 % CI, 12-16 %) for poor diet. Important contributions were also observed for overweight and obesity measured by waist-hip ratio (10 %; 95 % CI, 8-12 %) and high blood pressure (9 %; 95 % CI, 7-11 %). AFs for physical inactivity and excessive alcohol intake were 7 % and 4 %, respectively. Collectively, the AF for all six risk factors was 57 % (95 % CI, 55-59 %), being 35 % (95 % CI, 32-37 %) among never smokers and 74 % (95 % CI, 73-75 %) among current smokers.
CONCLUSIONS: While smoking remains the predominant risk factor for premature death in Europe, poor diet, overweight and obesity, hypertension, physical inactivity, and excessive alcohol consumption also contribute substantially. Any attempt to minimise premature deaths will ultimately require all six factors to be addressed.

J Clin Endocrinol Metab. 2016 Jun 10:jc20161885. [Epub ahead of print]

Which amount of BMI-SDS reduction is necessary to improve cardiovascular risk factors in overweight children?

Reinehr T, Lass N, Toschke C, Rothermel J, Lanzinger S, Holl RW.

CONTEXT: Knowing the changes of cardiovascular risk factors (CRF) in relation to weight loss would be helpful to advise overweight children and their parents and to decide whether drugs should be prescribed in addition to lifestyle intervention.
OBJECTIVE: To determine the BMI-SDS reduction to improve CRFs in overweight children.
DESIGN: Prospective observation study.
SETTING: Specialized outpatient obesity clinic.
PATIENTS: 1388 overweight children (mean BMI 27.9±0.1, mean age 11.4±0.1years, 43.8% male, 45.5% prepubertal).
INTERVENTION: 1-year lifestyle intervention.
MAIN OUTCOME MEASURES: We studied changes of blood pressure (BP), fasting HDL-, LDL-cholesterol, triglycerides, glucose, and insulin resistance index HOMA. Change of weight status was determined by delta BMI-SDS based on the recommended percentiles of the International Task Force of Obesity.
RESULTS: BMI-SDS change was associated with a significant improvement of all CRFs except fasting glucose and LDL-cholesterol after adjusting for multiple confounders such as baseline CRF, age, gender, BMI, pubertal stage and its changes. BMI-SDS reduction ≥0.25-0.5 was related to a decrease of systolic BP (-3.2±1.4mmHg), diastolic BP (-2.2±1.1mmHg), triglycerides (-6.9±5.8mg/dl), HOMA (-0.5±0.3), and triglyceride/HDL-cholesterol (-0.3±0.2), while HDL-cholesterol increased (+1.3±1.2mg/dl). A reduction of >0.5 BMI-SDS led to more pronounced improvement (systolic BP -6.0±1.3mmHg, diastolic BP -5.1±1.3mmHg, triglycerides -16.4±7.1mg/dl, HDL-cholesterol +1.6±1.5mg/dl, HOMA -0.9±0.3). Per 0.1 BMI-SDS reduction systolic BP (-1.0mmHg), diastolic BP (-0.8mmHg), triglycerides (-2.3mg/dl), HOMA (-0.2), and triglyceride/HDL-cholesterol (-0.5), decreased significantly, while HDL-cholesterol (0.2mg/dl) increased significantly in linear regression analyses accounted for multiple confounders.
CONCLUSIONS: A BMI-SDS reduction ≥0.25 improved significantly hypertension, hypertriglyceridemia and low HDL-cholesterol, while a BMI-SDS >0.5 doubled the effect.

Lancet Diabetes Endocrinol. 2016 Jun 6. pii: S2213-8587(16)30085-7.

Effect of a high-fat Mediterranean diet on bodyweight and waist circumference: a prespecified secondary outcomes analysis of the PREDIMED randomised controlled trial.

Estruch R, Martínez-González MA, Corella D, Salas-Salvadó J, Fitó M, Chiva-Blanch G, Fiol M, Gómez-Gracia E, Arós F, Lapetra J), Serra-Majem L, Pintó X, Buil-Cosiales P, Sorlí JV, Muñoz MA, Basora-Gallisá J, Lamuela-Raventós RM, Serra-Mir M, Ros E; PREDIMED Study Investigators.

BACKGROUND: Because of the high density of fat, high-fat diets are perceived as likely to lead to increased bodyweight, hence health-care providers are reluctant to recommend them to overweight or obese individuals. We assessed the long-term effects of ad libitum, high-fat, high-vegetable-fat Mediterranean diets on bodyweight and waist circumference in older people at risk of cardiovascular disease, most of whom were overweight or obese.

METHODS: PREDIMED was a 5 year parallel-group, multicentre, randomised, controlled clinical trial done in primary care centres affiliated to 11 hospitals in Spain. 7447 asymptomatic men (aged 55-80 years) and women (aged 60-80 years) who had type 2 diabetes or three or more cardiovascular risk factors were randomly assigned (1:1:1) with a computer-generated number sequence to one of three interventions: Mediterranean diet supplemented with extra-virgin olive oil (n=2543); Mediterranean diet supplemented with nuts (n=2454); or a control diet (advice to reduce dietary fat; n=2450). Energy restriction was not advised, nor was physical activity promoted. In this analysis of the trial, we measured bodyweight and waist circumference at baseline and yearly for 5 years in the intention-to-treat population. The PREDIMED trial is registered with ISRCTN.com, number ISRCTN35739639.

FINDINGS: After a median 4·8 years (IQR 2·8-5·8) of follow-up, participants in all three groups had marginally reduced bodyweight and increased waist circumference. The adjusted difference in 5 year changes in bodyweight in the Mediterranean diet with olive oil group was -0·43 kg (95% CI -0·86 to -0·01; p=0·044) and in the nut group was -0·08 kg (-0·50 to 0·35; p=0·730), compared with the control group. The adjusted difference in 5 year changes in waist Circumference was -0·55 cm (-1·16 to -0·06; p=0·048) in the Mediterranean diet with olive oil group and -0·94 cm (-1·60 to -0·27; p=0·006) in the nut group, compared with the control group.

INTERPRETATION: A long-term intervention with an unrestricted-calorie, high-vegetable-fat Mediterranean diet was associated with decreases in bodyweight and less gain in central adiposity compared with a control diet. These results lend support to advice not restricting intake of healthy fats for bodyweight maintenance.

FUNDING: Spanish Government, CIBERobn, Instituto de Salud Carlos III, Hojiblanca, Patrimonio Comunal Olivarero, California Walnut Commission, Borges SA, and Morella Nuts.

High Alt Med Biol. 2016 Jun;17(2):93-100.

Increased Cardiometabolic Risk and Worsening Hypoxemia at High Altitude.

Miele CH, Schwartz AR, Gilman RH, Pham L, Wise RA, Davila-Roman VG, Jun JC, Polotsky VY, Miranda JJ, Leon-Velarde F, Checkley W.

Metabolic syndrome, insulin resistance, diabetes, and dyslipidemia are associated with an increased risk of cardiovascular disease. While excessive erythrocytosis is associated with cardiovascular complications, it is unclear how worsening hypoxemia of any degree affects cardiometabolic risk factors in high-altitude populations. We studied the relationship between daytime resting oxyhemoglobin saturation and cardiometabolic risk factors in adult participants living in Puno, Peru (3825 m above sea level). We used multivariable logistic regression models to study the relationship between having a lower oxyhemoglobin saturation and markers of cardiometabolic risk. Nine hundred and fifty-four participants (mean age 55 years, 52% male) had information available on pulse oximetry and markers of cardiometabolic risk. Average oxyhemoglobin saturation was 90% (interquartile range 88%-92%) and 43 (4.5%) had excessive erythrocytosis. Older age, decreased height-adjusted lung function, and higher body mass index (BMI) were associated with having an oxyhemoglobin saturation ≤85%. When adjusting for age, sex, socioeconomic status, having excessive erythrocytosis, and site, we found that each 5% decrease in oxyhemoglobin saturation was associated with a higher adjusted odds of metabolic syndrome (OR = 1.35, 95% CI: 1.07-1.72, $p < 0.04$), insulin resistance as defined by homeostasis model assessment-insulin resistance (HOMA-IR) >2 mass units (OR = 1.29, 95% CI: 1.00-1.67, $p < 0.05$), hemoglobin A1c ≥6.5% (OR = 1.66, 95% CI: 1.09-2.51, $p < 0.04$), and high sensitivity C-reactive protein (hs-CRP) ≥3 mg/L (OR = 1.46, 95% CI: 1.09-1.96, $p < 0.01$). In high-altitude populations in Puno, Peru, a higher BMI and lower pulmonary function were associated with lower resting daytime oxyhemoglobin saturation. Lower resting oxyhemoglobin saturation, in turn, was associated with higher odds of having multiple unfavorable cardiometabolic factors. Worsening hypoxia of any degree in high-altitude dwellers may be an independent risk factor for cardiovascular disease.

Diabetol Metab Syndr. 2016 Jun 2;8:37.

LEADER 7: cardiovascular risk profiles of US and European participants in the LEADER diabetes trial differ.

Rutten GE, Tack CJ, Pieber TR, Comlekci A, Ørsted DD, Baeres FM, Marso SP, Buse JB; LEADER Investigators.

AIMS: To determine whether US and European participants in the Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results (LEADER) trial differ regarding risk factors for cardiovascular mortality and morbidity. METHODS: Baseline data, stratified for prior cardiovascular disease (CVD), were compared using multivariable logistic regression analysis to establish whether region is an independent determinant of achieved targets for glycated hemoglobin (HbA1c), blood pressure (BP), and low-density lipoprotein (LDL)-cholesterol. RESULTS: Independent of CVD history, US participants were more often of non-White origin and had a longer history of type 2 diabetes, higher body weight, and higher baseline HbA1c. They had substantially lower systolic and diastolic BP, and a marginally lower LDL-cholesterol level. Fewer US participants were diagnosed with left ventricular dysfunction. In the largest group of patients, those with prior CVD and the highest cardiovascular risk, US participants were more often female, had a higher waist circumference, and had a decreased estimated glomerular filtration rate, but less frequently prior myocardial infarction or angina pectoris.
CONCLUSIONS: There were baseline differences between US and European participants. These differences may result from variation in regional targets for cardiovascular risk factor management, and should be considered in the analysis and reporting of the trial results. Clinical trial identifier:

J Sports Sci Med. 2016 May 23;15(2):308-13. eCollection 2016.

Can Time Efficient Exercise Improve Cardiometabolic Risk Factors in Type 2 Diabetes? A Pilot Study.

Revdal A, Hollekim-Strand SM, Ingul CB

Exercise is considered a cornerstone in the prevention and treatment of type 2 diabetes, but few individuals with type 2 diabetes exercise according to guidelines. We investigated the effect of two time efficient high intensity exercise interventions on exercise capacity, glycemic control and other cardiometabolic risk factors in patients with type 2 diabetes. Twenty-one individuals with type 2 diabetes were randomly assigned to low volume high intensity interval exercise (HIIE; 27 minutes/bout; 10x1-minute at 90 % of HRmax; n = 10) or extremely low volume sprint interval exercise (SIE; 10 minutes/bout; 2x20 seconds at maximum achievable intensity; n = 11) 3 days/week for 12 weeks. Aerobic exercise capacity (VO2peak), glycosylated hemoglobin (HbA1c), blood pressure and body composition were measured at baseline and post test. Both HIIE and SIE improved VO2peak (3.3 mL·min(-1)·kg(-1), 10.4 %), p < 0.01, and 1.4 mL·min(-1)·kg(-1) (4.6 %), p = 0.03, respectively). Only HIIE reduced body fat percentage (4.5 %, p = 0.04) and two minute heart rate recovery (11.0 bpm, p = 0.02). Neither HIIE nor SIE improved HbA1c. In conclusion, this study indicates that substantially lower exercise volumes than recommended in current guidelines can improve aerobic exercise capacity in individuals with type 2 diabetes. However, 12 weeks of time efficient high intensity exercise did not improve glycemic control, and interventions of longer duration should be investigated. Key points Low volume high-intensity interval exercise can improve peak oxygen uptake in previously sedentary individuals with type 2 diabetes. The weekly exercise volumes in the two intervention groups of 81 and 30 minutes respectively, is substantially lower than recommended in current exercise guidelines and could reduce the time-barrier associated with exercise among patients with type 2 diabetes. However, 12 weeks of structured, supervised low-volume exercise did not improve glycemic control, indicating a need for exercise volumes or longer intervention period.

Diabetes Care. 2016 Jun 6. [Epub ahead of print]

Association of Weight Loss Maintenance and Weight Regain on 4-Year Changes in CVD Risk Factors: the Action for Health in Diabetes Clinical Trial.

Action for Health In Diabetes (Look AHEAD) Study Group.

OBJECTIVE: Short-term weight loss improves cardiovascular disease (CVD) risk factors. We sought to determine the longer-term effects of maintaining weight loss or, conversely, regaining weight.

RESEARCH DESIGN AND METHODS: We used data from Look AHEAD, a randomized trial of intensive lifestyle intervention (ILI) compared to a control condition in overweight/obese individuals with type 2 diabetes. ILI participants were grouped according to weight change patterns, as follows: 1) no weight loss (±3% at years 1 and 4); 2) moderate weight loss (3-8% at years 1 and 4); 3) large weight loss (8-20% at years 1 and 4); 4) moderate loss/full regain (3-8% at year 1/±3% at year 4); 5) large loss/full regain (8-20% at year 1/± 3% year 4); and 6) large loss/partial regain (8-20% at year 1/3-8% at year 4) and changes in CVD risk factors were compared.

RESULTS: Adjusting for baseline differences and medication use, larger weight losses produced greater improvements in HbA1c, systolic blood pressure, HDL cholesterol, and triglycerides at years 1 and 4 (all $P \leq 0.02$). Despite maintenance of weight loss, HbA1c levels worsened between years 1 and 4, and remained below baseline only in those with large weight losses. We found no negative associations of losing and regaining weight relative to not having lost weight. Moreover, those who had large initial weight loss but full regain of weight had greater improvements in HbA1c levels at year 4 than those with smaller or no initial weight loss.

CONCLUSIONS: Larger initial weight loss should be encouraged in individuals with type 2 diabetes, despite the possibility of regain.

Circulation. 2016 Jun 7;133 (23):2314-33.

Worldwide Exposures to Cardiovascular Risk Factors and Associated Health Effects:Current Knowledge and Data Gaps.

Tzoulaki I(1), Elliott P(1), Kontis V(1), Ezzati M(2).

Information on exposure to, and health effects of, cardiovascular disease (CVD) risk factors is needed to develop effective strategies to prevent CVD events and deaths. Here, we provide an overview of the data and evidence on worldwide exposures to CVD risk factors and the associated health effects. Global comparative risk assessment studies have estimated that hundreds of thousands or millions of CVD deaths are attributable to established CVD risk factors (high blood pressure and serum cholesterol, smoking, and high blood glucose), high body mass index, harmful alcohol use, some dietary and environmental exposures, and physical inactivity. The established risk factors plus body mass index are collectively responsible for ≈9.7 million annual CVD deaths, with high blood pressure accounting for more CVD deaths than any other risk factor. Age-standardized CVD death rates attributable to established risk factors plus high body mass index are lowest in high-income countries, followed by Latin America and the Caribbean; they are highest in the region of central and eastern Europe and central Asia. However, estimates of the health effects of CVD risk factors are highly uncertain because there are insufficient population-based data on exposure to most CVD risk factors and because the magnitudes of their effects on CVDs in observational studies are likely to be biased. We identify directions for research and surveillance to better estimate the effects of CVD risk factors and policy options for reducing CVD burden by modifying preventable risk factors.

Contraception. 2016 Jun 1. pii: S0010-7824(16)30110-X.

Combined hormonal contraceptive use among obese women and risk for cardiovascular events: A systematic review.

Horton LG, Simmons KB, Curtis KM.

CONTEXT: Combined hormonal contraceptive (CHC) use may modify the risk of cardiovascular events in obese [body mass index (BMI) ≥30kg/m (2)] women. OBJECTIVE: The objective was to evaluate from the literature whether CHC use modifies the risk of acute myocardial infarction (AMI), stroke, cerebral venous thrombosis (CVT) and venous thromboembolism (VTE) in obese women and to evaluate evidence for a dose-response relationship between BMI and VTE.
METHODS: We searched PubMed for all articles published between database inception and February 2016 providing direct evidence on BMI, CHCs, and cardiovascular outcomes. We also searched for indirect evidence related to a dose-response relationship between BMI and risk of VTE in the general population, as these data were lacking for CHC users. The quality of each individual study was assessed using the system for grading evidence developed by the United States Preventive Services Task Force.
RESULTS: The direct evidence search yielded 3 pooled analyses, 11 case-control studies and 1 cohort study. There was conflicting evidence about the risk of AMI or stroke among obese combined oral contraceptive (COC) users compared to obese nonusers, with one study finding no increased risk for AMI or stroke for COC users overall or stratified by BMI. A second study found significantly increased risk of AMI and stroke for COC users, with the highest risk estimates for high-BMI COC users. A single study suggested that obese COC users may be at higher risk for CVT compared with normal-weight nonusers. For VTE, obese COC users consistently had a risk that was 5 to 8 times that of obese nonusers and approximately 10 times that of nonobese nonusers. Five prospective cohort studies were identified as indirect evidence, and all found increased risk for VTE as BMI increased, suggesting a dose-response relationship between BMI and risk for VTE. No studies on the contraceptive patch or vaginal ring were identified that met the inclusion criteria.
CONCLUSION: Limited evidence of Level II-2, fair quality, concerning whether CHC use modifies the risk of AMI and stroke in obese women is inconclusive, while a single study of Level II-2, poor quality, found that obese COC users may be at higher risk for CVT compared with normal-weight nonusers. Both COC use and higher BMI increase risk for VTE, and the greatest relative risks are for those with both risk factors based on a body of evidence graded as Level II-2, fair to poor quality. It is not possible to estimate absolute risk of VTE among women with both of these risk factors; however, the absolute risk of VTE in healthy women of reproductive age is small.

PLoS One. 2016 Jun 3;11 (6):e0156804.

Lifestyle and Socioeconomic Determinants of Multimorbidity Patterns among Mid-Aged Women: A Longitudinal Study.

Jackson CA, Dobson AJ, Tooth LR, Mishra GD

BACKGROUND: Little is known about patterns of associative multimorbidity and their aetiology. We aimed to identify patterns of associative multimorbidity among mid-aged women and the lifestyle and socioeconomic factors associated with their development.

METHODS: Participants were from the Australian Longitudinal Study on Women's Health. We included 4896 women born 1946-51, without multimorbidity in 1998. We identified multimorbidity patterns at survey 6 (2010) using factor analysis, and related these patterns to baseline lifestyle and socioeconomic factors using logistic regression. We dichotomised factor scores and determined odds ratios (ORs) with 95% confidence intervals (CIs) for associations between characteristics and odds of a high versus low factor score.

RESULTS: We identified five multimorbidity patterns: psychosomatic; musculoskeletal; cardiometabolic; cancer; and respiratory. Overweight and obesity were respectively associated with increased odds of having a high score for the musculoskeletal (adjusted ORs 1.45 [95% CI 1.23, 1.70] and 2.14 [95% CI 1.75, 2.60]) and cardiometabolic (adjusted ORs 1.53 [95% CI 1.31, 1.79] and 2.46 [95% CI 2.02, 2.98]) patterns. Physical inactivity was associated with increased odds of a high score for the psychosomatic, musculoskeletal and cancer patterns (adjusted ORs 1.41 [95% CI 1.13, 1.76]; 1.39 [95% CI 1.11, 1.74]; and 1.35 [95% CI 1.08, 1.69]). Smoking was associated with increased odds of a high score for the respiratory pattern. Education and ability to manage on income were associated with increased odds of a high score for the psychosomatic pattern (adjusted ORs 1.34 [95% CI 1.03, 1.75] and 1.73 [95% CI 1.37, 1.28], respectively) and musculoskeletal pattern (adjusted ORs 1.43 [95% CI 1.10, 1.87] and 1.38 [1.09, 1.75], respectively).

CONCLUSIONS: Distinct multimorbidity patterns can be identified among mid-aged women. Social inequality, physical activity and BMI are risk factors common to multiple patterns and are appropriate targets for reducing the risk of specific multimorbidity groups in mid-life women.

Cardiovasc Diabetol. 2016 Jun 2;15 (1):83. doi: 10.1186/s12933-016-0399-0.

Diastolic orthostatic hypertension and cardiovascular prognosis in type 2 diabetes: a prospective cohort study.

Wijkman M, Länne T, Östgren CJ, Nystrom FH.

BACKGROUND: In patients with type 2 diabetes, the prognostic impact of an orthostatic rise in blood pressure is not known. Therefore, the aim of this study was to determine the prognostic implications of the diastolic orthostatic blood pressure response in a cohort of patients with type 2 diabetes. We also evaluated associations between different orthostatic blood pressure responses and markers of subclinical cardiovascular organ damage.

METHODS: Office blood pressures were measured in the sitting and in the standing position in 749 patients with type 2 diabetes who participated in the CARDIPP study (Cardiovascular Risk factors in Patients with Diabetes-a Prospective study in Primary care). Diastolic orthostatic hypertension was defined as a rise of diastolic blood pressure ≥10 mmHg and diastolic orthostatic hypotension was defined as a drop of diastolic blood pressure ≥10 mmHg. Recruitment took place between the years 2005-2008, and patients were followed until any of the primary outcome events (cardiovascular death or hospitalization for either myocardial infarction or stroke) occurred or until December 31st, 2014. Measurements of aortic pulse wave velocity and of carotid intima-media thickness were performed at base-line.

RESULTS: Diastolic orthostatic hypertension was found in 140 patients (18.7 %) and was associated with significantly lower risk of cardiovascular events (crude hazard ratio compared with patients with normal systolic and diastolic orthostatic blood pressure response: 0.450, 95 % C.I. 0.206-0.987, P = 0.046). Diastolic orthostatic hypotension was found in 31 patients (4.1 %) and was associated with higher values for aortic pulse wave velocity and carotid intima-media thickness, compared with patients with normal systolic and diastolic orthostatic blood pressure response.

CONCLUSIONS: Diastolic orthostatic hypertension is common in patients with type 2 diabetes, and may be a novel marker for decreased cardiovascular risk in these patients.

Ther Adv Musculoskelet Dis. 2016 Jun;8(3):86-101.

Cardiovascular risk in rheumatoid arthritis: assessment, management and next steps.

Zegkos T, Kitas G, Dimitroulas T.

Rheumatoid arthritis (RA) is associated with increased cardiovascular (CV) morbidity and mortality which cannot be fully explained by traditional CV risk factors; cumulative inflammatory burden and antirheumatic medication-related cardiotoxicity seem to be important contributors. Despite the acknowledgment and appreciation of CV disease burden in RA, optimal management of individuals with RA represents a challenging task which remains suboptimal. To address this need, the European League Against Rheumatism (EULAR) published recommendations suggesting the adaptation of traditional risk scores by using a multiplication factor of 1.5 if two of three specific criteria are fulfilled. Such guidance requires proper coordination of several medical specialties, including general practitioners, rheumatologists, cardiologists, exercise physiologists and psychologists to achieve a desirable result. Tight control of disease activity, management of traditional risk factors and lifestyle modification represent, amongst others, the most important steps in improving CV disease outcomes in RA patients. Rather than enumerating studies and guidelines, this review attempts to critically appraise current literature, highlighting future perspectives of CV risk management in RA.

J Med Internet Res. 2016 May 27;18 (5):e134.

The Electronic CardioMetabolic Program (eCMP) for Patients With Cardiometabolic Risk: A Randomized Controlled Trial.

Azar KM, Koliwad S, Poon T, Xiao L, Lv N, Griggs R, Ma J.

BACKGROUND: Effective lifestyle interventions targeting high-risk adults that are both practical for use in ambulatory care settings and scalable at a population management level are needed.
OBJECTIVE: Our aim was to examine the potential effectiveness, feasibility, and acceptability of delivering an evidence-based Electronic Cardio-Metabolic Program (eCMP) for improving health-related quality of life, improving health behaviors, and reducing cardiometabolic risk factors in ambulatory care high-risk adults.
METHODS: We conducted a randomized, wait-list controlled trial with 74 adults aged ≥18 years recruited from a large multispecialty health care organization. Inclusion criteria were (1) BMI ≥35 kg/m(2) and prediabetes, previous gestational diabetes and/or metabolic syndrome, or (2) BMI ≥30 kg/m(2) and type 2 diabetes and/or cardiovascular disease. Participants had a mean age of 59.7 years (SD 11.2), BMI 37.1 kg/m(2) (SD 5.4) and were 59.5% female, 82.4% white. Participants were randomized to participate in eCMP immediately (n=37) or 3 months later (n=37). eCMP is a 6-month program utilizing video conferencing, online tools, and pre-recorded didactic videos to deliver evidence-based curricula. Blinded outcome assessments were conducted at 3 and 6 months postbaseline. Data were collected and analyzed between 2014 and 2015. The primary outcome was health-related quality of life. Secondary outcomes included biometric cardiometabolic risk factors (eg, body weight), self-reported diet and physical activity, mental health status, retention, session attendance, and participant satisfaction.
RESULTS: Change in quality of life was not significant in both immediate and delayed participants. Both groups significantly lost weight and reduced waist circumference at 6 months, with some cardiometabolic factors trending accordingly. Significant reduction in self-reported anxiety and perceived stress was seen in the immediate intervention group at 6 months. Retention rate was 93% at 3 months and 86% at 6 months post-baseline. Overall eCMP attendance was high with 59.5-83.8% of immediate and delayed intervention participants attending 50% of the virtual stress management and behavioral lifestyle sessions and 37.8-62.2% attending at least 4 out of 7 in-person physical activity sessions. The intervention received high ratings for satisfaction.
CONCLUSIONS: The technology-assisted eCMP is a feasible and well-accepted intervention and may significantly decrease cardiometabolic risk among high-risk individuals.

Circ Res. 2016 May 27;118(11):1706-22.

Epigenetic Changes in Diabetes and Cardiovascular Risk.

Keating ST, Plutzky J, El-Osta A.

Cardiovascular complications remain the leading causes of morbidity and premature mortality in patients with diabetes mellitus. Studies in humans and preclinical models demonstrate lasting gene expression changes in the vasculopathies initiated by previous exposure to high glucose concentrations and the associated overproduction of reactive oxygen species. The molecular signatures of chromatin architectures that sensitize the genome to these and other cardiometabolic risk factors of the diabetic milieu are increasingly implicated in the biological memory underlying cardiovascular complications and now widely considered as promising therapeutic targets. Atherosclerosis is a complex heterocellular disease where the contributing cell types possess distinct epigenomes shaping diverse gene expression. Although the extent that pathological chromatin changes can be manipulated in human cardiovascular disease remains to be established, the clinical applicability of epigenetic interventions will be greatly advanced by a deeper understanding of the cell type-specific roles played by writers, erasers, and readers of chromatin modifications in the diabetic vasculature. This review details a current perspective of epigenetic mechanisms of macrovascular disease in diabetes mellitus and highlights recent key descriptions of chromatinized changes associated with persistent gene expression in endothelial, smooth muscle, and circulating immune cells relevant to atherosclerosis. Furthermore, we discuss the challenges associated with pharmacological targeting of epigenetic networks to correct abnormal or deregulated gene expression as a strategy to alleviate the clinical burden of diabetic cardiovascular disease.

Endocrine. 2016 May 25. [Epub ahead of print]

Glucose, cholesterol, and blood pressure: is lower always better for type 2 diabetes?

Giugliano D, Maiorino MI, Bellastella G, Esposito K.

Diabetes mellitus is a major risk factor for cardiovascular disease. However, the excess risk of death may vary substantially in subgroups of patients with type 2 diabetes, being highest in those younger than 55 years of age. A HbA1c value of 7.0 % or less is recommended for most patients with type 2 diabetes to reduce the incidence of microvascular disease, although individualized approaches that balance the benefits of glycemic control against the harms of hypoglycemia are encouraged. The selection of antidiabetic medications is of paramount importance, as the drug should not aggravate, and ideally even improve cardiovascular risk factors, with the hope to reduce cardiovascular morbidity and mortality. Patients with diabetes mellitus between 40 and 75 years of age with LDL-C between 70 and 189 mg/dL should be treated with a moderate-intensity statin. Implicit in this recommendation is the aim to reduce further LDL-C level in diabetes, in order to improve the cardiovascular outlook. The new PCSK9 inhibitors (evolocumab and arilocumab) are very promising, but, at present, their cost-effectiveness ratios exceed commonly accepted thresholds. For many people with diabetes mellitus and hypertension blood pressure should be <140/90 mmHg, although lower systolic targets (e.g., <130 mmHg) may be appropriate for certain individuals. With the likely exception of LDL-C, it is difficult to define a universal HbA1c and blood pressure target for all patients with type 2 diabetes mellitus. Ultimately, in the face of uncertainty in medicine, the final decision regarding a specific patient is best left to the clinician.

Cholesterol. 2016;2016: 6087981.

Trends of Prevalence of Uncontrolled Risk Factors for Cerebrocardiovascular Disease: outhern Italy from 1988/9 to 2008/9.

Capuano V, Lamaida N, Capuano E, Capuano R, Capuano E, Mazzotta G.

The aim of this study was to determine the trends of cardiovascular risk factor prevalence between 1988/9 and 2008/9 in the 25-74-year-old population in an area of Southern Italy. We compared three cross-sectional studies conducted in random population samples, in 1988/9, 1998/9, and 2008/9 in Salerno, Italy. The methodology of data collection (lipid profile, systolic and diastolic blood pressure, glycaemia, and smoking) and conducting tests which the population underwent during the three phases was standardized and comparable. Prevalence of diabetes, hypertension, hypercholesterolemia, and smoking was calculated and standardized for age. A total of 3491 subjects were included. From 1988/9 to 2008/9, in males, the prevalence of all four risk factors was reduced. In women, there was a clear reduction of hypertension, a similar prevalence of hypercholesterolemia, and an increase of smoking and diabetes. In the area of Salerno, our data confirm that the global prevalence of the major risk factors is decreasing in men, but their absolute values are still far from optimization. In women, diabetes and smoking showed a negative trend, therefore requiring targeted interventions. These data are now used as a base for executive targeted programs to improve prevention of cardiovascular disease in our community.

PLoS One. 2016 May 20;11 (5):e0155978.

Trajectories of Metabolic Risk Factors and Biochemical Markers prior to the Onset of Cardiovascular Disease - The Doetinchem Cohort Study.

Hulsegge G, Spijkerman AM, van der Schouw YT, Bakker SJ, Gansevoort RT, Smit HA, Verschuren WM.

Risk factors often develop at young age and are maintained over time, but it is not fully understood how risk factors develop over time preceding cardiovascular disease (CVD). Our objective was to examine how levels and trajectories of metabolic risk factors and biochemical markers prior to diagnosis differ between people with and without CVD over a period of up to 15-20 years. A total of 449 incident non-fatal and fatal CVD cases and 1,347 age- and sex-matched controls were identified in a prospective cohort between 1993 and 2011. Metabolic risk factors and biochemical markers were measured at five-year intervals prior to diagnosis. Trajectories of metabolic risk factors and biochemical markers were analysed using random coefficient analyses. Although not always statistically significant, participants with CVD had slightly more unfavourable levels for most metabolic risk factors and biochemical markers 15-20 years before diagnosis than controls. Subsequent trajectories until diagnosis were similar in participants with incident CVD and controls for body mass index, diastolic blood pressure, total cholesterol, HDL cholesterol, random glucose, triglycerides, gamma glutamyltransferase, C-reactive protein and uric acid. Trajectories were more unfavourable in participants with CVD than controls for systolic blood pressure, waist circumference and estimated glomerular filtration rate ($p \leq 0.05$). For example, among participants with CVD, systolic blood pressure increased on average by 9 mmHg over the 18-year period preceding diagnosis, whereas the increase among controls was 4 mmHg. In conclusion, unfavourable levels of metabolic risk factors and biochemical markers are present long before CVD, which indicates that the risk of CVD is already partly determined in young adulthood. This underscores the need for early prevention to reduce the burden of CVD.

Child Obes. 2016 May 19. [Epub ahead of print]

Associations Between Sleep Duration and Indicators of Cardiometabolic Disease in Canadian Children and Adolescents: Analyses of the 2007-2009 Canadian Health Measures Survey.

Sluggett L, Wagner SL, Hardy C, Harris RL.

BACKGROUND: Indicators of cardiometabolic disease-including obesity, hyperinsulinemia, and dyslipidemia-are associated with an increased risk of cardiovascular disease and type 2 diabetes. Rates of obesity and type 2 diabetes in Canadian children and adolescents have increased rapidly in recent years; research exploring modifiable risk factors is critical. Experimental and epidemiological research demonstrates that partial sleep loss is linked with deteriorations in indicators of cardiometabolic health. The objectives of this study are (1) to examine associations between short sleep duration and indicators of cardiometabolic disease in Canadian children and adolescents and (2) to identify determinants of short sleep duration in this population.

METHODS: Logistic regression models were developed to examine associations between sleep duration and indicators of cardiometabolic disease and to identify predictors of short sleep duration.

RESULTS: Compared with longer sleepers, children and adolescents with short sleep duration had greater odds of being overweight or obese. Sex- and age-stratified analyses indicated that short sleep duration was linked with greater odds of overweight/obesity in boys and adolescents only. Short sleepers did not have greater odds of having hyperinsulinemia, low HDL cholesterol, or high triglycerides. Age was a strong predictor of inadequate sleep duration.

CONCLUSION: Future studies should include longitudinal designs that address whether short sleep duration in boys and in adolescents contributes directly to the development of overweight and obesity.

Am Heart J. 2016 May;175: 66-76.

Changes in cardiovascular risk factors after 5 years of implementation of a population-based program to reduce cardiovascular disease: The Heart of New Ulm Project.

Sidebottom AC, Sillah A, Miedema MD, Vock DM, Pereira R, Benson G, Boucher JL, Knickelbine T, Lindberg R, VanWormer JJ.

BACKGROUND: Population-based interventions aimed at reducing cardiovascular disease (CVD) hold significant potential and will be increasingly relied upon as the model for health care changes in the United States.
METHODS: The Heart of New Ulm Project is a population-based project with health care, community, and workplace interventions addressing multiple levels of the social-ecological model designed to reduce modifiable CVD risk factors in rural New Ulm, MN. The community is served by one health system, enabling the use of electronic health record data for surveillance. Electronic health record data were extracted at baseline (2008-2009) and 2 follow-up periods (2010-2011, 2012-2013) for residents aged 40 to 79 years. Generalized estimating equations were used to fit longitudinal models of the risk factors.
RESULTS: Of 7,855 residents in the target population, 80% had electronic health record data for each period. The prevalence of at goal (blood pressure [BP] <140/90 mm Hg) and (low-density lipoprotein cholesterol [LDL-C] <130 mg/dL) increased from 79.3% to 86.4% and 68.9% to 71.1%, respectively, from baseline to 5 years, with the largest reductions in BP and LDL-C seen in individuals not at goal at baseline. Blood pressure and lipid-lowering medication use increased from 41.8% to 44.0% and 25.3% to 29.1%, respectively. The proportion at goal for glucose increased from 46.9% to 48.2%. The prevalence body mass index <30 kg/m(2) (55%) did not change, whereas the proportion at-goal for high-density lipoprotein decreased from 63.8% to 58%, and smoking showed an increase from 11.3% to 13.6%.
CONCLUSION: In a community participating in a multifaceted, population-based project aimed at reducing modifiable CVD risk factors, significant improvements in BP, LDL-C, and glucose were observed for 5 years, and body mass index remained stable in a state where obesity was increasing.

BMJ Open. 2016 May 13;6(5):e010639.

General practitioners' justifications for therapeutic inertia in cardiovascular prevention: an empirically grounded typology.

Lebeau JP, Cadwallader JS, Vaillant-Roussel H, Pouchain D, Yaouanc V, Aubin-Auger I, Mercier A, Rusch E, Remmen R, Vermeire E, Hendrickx K.

OBJECTIVE: To construct a typology of general practitioners' (GPs) responses regarding their justification of therapeutic inertia in cardiovascular primary prevention for high-risk patients with hypertension.
DESIGN: Empirically grounded construction of typology. Types were defined by attributes derived from the qualitative analysis of GPs' reported reasons for inaction.
PARTICIPANTS: 256 GPs randomised in the intervention group of a cluster randomised controlled trial.
SETTING: GPs members of 23 French Regional Colleges of Teachers in General Practice, included in the EffectS of a multifaceted intervention on CArdiovascular risk factors in high-risk hyPErtensive patients (ESCAPE) trial.
DATA COLLECTION AND ANALYSIS: The database consisted of 2638 written responses given by the GPs to an open-ended question asking for the reasons why drug treatment was not changed as suggested by the national guidelines. All answers were coded using constant comparison analysis. A matrix analysis of codes per GP allowed the construction of a response typology, where types were defined by codes as attributes. Initial coding and definition of types were performed independently by two teams.
RESULTS: Initial coding resulted in a list of 69 codes in the final codebook, representing 4764 coded references in the question responses. A typology including seven types was constructed. 100 GPs were allocated to one and only one of these types, while 25 GPs did not provide enough data to allow classification. Types (numbers of GPs allocated) were: 'optimists' (28), 'negotiators' (20), 'checkers' (15), 'contextualisers' (13), 'cautious' (11), 'rounders' (8) and 'scientists' (5). For the 36 GPs that provided 50 or more coded references, analysis of the code evolution over time and across patients showed a consistent belonging to the initial type for any given GP.
CONCLUSION: This typology could provide GPs with some insight into their general ways of considering changes in the treatment/management of cardiovascular risk factors and guide design of specific physician-centred interventions to reduce inappropriate inaction.

J Acad Nutr Diet. 2016 May 10. pii: S2212-2672(16)30108-3.

Adult Intake of Minimally Processed Fruits and Vegetables: Associations with Cardiometabolic Disease Risk Factors.

Cavallo DN, Horino M, McCarthy WJ.

BACKGROUND: The US Department of Agriculture launched ChooseMyPlate.gov nutrition recommendations designed to encourage increased fruit and vegetable intake, in part, as a strategy for improving weight control through the consumption of high-satiation foods.
OBJECTIVE: The purpose of this cross-sectional study was to assess the relationship between adults' reported daily intake of fruits and nonstarchy vegetables (ie, those thought to have the lowest energy density) expressed as a proportion of their total daily food intake and objectively measured cardiovascular and metabolic disease risk factors using data from the 2009-2010 National Health and Nutrition Examination Survey (NHANES). Physical activity was included as a moderator variable. DESIGN: This study employed a cross-sectional examination of 2009-2010 NHANES data to assess how daily fruit and nonstarchy vegetable intake was associated with anthropometric measures and cardiometabolic blood chemistry markers.
PARTICIPANTS/SETTING: Adults free of cardiac or metabolic disease (n=1,197) participated in 24-hour dietary recalls; a variety of cardiometabolic biomarkers and anthropometric measures were also collected from participants.
MAIN OUTCOME MEASURES: Among participants with complete data on all variables, the ratio of the combined cup-equivalents of fruit and nonstarchy vegetable intake to the total gram weight of all foods consumed daily (F/V ratio) served as the primary independent variable. Main dependent measures included fasting glucose, insulin, glycosylated hemoglobin, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, total cholesterol, waist circumference, and body mass index.
STATISTICAL ANALYSES PERFORMED: Demographic and behavioral predictors of the F/V ratio and the association between the F/V ratio and cardiometabolic disease risk factors were examined using multivariate regression.
RESULTS: Body mass index (β=-2.58; 95% CI -3.88 to -1.28), waist circumference (β=-6.33; 95% CI -9.81 to -2.84), and insulin (β=-0.21; 95% CI -0.37 to -0.05) were inversely associated with the F/V ratio. These associations were weakened for the subset that adhered to federal physical activity recommendations. No other statistically significant associations were found between F/V ratio and main dependent measures.
CONCLUSIONS: In this nationally representative sample, predicted inverse associations between the proportion of daily fruit and nonstarchy vegetable intake relative to total intake and measures reflective of body fat composition and fasting insulin were confirmed. Future research should examine whether a similar association is observed for other sources of resistant starch, such as whole grains, which are arguably more strongly linked with satiety and host insulin levels.

J Urban Health. 2016 Jun;93(3):589-606.

Cardiovascular Risk Factors of Taxi Drivers.

Elshatarat RA, Burgel BJ.

In the United States (U.S.), cardiovascular disease (CVD) is a major leading cause of death. Despite the high mortality rate related to CVD, little is known about CVD risk factors among urban taxi drivers in the U.S. A cross-sectional design was used to identify the predictors of high cardiovascular risk factors among taxi drivers. Convenience sampling method was used to recruit 130 taxi drivers. A structured questionnaire was used to obtain the data. The sample was male (94 %), age mean (45 ± 10.75) years, married (54 %), born outside of the USA (55 %), had some college or below (61.5 %), night drivers (50.8 %), and driving on average 9.7 years and 41 h/week. About 79 % of them were eligible for CVD prevention, and 35.4 % had high CVD risk factors (4-9 risk factors). A CVD high-risk profile had a significant relationship with the subjects who were ≥55 years old; had hypertension, diabetes, or hyperlipidemia; were drinking alcohol ≥2 times/week; and had insufficient physical activity. Subjects who worked as a taxi driver for more than 10 years (OR 4.37; 95 % CI 1.82, 10.50) and had mental exertion from cab driving >5 out of 10 (OR 2.63; 95 % CI 1.05, 6.57) were more likely to have a CVD high-risk profile. As a conclusion, system-level or worksite interventions include offering healthy food at taxi dispatching locations, creating a work culture of frequent walking breaks, and interventions focusing on smoking, physical activity, and weight management. Improving health insurance coverage for this group of workers is recommended.

J Intellect Disabil Res. 2016 Jun;60(6):594-605.

The prevalence and risk factors of the metabolic syndrome in inpatients with intellectual disability.

Room B, Timmermans O, Roodbol P.

BACKGROUND: The aim of this study is to explore the prevalence and influencing factors of metabolic syndrome (MetS) in people with intellectual disabilities (IDs) and behavioural problems in a Dutch special healthcare institution.METHODS: This observational study was conducted from medical records of physical examinations, laboratory results, medication (history), ethnicity and length of stay, as well as from questionnaires about lifestyle and smoking habits. MetS was defined by using the criteria of the 2009 consensus guidelines. The questions in this study were about the prevalence of MetS over a 1-year period and exploration of the differences between the people with and without MetS to determine the factors associated with it.

RESULTS: The overall prevalence of MetS in the selected population of people with IDs and behavioural problems was 46%. The factors 'use of conventional antipsychotics', 'age', and a ' low nutrition score' increased the risk of developing MetS. Together, these variables determine 19% of the variance in the incidence of MetS.

CONCLUSIONS: The study indicates a firm prevalence of MetS in a vulnerable population, whereby a minority of contributing factors was determined.Professionals should be particularly alert during the provision of antipsychotics, diet and exercise habits to prevent MetS when treating people with IDs and behavioural problems, and further studies are needed to explore the factors that contribute to the nascence and prevalence of MetS.

Rev Neurol. 2016 May 16;62(10):433-438.

Co-morbidities and sleep apnea severity. A study in a cohort of Portuguese patients.

Silva L, Cunha D, Lopes J, Ramalheira J, Freire M, Novio S, Nunez MJ, Mendonca D, Martins-da-Silva A.

INTRODUCTION: Obstructive sleep apnoea syndrome (OSAS) is frequently associated to other morbid conditions that act as risk factors influencing OSAS morbidity and mortality.
AIM: To analyse the presence of co-morbidities in OSAS patients, recruited from a sleep outpatient clinic in Northern Portugal, stratified as a function of OSAS severity.
PATIENTS AND METHODS: A cohort of 319 sleep-disordered patients was assessed by clinical and sleep video-polygraphic recording. Patients (n = 209) with sleep respiratory distress had OSAS (n = 145) and severity defined according to Apnea/Hypopnea Index (AHI); 64 had primary snoring or respiratory distress with AHI < 5; and 110 had other sleep disorders. A full individual background study was possible in 128 OSAS patients. The association to unique or multiple co-morbidities was assessed by clinical and analytical studies in general group or as a function of OSAS severity.
RESULTS: The presence of co-morbidities was of 75% in all OSAS patients and of 79.5% in the severe group of OSAS. Forty seven of patients had only one co-morbidity. The most common was obesity (56.3%) followed by high blood pressure, diabetes and other cardiovascular disorders. Obesity was present in 84% among the most severe OSAS cases and always present in those with multiple co-morbidities. When compared with the group of patients without sleep respiratory distress the co-morbidity condition was more frequently related to OSAS ($p = 0.0196$).
CONCLUSION: Comorbidities are commonly associated to OSAS independently of disease severity. Among the comorbidities present obesity was the most common in the most severe OSAS cases.

Curr Cardiol Rep. 2016 Jun;18(6):56. doi: 10.1007/s11886-016-0728-7.

The Role of Healthy Lifestyle in the Primordial Prevention of Cardiovascular Disease.

Claas SA, Arnett DK.

Whereas primary prevention seeks to forestall development of disease in individuals with elevated risk, primordial prevention seeks to preempt the development of risk factors. Health behaviors-characterized as "lifestyle" factors-are key interventional targets in primordial prevention of cardiovascular disease. Appropriate dietary intake, including limiting salt and saturated fat consumption, can reduce the risk of developing hypertension and dyslipidemias. Regular physical activity is associated with lower blood pressure and healthier lipid profiles. Diet and exercise are critical to maintaining weight conducive to cardiovascular health. Behavioral factors such as stress management, sleep duration, portion control, and meal timing may play a role in weight management and offer additional routes of intervention. Any smoking elevates cardiovascular risk. Although lifestyle modification programs can be instrumental in reaching public health goals, maintaining cardiovascular health should not be a matter solely of willpower. Ideally, structural and social forces should make healthy lifestyles the default option.

Curr Pharm Des. 2016 May 2. [Epub ahead of print]

Gender and Cardiovascular Mortality in Northern and Southern European Populations.

Puddu PE, Schiariti M, Torromeo C.

BACKGROUND: There are no ready explanations for differences in ischemic heart disease incidence between women and men under an epidemiological perspective. However, when myocardial infarction occurs, there are more likely individuals who happen to die.
METHODS: This review from a more recent literature was performed for a two-fold purpose, to describe gender wise: a) the role of classical and novel factors defined to evaluate coronary artery disease (CAD) risk and mortality, aimed at assessing applicability and relevance for primary and secondary prevention; b) the differences in northern versus southern European Countries in risk factors and CAD mortality.
RESULTS: Age-related risk patterns differ in men and women. It is uncertain whether standard factors may index CAD risk, including mortality, in different ways and/or whether specific factors might be targeted gender-wise. A list might be compiled: HDL-cholesterol levels, higher in pre-menopausal women than in men, are more strictly related to CAD; high triglycerides and Lp(a) have a similar relationship; HDL-cholesterol levels have an inverse relation with CAD incidence and mortality. The role of statins is not completely defined in primary prevention for women. However, in secondary prevention statins are equally effective in both genders. Weight and glycemic control are effective to reduce cardiovascular disease (CVD) mortality in women from middle to older age. Similarly, cardiovascular disease (CVD) mortality in women, from middle to older age, might be reduced by controlling blood pressure, particularly among diabetic or over weighted women. Renal dysfunction, either defined by UAE or eGFR or both may usefully predict primary CVD incidence and risk in both genders. In secondary prediction, kidney dysfunction predicts sudden death in women when left ventricular ejection fraction is also evaluated. Serum uric acid that normally increases with age, differentiates gender-related CVD incidences with a peculiar importance in women as compared to men. There has been much interest to investigate loss of ovarian function in explaining age-related differences between genders. More recently, some emphasis has been laid on the loss of ovarian function-related iron stores. There are subgroups of women as those with mitral valve prolapse and increased circulating levels of catecholamines in whom QT interval, physiologically longer in women than men, may be an arrhythmogenic risk index. However, no large population-based studies were ever conducted to assess this. Therefore, in the future, it will be important to implement risk score instruments (charts and soft wares) in women using novel parameters, and among these inflammatory markers and reproductive hormones and serum uric acid.The important results of the WHO MONICA Project confirmed the northern versus southern European gradient in both men and women, for death rates and the proportion of all deaths from cardiovascular causes (including CAD, stroke and other CVD causes). The coronary event rate was initially as high as

1, 000 per 100, 000 inhabitants in Finland and less than 1 fifth of that in Spain with the corresponding figures in women of 200 and 30, respectively.

CONCLUSION: No doubt might still exist that all efforts were undertaken for both men and women, for health and prolongation of life to effectively treat common risk factors such as cigarette consumption, high blood pressure, cholesterol levels and physical inactivity by also paying attention to optimal diet.

Physiol Rep. 2016 Apr;4(8). pii: e12733.

Cardiometabolic risk factors predict cerebrovascular health in older adults:results from the Brain in Motion study.

Tyndall AV, Argourd L, Sajobi TT, Davenport MH, Forbes SC, Gill SJ, Parboosingh JS, Anderson TJ, Wilson BJ, Smith EE, Hogan DB, Hill MD, Poulin MJ.

Aging and physical inactivity are associated with an increased risk of developing metabolic syndrome (MetS). With the rising prevalence of MetS, it is important to determine the extent to which it affects cerebrovascular health. The primary purpose of this report is to examine the impact of MetS on cerebrovascular health (resting cerebral blood flow (CBF) peak velocity ($\bar{V}P$), cerebrovascular conductance (CVC), and CBF responses to hypercapnia) in healthy older adults with normal cognition. A secondary goal was to examine the influence of apolipoprotein E (APOE) ε4 expression on these indices. In a sample of 258 healthy men and women older than 53 years, 29.1% met criteria for MetS. MetS, sex, and age were found to be significant predictors of CVC, and $\bar{V}P$, MetS, and APOE status were significant predictors of $\bar{V}P$-reactivity, and CVC-reactivity was best predicted by MetS status. After controlling for these factors, participants with MetS demonstrated lower cerebrovascular measures (CVC, $\bar{V}P$, CVC-reactivity, and $\bar{V}P$-reactivity) compared to participants without MetS. APOE ε4 carriers had higher $\bar{V}P$-reactivity than noncarriers. These results provide evidence that cardiometabolic and vascular risk factors clustered together as the MetS predict measures of cerebrovascular health indices in older adults. Higher $\bar{V}P$-reactivity in APOE ε4 carriers suggests vascular compensation for deleterious effects of this known risk allele for Alzheimer's disease and stroke.

J Gerontol A Biol Sci Med Sci. 2016 Apr 26. pii: glw077. [Epub ahead of print]

Association of an Index of Healthy Aging With Incident Cardiovascular Disease and Mortality in a Community-Based Sample of Older Adults.

McCabe EL, Larson MG, Lunetta KL, Newman AB, Cheng S, Murabito JM.

BACKGROUND: The healthy aging index (HAI) was developed as a marker of health in multiple systems that can identify individuals who age most successfully.
METHODS: We calculated an HAI in 934 Framingham Offspring Study participants aged 60 or older at baseline. Heart rate and C-reactive protein (CRP) were added in modified versions of the HAI. Cox proportional hazard models were used to quantify the association of the HAI with mortality, cardiovascular disease (CVD), and cancer. We used fully conditional specification to multiply impute missing values for HAI components, increasing the sample size by 44%.
RESULTS: Over 10 years of follow-up, there were 138 deaths, 103 incident cases of CVD, and 138 incident cases of cancer. In models adjusted for age, sex, and behavioral risk factors, the HAI was associated with mortality (hazard ratio [HR] per unit of HAI 1.24, 95% confidence interval [CI] 1.13-1.36) and with CVD (HR 1.27, 95% CI 1.13-1.42), but not with cancer (HR 1.01, 95% CI 0.91-1.11) in observed (non-missing) data. In multivariable models further adjusting for prevalent diseases, results were slightly attenuated. When including heart rate and CRP, a modified HAI gave stronger associations. Results with imputed data are similar to results from complete case analyses.
CONCLUSIONS: In our large community-based sample, the HAI is a strong predictor of mortality and CVD. Other factors that are strongly associated with mortality, such as heart rate and CRP can improve the ability of the HAI to identify the healthiest older adults.

Int J Cardiol. 2016 Jul 15;215:41-6.

Psychosocial risk factors for the metabolic syndrome: A prospective cohort study.

Pedersen JM, Lund R, Andersen I, Clark AJ, Prescott E, Rod NH.

BACKGROUND/OBJECTIVES: Metabolic deregulations and development of metabolic syndrome may be an important pathway underlying the relationship between stress and cardiovascular disease. We aim to estimate the effect of a comprehensive range of psychosocial factors on the risk of developing metabolic syndrome in men and women.
METHODS: The study population consisted of 3621 men and women from the Copenhagen City Heart Study who were free of metabolic syndrome at baseline and reexamined after 10years. The data was analyzed by multivariable logistic regression models adjusted for age, education, income, menopausal status and life style factors.
RESULTS: We found major life events in adult life (OR 1.48, 95% CI 0.93 to 2.36) and major life events at work (OR 2.75, 95% CI 1.38 to 5.50), lacking a confidant (OR 1.94, 95% CI 1.07 to 3.53) and dissatisfaction with social network (OR 1.53, 95% CI 1.11 to 2.11) to be risk factors for developing the metabolic syndrome in women, while vital exhaustion (OR 2.09, 95% CI 0.95 to 4.59) and intake of sleep medications (OR 2.54, 95% CI 0.92 to 5.96) may play a more important role in men.
CONCLUSIONS: Experiencing major life events in work and adult life and/or dysfunctional social networks is a risk factor for metabolic syndrome in women, and stress reactions such as vital exhaustion and intake of sleep medications may play a more important role in the development of metabolic syndrome men.

Circ Cardiovasc Genet. 2016 Jun;9(3):279-86.

Cardiovascular Risk Factors and Ischemic Heart Disease: Is the Confluence of Risk Factors Greater Than the Parts? A Genetic Approach.

Elosua R, Lluís-Ganella C, Subirana I, Havulinna A, Läll K, Lucas G, Sayols-Baixeras S, Pietilä A, Alver M, Cabrera de León A, Sentí M, Siscovick D, Mellander O, Fischer K, Salomaa V, Marrugat J.

BACKGROUND: Cardiovascular risk factors tend to aggregate. The biological and predictive value of this aggregation is questioned and genetics could shed light on this debate. Our aims were to reappraise the impact of risk factor confluence on ischemic heart disease (IHD) risk by testing whether genetic risk scores (GRSs) associated with these factors interact on an additive or multiplicative scale, and to determine whether these interactions provide additional value for predicting IHD risk.

METHODS AND RESULTS: We selected genetic variants associated with blood pressure, body mass index, waist circumference, triglycerides, type-2 diabetes mellitus, high-density lipoprotein and low-density lipoprotein cholesterol, and IHD to create GRSs for each factor. We tested and meta-analyzed the impact of additive (synergy index) and multiplicative (βinteraction) interactions between each GRS pair in 1 case-control (n=6042) and 4 cohort studies (n=17794) and evaluated the predictive value of these interactions. We observed 2 multiplicative interactions: GRSLDL·GRSTriglycerides (βinteraction=-0.096; SE=0.028) and nonpleiotropic GRSIHD·GRSLDL (βinteraction=0.091; SE=0.028). Inclusion of these interaction terms did not improve predictive capacity.

CONCLUSIONS: The confluence of low-density lipoprotein cholesterol and triglycerides genetic risk load has an additive effect on IHD risk. The interaction between low-density lipoprotein cholesterol and IHD genetic load is more than multiplicative, supporting the hazardous impact on atherosclerosis progression of the combination of inflammation and increased lipid levels. The capacity of risk factor confluence to improve IHD risk prediction is questionable. Further studies in larger samples are warranted to confirm and expand our results.

PLoS One. 2016 Apr 21;11(4):e0154273.

Metabolically Healthy Obesity and the Risk of Cardiovascular Disease in the Elderly Population.

Dhana K, Koolhaas CM, van Rossum EF, Ikram MA, Hofman A, Kavousi M, Franco OH.

BACKGROUND: Whether being metabolically healthy obese (MHO)-defined by the presence of obesity in the absence of metabolic syndrome-is associated with subsequent cardiovascular disease (CVD) remains unclear and may depend on the participants' age. We examined the association of being MHO with CVD risk in the elderly.

METHODS AND FINDINGS: This study included 5,314 individuals (mean age 68 years) from the prospective population-based Rotterdam Study. We categorized our population in groups according to body mass index (BMI) and presence and absence of metabolic syndrome, and estimated the hazard ratio (HR) and 95% confidence interval (95%CI) for every group by using Cox proportional hazard models. Among 1048 (19.7%) obese individuals we identified 260 (24.8%) MHO subjects. Over 14 years of follow-up there were 861 incident CVD cases. In the multivariable adjusted analysis, we did not observe an increased CVD risk in MHO individuals (HR 1.07, 95%CI 0.75-1.53), compared to normal weight individuals without metabolic syndrome. CVD risk was increased by the presence of metabolic syndrome in normal weight (HR 1.35, 95%CI 1.02-1.80), overweight (HR 1.32, 95%CI 1.09-1.60) and obese (HR 1.33, 95%CI 1.07-1.66) individuals, compared to those with normal weight without metabolic syndrome. In a mediation analysis, 71.3% of the association between BMI and CVD was explained by the presence of metabolic syndrome.

CONCLUSIONS: In our elderly population, we found that the presence of obesity without metabolic syndrome did not confer a higher CVD risk. However, metabolic syndrome was strongly associated with CVD risk, and was associated with an increased risk in all BMI categories. Therefore, preventive interventions targeting cardiometabolic risk factors could be considered in elderly, regardless of weight status.

PLoS One. 2016 Apr 19;11(4):e0152657.

Workplace Digital Health Is Associated with Improved Cardiovascular Risk Factors in a Frequency-Dependent Fashion: A Large Prospective Observational Cohort Study.

Widmer RJ, Allison TG, Keane B, Dallas A, Bailey KR, Lerman LO, Lerman A.

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the US. Emerging employer-sponsored work health programs (WHP) and Digital Health Intervention (DHI) provide monitoring and guidance based on participants' health risk assessments, but with uncertain success. DHI-mobile technology including online and smartphone interventions-has previously been found to be beneficial in reducing CVD outcomes and risk factors, however its use and efficacy in a large, multisite, primary prevention cohort has not been described to date. We analyzed usage of DHI and change in intermediate markers of CVD over the course of one year in 30,974 participants of a WHP across 81 organizations in 42 states between 2011 and 2014, stratified by participation log-ins categorized as no (n = 14,173), very low (<12/yr, n = 12,260), monthly (n = 3,360), weekly (n = 651), or semi-weekly (at least twice per week). We assessed changes in weight, waist circumference, body mass index (BMI), blood pressure, lipids, and glucose at one year, as a function of participation level. We utilized a Poisson regression model to analyze variables associated with increased participation. Those with the highest level of participation were slightly, but significantly (p<0.0001), older (48.3±11.2 yrs) than non-participants (47.7±12.2 yr) and more likely to be females (63.7% vs 37.3% p<0.0001). Significant improvements in weight loss were demonstrated with every increasing level of DHI usage with the largest being in the semi-weekly group (-3.39±1.06 lbs; p = 0.0013 for difference from weekly). Regression analyses demonstrated that greater participation in the DHI (measured by log-ins) was significantly associated with older age (p<0.001), female sex (p<0.001), and Hispanic ethnicity (p<0.001). The current study demonstrates the success of DHI in a large, community cohort to modestly reduce CVD risk factors in individuals with high participation rate. Furthermore, participants previously underrepresented in WHPs (females and Hispanics) and those with an increased number of CVD risk factors including age and elevated BMI show increased adherence to DHI, supporting the use of this low-cost intervention to improve CVD health.

Heart. 2016 Jul 1;102(13):1009-16.

Loneliness and social isolation as risk factors for coronary heart disease and stroke: systematic review and meta-analysis of longitudinal observational studies.

Valtorta NK, Kanaan M, Gilbody S, Ronzi S, Hanratty B.

BACKGROUND: The influence of social relationships on morbidity is widely accepted, but the size of the risk to cardiovascular health is unclear.
OBJECTIVE: We undertook a systematic review and meta-analysis to investigate the association between loneliness or social isolation and incident coronary heart disease (CHD) and stroke.
METHODS: Sixteen electronic databases were systematically searched for longitudinal studies set in high-income countries and published up until May 2015. Two independent reviewers screened studies for inclusion and extracted data. We assessed quality using a component approach and pooled data for analysis using random effects models.
RESULTS: Of the 35 925 records retrieved, 23 papers met inclusion criteria for the narrative review. They reported data from 16 longitudinal datasets, for a total of 4628 CHD and 3002 stroke events recorded over follow-up periods ranging from 3 to 21 years. Reports of 11 CHD studies and 8 stroke studies provided data suitable for meta-analysis. Poor social relationships were associated with a 29% increase in risk of incident CHD (pooled relative risk: 1.29, 95% CI 1.04 to 1.59) and a 32% increase in risk of stroke (pooled relative risk: 1.32, 95% CI 1.04 to 1.68). Subgroup analyses did not identify any differences by gender.
CONCLUSIONS: Our findings suggest that deficiencies in social relationships are associated with an increased risk of developing CHD and stroke. Future studies are needed to investigate whether interventions targeting loneliness and social isolation can help to prevent two of the leading causes of death and disability in high-income countries.

Medicine (Baltimore). 2016 Apr;95 (15):e3156.

Cardiovascular Risk Factors in Parents of Food-Allergic Children.

Walker SO, Mao G, Caruso D, Hong X, Pongracic JA, Wang X.

Previous studies suggest that chronic stress may induce immune system malfunction and a broad range of adverse health outcomes; however, the underlying pathways for this relationship are unclear. Our study aimed to elucidate this question by examining the relationship between parental cardiovascular risk factors including systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), and waist-to-hip ratio (WHR) and maternal psychological stress score (MPSS) relative to the severity of the child's food allergy (FA) and number of affected children. SBP, DBP, BMI, and WHR were measured and calculated at the time of recruitment by trained nurses. MPSS was obtained based on self-report questionnaires covering lifestyle adjustments, perceived chronic stress, and quality of life. General linear models examined whether caregiver chronic stress was associated with FA. For mothers with children under age 5 years, SBP, DBP and number of affected children had strong and graded relationships with severity of the child's FA. MPSS was also significantly and positively associated with child FA severity ($P<0.001$). However, no relationships were found between FA severity, BMI, or WHR for either parent. This was also the case for paternal SBP, DBP, and number of affected children of any age. There is a strong and graded link between cardiovascular risk and perceived stress in mothers of food-allergic children under age 5. Findings may have important implications for family-centered care of FA, may generalize to caregivers of children with chronic conditions, and extend the literature on allostatic load.

BMC Public Health. 2016 Apr 11;16(1):305.

A qualitative study of factors related to cardiometabolic risk in rural men.

Morgan EH, Graham ML(1), Folta SC, Seguin RA.

BACKGROUND: Rural men are known to have poor health behaviors, which contribute to their elevated burden of cardiometabolic disorders in the United States. Although regular physical activity, healthy eating, and avoiding tobacco can reduce cardiometabolic risk, little is known about how to engage rural men in health promotion programs. To bridge this gap in evidence, we investigate knowledge of modifiable cardiometabolic risk factors among rural men in the western United States, identify their concerns related to heart health and motivation to reduce risk, and explore individual, social, and community-level influences on heart-healthy behaviors, specifically diet, physical activity, and tobacco use.

METHODS: We conducted seven focus groups with 54 sedentary, overweight/obese men (mean body mass index [BMI] = 31.3 ± 4.6) aged 43-88 residing in government-designated "medically underserved" rural Montana towns in September and October 2014. All sessions were audio-recorded and transcribed verbatim. Transcripts were coded and analyzed thematically using Nvivo software. Participants also completed a brief questionnaire about personal characteristics and health behaviors. These data were explored descriptively.

RESULTS: Despite being classified as overweight/obese and sedentary, no participants reported to be in poor health. Many men described health relative to self-reliance and the ability to participate in outdoor recreation; concern with health appeared to be related to age. Participants were generally knowledgeable of heart-healthy behaviors, but many felt fatalistic about their own risk. Catalysts for behavior change included a serious medical event in the household and desire to reduce aging-associated functional decline. Barriers to adopting and maintaining healthy eating and physical activity habits and abstaining from tobacco included normative beliefs around masculinity and individual liberty, the limited social universe of small towns, winter weather, time constraints, and preferences for unhealthy foods. Facilitators included behavioral self-monitoring, exercising with a partner, and opportunities for preferred activities, such as hunting and team sports.

CONCLUSIONS: These findings provide important insight about influences on rural men's health behaviors and provide guidance for possible intervention strategies to promote cardiometabolic health.

Occup Med (Lond). 2016 Apr 9. pii: kqw029. [Epub ahead of print]

Active commuting and cardiovascular risk among health care workers.

Lerssrimongkol C, Wisetborisut A, Angkurawaranon C, Jiraporncharoen W, Lam KB.

BACKGROUND: Although the benefit of physical activity on cardiovascular health has been well demonstrated, being physically active can be difficult for health care workers. Active commuting such as walking or cycling may be a good way to promote physical activity.
AIMS: To investigate the relationship between active commuting and cardiovascular disease risk factors in health care workers.
METHODS: A cross-sectional study of health care workers conducted in Chiang Mai University Hospital, Thailand. Information on demographics and lifestyle, including active commuting, was obtained from questionnaires. Results were analysed with multiple logistic regression, adjusting for other physical activity and possible confounders.
RESULTS: Among 3204 participants, fewer than half engaged in active commuting. After adjustment for possible confounders, low active commuting was associated with increased risk of hypertension [adjusted odds ratio (aOR) 1.3, 95% confidence interval (CI) 1.1-1.7]. High active commuting was associated with central obesity (aOR 1.4, 95% CI 1.0-1.8). Compared with non-active commuters, younger active commuters (aged under 40) had reduced prevalence of hypertension (aOR 0.4, 95% CI 0.2-1.0), while older active commuters (aged 40 or over) demonstrated increased hypertension (aOR 1.6, 95% CI 1.1-2.3) and central obesity (aOR 1.5, 95% CI 1.1-2.1).
CONCLUSIONS: We found conflicting evidence on the relationship between active commuting and cardiovascular risk factors. Reverse causation may explain the association between active commuting and hypertension and central obesity and should be investigated further.

Expert Rev Cardiovasc Ther. 2016 Jul;14(7):855-69.

Epidemiology of cardiovascular disease: recent novel outlooks on risk factors and clinical approaches.

Niiranen TJ, Vasan RS.

INTRODUCTION: Cardiovascular (CVD) risk assessment with traditional risk factors (age, sex, blood pressure, lipids, smoking and diabetes) has remained relatively invariant over the past decades despite some inaccuracies associated with this approach. However, the search for novel, robust and cost-effective risk markers of CVD risk is ongoing.
AREAS COVERED: A large share of the major developments in CVD risk prediction during the past five years has been made in large-scale biomarker discovery and the so called 'omics' - the rapidly growing fields of genomics, transcriptomics, epigenetics and metabolomics. This review focuses on how these new technologies are helping drive primary CVD risk estimation forward in recent years, and speculates on how they could be utilized more effectively for discovering novel risk factors in the future. Expert commentary: The search for new CVD risk factors is currently undergoing a significant revolution as the simple relationship between single risk factors and disease will have to be replaced by models that strive to integrate the whole field of omics into medicine.

PLoS One. 2016 Apr 4;11(4):e0153031.

Comparison of Visceral Fat Measures with Cardiometabolic Risk Factors in Healthy Adults.

Pak K, Lee SH, Lee JG, Seok JW, Kim IJ.

We aimed to evaluate the associations of visceral adiposity with cardiometabolic risk factors in normal subjects with integrated 18F-Fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT). A total of 58 normal subjects who underwent 18F-FDG PET/CT scan for cancer screening were included in this study. Volume and average Hounsfield unit (HU) of visceral adipose tissue (VAT) was measured from CT components of integrated PET/CT. Standardized uptake values (SUVmax) of liver, spleen, lumbar spine and ascending aorta (AA) were measured from PET components of integrated PET/CT. Body mass index (coefficient 78.25, $p = 0.0259$), glucose (37.62, $p<0.0001$), insulin (348.90, $p = 0.0011$), logarithmic transformation of homeostatic model assessment index-insulin resistance (-2118.37, $p = 0.0007$), and VAT HU (-134.99, $p<0.0001$) were independently associated with VAT volume. Glucose (0.1187, $p = 0.0098$) and VAT volume (-0.004, $p<0.0001$) were found to be associated with VAT HU. Both VAT volume and VAT HU of whole abdominal cavity is significantly associated with cardiometabolic risk factors.

Int J Cardiol. 2016 Jun 1; 212:131-7.

Coffee consumption and risk of cardiovascular events in hypertensive patients. Results from the HARVEST.

Palatini P, Fania C, Mos L, Garavelli G, Mazzer A, Cozzio S, Saladini F, Casiglia E.

BACKGROUND: Controversy still exists about the long-term cardiovascular effects of coffee consumption in hypertension.
METHODS: The predictive capacity of coffee use for cardiovascular events (CVEs) was investigated in 1204 participants from the HARVEST, a prospective cohort study of non-diabetic subjects aged 18-45years, screened for stage 1 hypertension. Subjects were grouped into three categories of coffee drinking, non-drinkers (none), moderate drinkers (1 to 3cups/day) and heavy drinkers (4or more cups/day). Multivariate Cox proportional hazards models were developed adjusting for possible confounding variables and risk factors.
RESULTS: During a median follow-up of 12.6years, CVEs were developed by 60 participants. CVEs were more common among coffee drinkers than abstainers (abstainers, 2.2%; moderate drinkers, 7.0%; heavy drinkers, 14.0%; p for trend=0.0003). In a multivariable Cox regression model, coffee use was a significant predictor of CVE in both coffee categories, with a hazard ratio of 2.8 (95% CI, 1.0-7.9) in moderate coffee drinkers and of 4.5 (1.4-14.2) in heavy drinkers compared to abstainers. After inclusion of change in body weight (p=ns), incident hypertension (p=0.027) and presence of diabetes/prediabetes (p=ns) at follow-up end, the association with CVE was attenuated but remained significant in heavy coffee drinkers (HR, 95% CI, 3.4, 1.04-11.3).
CONCLUSIONS: These data show that coffee consumption increases the risk of CVE in a linear fashion in hypertension. This association may be explained in part by the association between coffee and development of hypertension. Hypertensive patients should be discouraged from drinking coffee.

Ir J Med Sci. 2016 May;185 (2):403-12.

Lifestyle risk factors for cardiovascular disease and diabetic risk in a sedentary occupational group: the Galway taxi driver study.

Martin WP, Sharif F, Flaherty G.

BACKGROUND: Taxi drivers are at increased risk of cardiovascular disease (CVD), something which persists after correcting for the overrepresentation of traditional risk factors for CVD in this cohort. The contribution of lifestyle risk factors to this residually elevated CVD risk remains under-evaluated.
AIMS: We aimed to determine the prevalence of lifestyle risk factors for CVD, self-reported medical risk factors for CVD, and future risk of type 2 diabetes amongst Irish taxi drivers.
METHODS: Male taxi drivers with no history of CVD and type 2 diabetes and working in Galway city in the west of Ireland were invited to participate. Physical activity levels, dietary patterns, anthropometry, smoking, hypertension, hypercholesterolaemia, and Finnish Diabetes Risk Score (FINDRISC) values were recorded in a cross-sectional manner.
RESULTS: 41 taxi drivers (mean age 56.7 ± 9.8 years) participated. 37 % were insufficiently active based on self-report, although only 8 % objectively achieved 10, 000 steps per day. Mean modified Mediterranean diet score (mMDS) was 4.6 ± 2.2, and only 13 % of participants had a normal body mass index (BMI) or waist circumference (WC). Those who worked for taxi companies tended to have a higher BMI ($p = .07$) and WC ($p = .04$) by multivariable regression. 22 % were current smokers, although a quit rate of 72 % was observed amongst the 78 % of taxi drivers who had ever smoked. 25 % were at high or very high risk of future type 2 diabetes.
CONCLUSION: Lifestyle risk factors for CVD and dysglycaemia are prevalent amongst Irish taxi drivers.

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PMID: 26984791 [PubMed - in process]

Br J Nutr. 2016 May;115(9):1661-8.

Daily chocolate consumption is inversely associated with insulin resistance and liver enzymes in the Observation of Cardiovascular Risk Factors in Luxembourg study.

Alkerwi A, Sauvageot N, Crichton GE, Elias MF, Stranges S

This study examined the association of chocolate consumption with insulin resistance and serum liver enzymes in a national sample of adults in Luxembourg. A random sample of 1153 individuals, aged 18-69 years, was recruited to participate in the cross-sectional Observation of Cardiovascular Risk Factors in Luxembourg study. Chocolate consumption (g/d) was obtained from a semi-quantitative FFQ. Blood glucose and insulin levels were used for the homoeostasis model assessment of insulin resistance (HOMA-IR). Hepatic biomarkers such as serum γ-glutamyl-transpeptidase (γ-GT), serum aspartate transaminase and serum alanine transaminase (ALT) (mg/l) were assessed using standard laboratory assays. Chocolate consumers (81·8 %) were more likely to be younger, physically active, affluent people with higher education levels and fewer chronic co-morbidities. After excluding subjects taking antidiabetic medications, higher chocolate consumption was associated with lower HOMA-IR (β=-0·16, P=0·004), serum insulin levels (β=-0·16, P=0·003) and γ-GT (β=-0·12, P=0·009) and ALT (β=-0·09, P=0·004), after adjustment for age, sex, education, lifestyle and dietary confounding factors, including intakes of fruits and vegetables, alcohol, polyphenol-rich coffee and tea. This study reports an independent inverse relationship between daily chocolate consumption and levels of insulin, HOMA-IR and liver enzymes in adults, suggesting that chocolate consumption may improve liver enzymes and protect against insulin resistance, a well-established risk factor for cardiometabolic disorders. Further observational prospective research and well-designed randomised-controlled studies are needed to confirm this cross-sectional relationship and to comprehend the role and mechanisms that different types of chocolate may play in insulin resistance and cardiometabolic disorders.

Diabetes. 2016 May; 65(5):1370-9.

Risk Factors for Cardiovascular Disease in Type 1 Diabetes.

Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group.

Risk factors for cardiovascular disease (CVD) are well-established in type 2 but not type 1 diabetes (T1DM). We assessed risk factors in the long-term (mean 27 years) follow-up of the Diabetes Control and Complications Trial (DCCT) cohort with T1DM. Cox proportional hazards multivariate models assessed the association of traditional and novel risk factors, including HbA1c, with major atherosclerotic cardiovascular events (MACE) (fatal or nonfatal myocardial infarction [MI] or stroke) and any-CVD (MACE plus confirmed angina, silent MI, revascularization, or congestive heart failure). Age and mean HbA1c were strongly associated with any-CVD and with MACE. For each percentage point increase in mean HbA1c, the risk for any-CVD and for MACE increased by 31 and 42%, respectively. CVD and MACE were associated with seven other conventional factors, such as blood pressure, lipids, and lack of ACE inhibitor use, but not with sex. The areas under the receiver operating characteristics curves for the association of age and HbA1c, taken together with any-CVD and for MACE, were 0.70 and 0.77, respectively, and for the final models, including all significant risk factors, were 0.75 and 0.82. Although many conventional CVD risk factors apply in T1DM, hyperglycemia is an important risk factor second only to age.

Metab Syndr Relat Disord. 2016 Apr;14 (3):145-53.

Neck Circumference Is Independently Associated with Cardiometabolic Risk Factors: Cross-Sectional Analysis from ELSA-Brasil.

Baena CP, Lotufo PA, Fonseca MG, Santos IS, Goulart AC, Benseñor IM.

BACKGROUND: Neck circumference (NC) is a simple anthropometric measurement that may be linked with cardiometabolic risk factors. We analyzed the association between NC and a range of cardiometabolic risk factors.

METHODS: In a cross-sectional and sex-specific analysis of the ELSA-Brasil study (15,105 civil servants aged 35-74 years), we excluded participants with diabetes, taking antihypertensive and/or lipid-lowering drugs. Cardiometabolic risk factors were homeostasis model assessment of insulin resistance (≥75th percentile), low high-density lipoprotein (HDL; <50 mg/dL for women and <40 mg/dL for men), high triglycerides ≥150 mg/dL, systolic blood pressure ≥130 mmHg, or diastolic blood pressure ≥85 mmHg. Logistic regression models were built to analyze the association between individual and clustered risk factors and 1-standard deviation (SD) increase in NC after adjustments for age, smoking, alcohol, body mass index, and waist circumference.

RESULTS: We analyzed 8726 participants (56.3% women), with a mean age of 49.2±8.0 years. Mean NC was 38.9±2.6 cm for men and 33.4±2.6 cm for women. Fully adjusted odds ratios (ORs) [95% confidence intervals (CIs)] per 1-SD increase in NC in men and women were, respectively, 1.32 (1.16-1.51) and 1.47 (1.31-1.64) for insulin resistance; 1.24 (1.11-1.39) and 1.25 (1.11-1.40) for raised blood pressure; 1.50 (1.33-1.70) and 1.51 (1.33-1.70) for high triglycerides; and 1.22 (0.92-1.61) and 1.54 (1.23-1.86) for low HDL. Fully adjusted ORs (95% CI) of three or more clustered risk factors per 1-SD increase in NC in men and women were 1.54 (1.34-1.79) and 1.71 (1.41-2.06).

CONCLUSION: NC is significantly and independently associated with cardiometabolic risk factors in a well-defined apparently healthy population.

Diabetes Metab. 2016 Apr;42 (2):112-21.

Determining the association between types of sedentary behaviours and cardiometabolic risk factors: A 6-year longitudinal study of French adults.

Menai M, Charreire H, Kesse-Guyot E, Andreeva VA, Hercberg S, Galan P, Oppert JM, Fezeu LK.

AIM: This study identified the longitudinal associations between leisure-time sedentary behaviours [television (TV) viewing, computer use and reading (h/week)] and cardiometabolic risk factors, including the metabolic syndrome.
METHODS: A total of 2517 participants (mean±SD age: 55.5±4.9years) were assessed in 2001 and in 2007 for physical activity and leisure-time sedentary behaviours, anthropometry, body composition, blood pressure, fasting blood glucose and lipids, using standardized methods. Multivariate generalized linear (beta, 95% CI and P values) and logistic (OR and 95% CI) regression models were used to assess cross-sectional associations between sedentary behaviours and cardiometabolic risk factors, while a 6-year longitudinal study explored these associations as well as the odds of developing the metabolic syndrome, as defined by the NCEP ATPIII.
RESULTS: Increased TV viewing time over the follow-up period was positively associated with increases in body mass index (BMI; P<0.01) and percent body fat (P<0.001), and marginally with waist circumference (P=0.06). Reverse associations were also found, with changes in BMI, percent fat mass and waist circumference positively associated with TV viewing and computer use. Associations between reading and cardiometabolic risk factors were less consistent. Each 1-h/week increase in baseline TV viewing and in reading was associated with an increase in the chances of developing the metabolic syndrome (OR=1.031, 95% CI: 0.998-1.060, P=0.07; and OR=1.032, 95% CI: 1.002-1.065, P=0.02; respectively).
CONCLUSION: The present study data emphasizes the notion of differential associations of specific sedentary behaviours with cardiometabolic risk factors. They are also evidence that different longitudinal associations should be taken into account when designing public health objectives of interventions aimed at improving cardiometabolic health.

Ann Hum Biol. 2016 May;43 (3):183-90.

Exercise intervention and cardiovascular risk factors in obese children. Comparison between obese youngsters taking part in a physical activity school-based programme with and without individualised diet counselling: the ACORDA project.

Aires L, Silva G, Martins C, Marques E, Lagoa MJ, Ribeiro JC, Rêgo C, Nascimento H, Pereira PR, Santos-Silva A, Belo L, Mota J.

AIM: To determine the effects of a school-based exercise intervention programme on cardiovascular risk factors, including body fat (BF), metabolic profile and physical activity (PA) in children with and without individualised dietary counselling approach (IDC and WIDC).
SUBJECTS AND METHODS: Forty-six overweight children from 6-16 years old (25 girls, 54.3%; age=10.3±2.8) of six schools took part in an 8-month interdisciplinary, school-based intervention programme. All children were engaged in PA classes, but only one group was exposed to individualised counselling. Blood pressure (BP), lipids and lipoproteins, accelerometer-based PA, percentage of body fat (%BF) and trunk fat (%TF) measures were taken before and after intervention. General Linear Model (Repeated Measures ANOVA) adjusted for age, maturation and height change was used to analyse the longitudinal effect of individualised counselling between two evaluations in each group.
RESULTS: Favourable changes were observed for %BF, %TF, systolic BP and total cholesterol in the IDC group. Subjects WIDC only increased light and moderate-vigorous PA. In IDC, significant effects for time * group interactions were found for systolic BP, total cholesterol and LDL-cholesterol, indicating that counselling might add favourable changes in these markers, beyond those explained by PA and growth.
CONCLUSION: School-based interventions can contribute to counteracting obesity in youth, particularly when individualised dietary counselling is provided. Therefore, the link between schools and professional counselling should be strengthened to ensure consolidated changes towards healthy behaviours.

J Hum Nutr Diet. 2016 Jun;29(3):363-73.

Alternative health eating index and the Dietary Guidelines from American Diabetes Association both may reduce the risk of cardiovascular disease in type 2 diabetes patients.

Wu PY, Huang CL, Lei WS, Yang SH.

BACKGROUND: In the general population, a higher Alternate Healthy Eating Index (AHEI)-2010 score is related to decreased cardiovascular disease (CVD) risk. Few studies have described the dietary patterns that reduce the risk of CVD or coronary heart disease (CHD) in type 2 diabetes mellitus (T2DM) patients. In the present study, the association between the American Diabetes Association (ADA)-recommended dietary pattern, AHEI-2010 , and CVD risk factors and the CVD incidence over 52 months in T2DM patients was evaluated.

METHODS: The ADA score was developed from the ADA dietary recommendations. In this prospective study, the 24-h dietary recall of 124 adult T2DM patients without nephropathy or chronic kidney disease was collected. The CVD risk factors were collected at baseline and at 6-month follow-up.

RESULTS: Compared with lower ADA and AHEI-2010 score participants, the higher score participants exhibited a significantly lower waist circumference, serum low-density lipoprotein cholesterol level and 10-year risk of CHD. Participants with higher ADA dietary scores had a significantly reduced risk of central obesity and systolic blood pressure >140 mmHg. Higher AHEI-2010 scores were significantly related to a reduced risk of serum low-density lipoprotein cholesterol > 100 mg dL(-1) . Seven participants had their first-ever CVD during the follow-up period, although neither ADA score, nor AHEI-2010 score could predict CVD incidence.

CONCLUSIONS: The ADA-recommended dietary pattern and a higher AHEI-2010 score might both exhibit reduced risk factors of CVD in T2DM patients.

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Body-Mass Index in 2.3 Million Adolescents and Cardiovascular Death in Adulthood

Twig G. et al

BACKGROUND In light of the worldwide increase in childhood obesity, we examined the association between body-mass index (BMI) in late adolescence and death from cardiovascular causes in adulthood.

METHODS We grouped data on BMI, as measured from 1967 through 2010 in 2.3 million Israeli adolescents (mean age, 17.3±0.4 years), according to age- and sex-specific percentiles from the U.S. Centers for Disease Control and Prevention. Primary outcomes were the number of deaths attributed to coronary heart disease, stroke, sudden death from an unknown cause, or a combination of all three categories (total cardiovascular causes) by mid-2011. Cox proportional-hazards models were used.

RESULTS During 42,297,007 person-years of follow-up, 2918 of 32,127 deaths (9.1%) were from cardiovascular causes, including 1497 from coronary heart disease, 528 from stroke, and 893 from sudden death. On multivariable analysis, there was a graded increase in the risk of death from cardiovascular causes and all causes that started among participants in the group that was in the 50th to 74th percentiles of BMI (i.e., within the accepted normal range). Hazard ratios in the obese group (≥95th percentile for BMI), as compared with the reference group in the 5th to 24th percentiles, were 4.9 (95% confidence interval [CI], 3.9 to 6.1) for death from coronary heart disease, 2.6 (95% CI, 1.7 to 4.1) for death from stroke, 2.1 (95% CI, 1.5 to 2.9) for sudden death, and 3.5 (95% CI, 2.9 to 4.1) for death from total cardiovascular causes, after adjustment for sex, age, birth year, sociodemographic characteristics, and height. Hazard ratios for death from cardiovascular causes in the same percentile groups increased from 2.0 (95% CI, 1.1 to 3.9) during follow-up for 0 to 10 years to 4.1 (95% CI, 3.1 to 5.4) during follow-up for 30 to 40 years; during both periods, hazard ratios were consistently high for death from coronary heart disease. Findings persisted in extensive sensitivity analyses.

CONCLUSIONS A BMI in the 50th to 74th percentiles, within the accepted normal range, during adolescence was associated with increased cardiovascular and all-cause mortality during 40 years of follow-up. Overweight and obesity were strongly associated with increased cardiovascular mortality in adulthood.

NEJM 2016; 374:2009-2020

Blood-Pressure Lowering in Intermediate-Risk Persons without Cardiovascular Disease

Lonn Eva M. et al , for the HOPE-3 Investigators

BACKGROUND Antihypertensive therapy reduces the risk of cardiovascular events among high-risk persons and among those with a systolic blood pressure of 160 mm Hg or higher, but its role in persons at intermediate risk and with lower blood pressure is unclear.

METHODS In one comparison from a 2-by-2 factorial trial, we randomly assigned 12,705 participants at intermediate risk who did not have cardiovascular disease to receive either candesartan at a dose of 16 mg per day plus hydrochlorothiazide at a dose of 12.5 mg per day or placebo. The first coprimary outcome was the composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke; the second coprimary outcome additionally included resuscitated cardiac arrest, heart failure, and revascularization. The median follow-up was 5.6 years.

RESULTS The mean blood pressure of the participants at baseline was 138.1/81.9 mm Hg; the decrease in blood pressure was 6.0/3.0 mm Hg greater in the active-treatment group than in the placebo group. The first coprimary outcome occurred in 260 participants (4.1%) in the active-treatment group and in 279 (4.4%) in the placebo group (hazard ratio, 0.93; 95% confidence interval [CI], 0.79 to 1.10; P=0.40); the second coprimary outcome occurred in 312 participants (4.9%) and 328 participants (5.2%), respectively (hazard ratio, 0.95; 95% CI, 0.81 to 1.11; P=0.51). In one of the three prespecified hypothesis-based subgroups, participants in the subgroup for the upper third of systolic blood pressure (>143.5 mm Hg) who were in the active-treatment group had significantly lower rates of the first and second coprimary outcomes than those in the placebo group; effects were neutral in the middle and lower thirds (P=0.02 and P=0.009, respectively, for trend in the two outcomes).

CONCLUSIONS Therapy with candesartan at a dose of 16 mg per day plus hydrochlorothiazide at a dose of 12.5 mg per day was not associated with a lower rate of major cardiovascular events than placebo among persons at intermediate risk who did not have cardiovascular disease .

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Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease

Yusuf Salim et al for the HOPE-3 Investigators†

BACKGROUND Previous trials have shown that the use of statins to lower cholesterol reduces the risk of cardiovascular events among persons without cardiovascular disease. Those trials have involved persons with elevated lipid levels or inflammatory markers and involved mainly white persons. It is unclear whether the benefits of statins can be extended to an intermediate-risk, ethnically diverse population without cardiovascular disease.

METHODS In one comparison from a 2-by-2 factorial trial, we randomly assigned 12,705 participants in 21 countries who did not have cardiovascular disease and were at intermediate risk to receive rosuvastatin at a dose of 10 mg per day or placebo. The first coprimary outcome was the composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, and the second coprimary outcome additionally included revascularization, heart failure, and resuscitated cardiac arrest. The median follow-up was 5.6 years.

RESULTS The overall mean low-density lipoprotein cholesterol level was 26.5% lower in the rosuvastatin group than in the placebo group. The first coprimary outcome occurred in 235 participants (3.7%) in the rosuvastatin group and in 304 participants (4.8%) in the placebo group (hazard ratio, 0.76; 95% confidence interval [CI], 0.64 to 0.91; P=0.002). The results for the second coprimary outcome were consistent with the results for the first (occurring in 277 participants [4.4%] in the rosuvastatin group and in 363 participants [5.7%] in the placebo group; hazard ratio, 0.75; 95% CI, 0.64 to 0.88; P<0.001). The results were also consistent in subgroups defined according to cardiovascular risk at baseline, lipid level, C-reactive protein level, blood pressure, and race or ethnic group. In the rosuvastatin group, there was no excess of diabetes or cancers, but there was an excess of cataract surgery (in 3.8% of the participants, vs. 3.1% in the placebo group; P=0.02) and muscle symptoms (in 5.8% of the participants, vs. 4.7% in the placebo group; P=0.005).

CONCLUSIONS Treatment with rosuvastatin at a dose of 10 mg per day resulted in a significantly lower risk of cardiovascular events than placebo in an intermediate-risk, ethnically diverse population without cardiovascular disease.

N Engl J Med 2016; 374:2032-2043

Blood-Pressure and Cholesterol Lowering in Persons without Cardiovascular Disease

Salim Yusuf et al for the HOPE-3 Investigators

BACKGROUND Elevated blood pressure and elevated low-density lipoprotein (LDL) cholesterol increase the risk of cardiovascular disease. Lowering both should reduce the risk of cardiovascular events substantially.

METHODS In a trial with 2-by-2 factorial design, we randomly assigned 12,705 participants at intermediate risk who did not have cardiovascular disease to rosuvastatin (10 mg per day) or placebo and to candesartan (16 mg per day) plus hydrochlorothiazide (12.5 mg per day) or placebo. In the analyses reported here, we compared the 3180 participants assigned to combined therapy (with rosuvastatin and the two antihypertensive agents) with the 3168 participants assigned to dual placebo. The first coprimary outcome was the composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, and the second coprimary outcome additionally included heart failure, cardiac arrest, or revascularization. The median follow-up was 5.6 years.

RESULTS The decrease in the LDL cholesterol level was 33.7 mg per deciliter (0.87 mmol per liter) greater in the combined-therapy group than in the dual-placebo group, and the decrease in systolic blood pressure was 6.2 mm Hg greater with combined therapy than with dual placebo. The first coprimary outcome occurred in 113 participants (3.6%) in the combined-therapy group and in 157 (5.0%) in the dual-placebo group (hazard ratio, 0.71; 95% confidence interval [CI], 0.56 to 0.90; P=0.005). The second coprimary outcome occurred in 136 participants (4.3%) and 187 participants (5.9%), respectively (hazard ratio, 0.72; 95% CI, 0.57 to 0.89; P=0.003). Muscle weakness and dizziness were more common in the combined-therapy group than in the dual-placebo group, but the overall rate of discontinuation of the trial regimen was similar in the two groups.

CONCLUSIONS The combination of rosuvastatin (10 mg per day), candesartan (16 mg per day), and hydrochlorothiazide (12.5 mg per day) was associated with a significantly lower rate of cardiovascular events than dual placebo among persons at intermediate risk who did not have cardiovascular disease

N Engl J Med 2016; 374:1744-1753

Perioperative Rosuvastatin in Cardiac Surgery

Zhe Zheng, Raja Jayaram, Lixin Jiang et al

BACKGROUND Complications after cardiac surgery are common and lead to substantial increases in morbidity and mortality. Meta-analyses of small randomized trials have suggested that perioperative statin therapy can prevent some of these complications.

METHODS We randomly assigned 1922 patients in sinus rhythm who were scheduled for elective cardiac surgery to receive perioperative rosuvastatin (at a dose of 20 mg daily) or placebo. The primary outcomes were postoperative atrial fibrillation within 5 days after surgery, as assessed by Holter electrocardiographic monitoring, and myocardial injury within 120 hours after surgery, as assessed by serial measurements of the cardiac troponin I concentration. Secondary outcomes included major in-hospital adverse events, duration of stay in the hospital and intensive care unit, left ventricular and renal function, and blood biomarkers.

RESULTS The concentrations of low-density lipoprotein cholesterol and C-reactive protein after surgery were lower in patients assigned to rosuvastatin than in those assigned to placebo (P<0.001). However, the rate of postoperative atrial fibrillation did not differ significantly between the rosuvastatin group and the placebo group (21.1% and 20.5%, respectively; odds ratio 1.04; 95% confidence interval [CI], 0.84 to 1.30; P=0.72), nor did the area under the troponin I–release curve (102 ng×hour per milliliter and 100 ng×hour per milliliter, respectively; between-group difference, 1%; 95% CI, −9 to 13; P=0.80). Subgroup analyses did not indicate benefit in any category of patient. Rosuvastatin therapy did not result in beneficial effects on any of the secondary outcomes but was associated with a significant absolute (±SE) excess of 5.4±1.9 percentage points in the rate of postoperative acute kidney injury (P=0.005).

CONCLUSIONS In this trial, perioperative statin therapy did not prevent postoperative atrial fibrillation or perioperative myocardial damage in patients undergoing elective cardiac surgery. Acute kidney injury was more common with rosuvastatin.

N Engl J Med 2016; 374:1521-153

Aliskiren, Enalapril, or Aliskiren and Enalapril in Heart Failure

John J.V. McMurray, Henry Krum., William T. Abraham, for the ATMOSPHERE Committees Investigators

BACKGROUND Among patients with chronic heart failure, angiotensin-converting–enzyme (ACE) inhibitors reduce mortality and hospitalization, but the role of a renin inhibitor in such patients is unknown. We compared the ACE inhibitor enalapril with the renin inhibitor aliskiren (to test superiority or at least noninferiority) and with the combination of the two treatments (to test superiority) in patients with heart failure and a reduced ejection fraction.

METHODS After a single-blind run-in period, we assigned patients, in a double-blind fashion, to one of three groups: 2336 patients were assigned to receive enalapril at a dose of 5 or 10 mg twice daily, 2340 to receive aliskiren at a dose of 300 mg once daily, and 2340 to receive both treatments (combination therapy). The primary composite outcome was death from cardiovascular causes or hospitalization for heart failure.

RESULTS After a median follow-up of 36.6 months, the primary outcome occurred in 770 patients (32.9%) in the combination-therapy group and in 808 (34.6%) in the enalapril group (hazard ratio, 0.93; 95% confidence interval [CI], 0.85 to 1.03). The primary outcome occurred in 791 patients (33.8%) in the aliskiren group (hazard ratio vs. enalapril, 0.99; 95% CI, 0.90 to 1.10); the prespecified test for noninferiority was not met. There was a higher risk of hypotensive symptoms in the combination-therapy group than in the enalapril group (13.8% vs. 11.0%, P=0.005), as well as higher risks of an elevated serum creatinine level (4.1% vs. 2.7%, P=0.009) and an elevated potassium level (17.1% vs. 12.5%, P<0.001).

CONCLUSIONS In patients with chronic heart failure, the addition of aliskiren to enalapril led to more adverse events without an increase in benefit. Noninferiority was not shown for aliskiren as compared with enalapril

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Pioglitazone after Ischemic Stroke or Transient Ischemic Attack

Walter N. Kernan, Catherine M. Viscoli, , Karen L. Furie, for the IRIS Trial Investigators

BACKGROUND Patients with ischemic stroke or transient ischemic attack (TIA) are at increased risk for future cardiovascular events despite current preventive therapies. The identification of insulin resistance as a risk factor for stroke and myocardial infarction raised the possibility that pioglitazone, which improves insulin sensitivity, might benefit patients with cerebrovascular disease.

METHODS In this multicenter, double-blind trial, we randomly assigned 3876 patients who had had a recent ischemic stroke or TIA to receive either pioglitazone (target dose, 45 mg daily) or placebo. Eligible patients did not have diabetes but were found to have insulin resistance on the basis of a score of more than 3.0 on the homeostasis model assessment of insulin resistance (HOMA-IR) index. The primary outcome was fatal or nonfatal stroke or myocardial infarction.

RESULTS By 4.8 years, a primary outcome had occurred in 175 of 1939 patients (9.0%) in the pioglitazone group and in 228 of 1937 (11.8%) in the placebo group (hazard ratio in the pioglitazone group, 0.76; 95% confidence interval [CI], 0.62 to 0.93; P=0.007). Diabetes developed in 73 patients (3.8%) and 149 patients (7.7%), respectively (hazard ratio, 0.48; 95% CI, 0.33 to 0.69; P<0.001). There was no significant between-group difference in all-cause mortality (hazard ratio, 0.93; 95% CI, 0.73 to 1.17; P=0.52). Pioglitazone was associated with a greater frequency of weight gain exceeding 4.5 kg than was placebo (52.2% vs. 33.7%, P<0.001), edema (35.6% vs. 24.9%, P<0.001), and bone fracture requiring surgery or hospitalization (5.1% vs. 3.2%, P=0.003).

CONCLUSIONS In this trial involving patients without diabetes who had insulin resistance along with a recent history of ischemic stroke or TIA, the risk of stroke or myocardial infarction was lower among patients who received pioglitazone than among those who received placebo. Pioglitazone was also associated with a lower risk of diabetes but with higher risks of weight gain, edema, and fracture.

N Engl J Med 2016; 374:1332-1343

Fresh Fruit Consumption and Major Cardiovascular Disease in China

Huaidong Du, Liming Li, Derrick Bennett, for the China Kadoorie Biobank Study

BACKGROUND In Western populations, a higher level of fruit consumption has been associated with a lower risk of cardiovascular disease, but little is known about such associations in China, where the consumption level is low and rates of stroke are high

METHODS Between 2004 and 2008, we recruited 512,891 adults, 30 to 79 years of age, from 10 diverse localities in China. During 3.2 million person-years of follow-up, 5173 deaths from cardiovascular disease, 2551 incident major coronary events (fatal or nonfatal), 14,579 ischemic strokes, and 3523 intracerebral hemorrhages were recorded among the 451,665 participants who did not have a history of cardiovascular disease or antihypertensive treatments at baseline. Cox regression yielded adjusted hazard ratios relating fresh fruit consumption to disease rates.

RESULTS Overall, 18.0% of participants reported consuming fresh fruit daily. As compared with participants who never or rarely consumed fresh fruit (the “nonconsumption” category), those who ate fresh fruit daily had lower systolic blood pressure (by 4.0 mm Hg) and blood glucose levels (by 0.5 mmol per liter [9.0 mg per deciliter]) ($P<0.001$ for trend for both comparisons). The adjusted hazard ratios for daily consumption versus nonconsumption were 0.60 (95% confidence interval [CI], 0.54 to 0.67) for cardiovascular death, and 0.66 (95% CI, 0.58 to 0.75), 0.75 (95% CI, 0.72 to 0.79), and 0.64 (95% CI, 0.56 to 0.74), respectively, for incident major coronary events, ischemic stroke, and hemorrhagic stroke. There was a strong log-linear dose–response relationship between the incidence of each outcome and the amount of fresh fruit consumed. These associations were similar across the 10 study regions and in subgroups of participants defined by baseline characteristics.

CONCLUSIONS Among Chinese adults, a higher level of fruit consumption was associated with lower blood pressure and blood glucose levels and, largely independent of these and other dietary and nondietary factors, with significantly lower risks of major cardiovascular diseases. (Funded by the Wellcome Trust and others.)

Circulation. 2016;133:1838-1850

High-Density Lipoprotein Proteomic Composition, and not Efflux Capacity, Reflects Differential Modulation of Reverse Cholesterol Transport by Saturated and Monounsaturated Fat Diets

Marcella O'Reilly, Eugene Dillon, Weili Guo, et al

Background—Acute inflammation impairs reverse cholesterol transport (RCT) and reduces high-density lipoprotein (HDL) function in vivo. This study hypothesized that obesity-induced inflammation impedes RCT and alters HDL composition, and investigated if dietary replacement of saturated (SFA) for monounsaturated (MUFA) fatty acids modulates RCT.

Methods and Results—Macrophage-to-feces RCT, HDL efflux capacity, and HDL proteomic profiling was determined in C57BL/6j mice following 24 weeks on SFA- or MUFA-enriched high-fat diets (HFDs) or low-fat diet. The impact of dietary SFA consumption and insulin resistance on HDL efflux function was also assessed in humans. Both HFDs increased plasma 3H-cholesterol counts during RCT in vivo and ATP-binding cassette, subfamily A, member 1–independent efflux to plasma ex vivo, effects that were attributable to elevated HDL cholesterol. By contrast, ATP-binding cassette, subfamily A, member 1–dependent efflux was reduced after both HFDs, an effect that was also observed with insulin resistance and high SFA consumption in humans. SFA-HFD impaired liver-to-feces RCT, increased hepatic inflammation, and reduced ABC subfamily G member 5/8 and ABC subfamily B member 11 transporter expression in comparison with low-fat diet, whereas liver-to-feces RCT was preserved after MUFA-HFD. HDL particles were enriched with acute-phase proteins (serum amyloid A, haptoglobin, and hemopexin) and depleted of paraoxonase-1 after SFA-HFD in comparison with MUFA-HFD.

Conclusions—Ex vivo efflux assays validated increased macrophage-to-plasma RCT in vivo after both HFDs but failed to capture differential modulation of hepatic cholesterol trafficking. By contrast, proteomics revealed the association of hepatic-derived inflammatory proteins on HDL after SFA-HFD in comparison with MUFA-HFD, which reflected differential hepatic cholesterol trafficking between groups. Acute-phase protein levels on HDL may serve as novel biomarkers of impaired liver-to-feces RCT in vivo.

Circulation. 2016;133:1851-1860

Long-Term Effectiveness and Safety of Pravastatin in Patients With Coronary Heart Disease

Wendy E. Hague, John Simes, Adrienne Kirby, for the LIPID study investigators

Background—We aimed to assess the long-term effects of treatment with statin therapy on all-cause mortality, cause-specific mortality, and cancer incidence from extended follow-up of the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) trial.

Methods and Results—LIPID initially compared pravastatin and placebo over 6 years in 9014 patients with previous coronary heart disease. After the double-blind period, all patients were offered open-label statin therapy. Data were obtained over a further 10 years from 7721 patients, by direct contact for 2 years, by questionnaires thereafter, and from mortality and cancer registries. During extended follow-up, 85% assigned pravastatin and 84% assigned placebo took statin therapy. Patients assigned pravastatin maintained a significantly lower risk of death from coronary heart disease (relative risk [RR] 0.89; 95% confidence interval [CI], 0.81−0.97; P=0.009), from cardiovascular disease (RR, 0.88; 95% CI, 0.81−0.95; P=0.002), and from any cause (RR, 0.91; 95% CI, 0.85−0.97; absolute risk reduction, 2.6%; P=0.003).Cancer incidence was similar by original treatment group during the double-blind period (RR, 0.94; 95% CI, 0.82–1.08; P=0.41), later follow-up (RR, 1.02; 95% CI, 0.91–1.14; P=0.74), and overall (RR, 0.99; 95% CI, 0.91–1.08; P=0.83). There were no significant differences in cancer mortality, or in the incidence of organ-specific cancers. Cancer findings were confirmed in a meta-analysis with other large statin trials with extended follow-up.

Conclusions—In LIPID, the absolute survival benefit from 6 years of pravastatin treatment appeared to be maintained for the next 10 years, with a similar risk of death among survivors in both groups after the initial period. Treatment with statins does not influence cancer or death from noncardiovascular causes during long-term follow-up.

Circulation. 2016;133:1449-1457

ABO Blood Group and Risk of Thromboembolic and Arterial Disease

Senthil K. Vasan, Klaus Rostgaard, Ammar Majeed, et al

Background—ABO blood groups have been shown to be associated with increased risks of venous thromboembolic and arterial disease. However, the reported magnitude of this association is inconsistent and is based on evidence from small-scale studies.

Methods and Results—We used the SCANDAT2 (Scandinavian Donations and Transfusions) database of blood donors linked with other nationwide health data registers to investigate the association between ABO blood groups and the incidence of first and recurrent venous thromboembolic and arterial events. Blood donors in Denmark and Sweden between 1987 and 2012 were followed up for diagnosis of thromboembolism and arterial events. Poisson regression models were used to estimate incidence rate ratios as measures of relative risk. A total of 9170 venous and 24 653 arterial events occurred in 1 112 072 individuals during 13.6 million person-years of follow-up. Compared with blood group O, non-O blood groups were associated with higher incidence of both venous and arterial thromboembolic events. The highest rate ratios were observed for pregnancy-related venous thromboembolism (incidence rate ratio, 2.22; 95% confidence interval, 1.77–2.79), deep vein thrombosis (incidence rate ratio, 1.92; 95% confidence interval, 1.80–2.05), and pulmonary embolism (incidence rate ratio, 1.80; 95% confidence interval, 1.71–1.88).

Conclusions—In this healthy population of blood donors, non-O blood groups explain >30% of venous thromboembolic events. Although ABO blood groups may potentially be used with available prediction systems for identifying at-risk individuals, its clinical utility requires further comparison with other risk markers

The Lancet 387,10029, p1723–1731

Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials

Mayank Goyal, Bijoy K Menon, Wim H van Zwam, for the HERMES collaborators

Background:In 2015, five randomised trials showed efficacy of endovascular thrombectomy over standard medical care in patients with acute ischaemic stroke caused by occlusion of arteries of the proximal anterior circulation. In this meta-analysis we, the trial investigators, aimed to pool individual patient data from these trials to address remaining questions about whether the therapy is efficacious across the diverse populations included.

Methods:We formed the HERMES collaboration to pool patient-level data from five trials (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND IA) done between December, 2010, and December, 2014. In these trials, patients with acute ischaemic stroke caused by occlusion of the proximal anterior artery circulation were randomly assigned to receive either endovascular thrombectomy within 12 h of symptom onset or standard care (control), with a primary outcome of reduced disability on the modified Rankin Scale (mRS) at 90 days. By direct access to the study databases, we extracted individual patient data that we used to assess the primary outcome of reduced disability on mRS at 90 days in the pooled population and examine heterogeneity of this treatment effect across prespecified subgroups. To account for between-trial variance we used mixed-effects modelling with random effects for parameters of interest. We then used mixed-effects ordinal logistic regression models to calculate common odds ratios (cOR) for the primary outcome in the whole population (shift analysis) and in subgroups after adjustment for age, sex, baseline stroke severity (National Institutes of Health Stroke Scale score), site of occlusion (internal carotid artery vs M1 segment of middle cerebral artery vs M2 segment of middle cerebral artery), intravenous alteplase (yes vs no), baseline Alberta Stroke Program Early CT score, and time from stroke onset to randomisation.

Findings: We analysed individual data for 1287 patients (634 assigned to endovascular thrombectomy, 653 assigned to control). Endovascular thrombectomy led to significantly reduced disability at 90 days compared with control (adjusted cOR 2·49, 95% CI 1·76–3·53; p<0·0001). The number needed to treat with endovascular thrombectomy to reduce disability by at least one level on mRS for one patient was 2·6. Subgroup analysis of the primary endpoint showed no heterogeneity of treatment effect across prespecified subgroups for reduced disability (pinteraction=0·43). Effect sizes favouring endovascular thrombectomy over control

were present in several strata of special interest, including in patients aged 80 years or older (cOR 3·68, 95% CI 1·95–6·92), those randomised more than 300 min after symptom onset (1·76, 1·05–2·97), and those not eligible for intravenous alteplase (2·43, 1·30–4·55). Mortality at 90 days and risk of parenchymal haematoma and symptomatic intracranial haemorrhage did not differ between populations.

Interpretation: Endovascular thrombectomy is of benefit to most patients with acute ischaemic stroke caused by occlusion of the proximal anterior circulation, irrespective of patient characteristics or geographical location. These findings will have global implications on structuring systems of care to provide timely treatment to patients with acute ischaemic stroke due to large vessel occlusion

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Relationship Among Body Fat Percentage, Body Mass Index, and All-Cause Mortality: A Cohort Study

Raj Padwal, William D. Leslie,; Lisa M. Lix, P. and Sumit R. Majumdar

Background: Prior mortality studies have concluded that elevated body mass index (BMI) may improve survival. These studies were limited because they did not measure adiposity directly.

Objective: To examine associations of BMI and body fat percentage (separately and together) with mortality.

Design: Observational study.

Participants: Adults aged 40 years or older referred for bone mineral density (BMD) testing.

Measurements: Participants had dual-energy x-ray absorptiometry (DXA), entered a clinical BMD registry, and were followed using linked administrative databases. Adjusted, sex-stratified Cox models were constructed. Body mass index and DXA-derived body fat percentage were divided into quintiles, with quintile 1 as the lowest, quintile 5 as the highest, and quintile 3 as the reference.

Results: The final cohort included 49 476 women (mean age, 63.5 years; mean BMI, 27.0 kg/m2; mean body fat, 32.1%) and 4944 men (mean age, 65.5 years; mean BMI, 27.4 kg/m2; mean body fat, 29.5%). Death occurred in 4965 women over a median of 6.7 years and 984 men over a median of 4.5 years. In fully adjusted mortality models containing both BMI and body fat percentage, low BMI (hazard ratio [HR], 1.44 [95% CI, 1.30 to 1.59] for quintile 1 and 1.12 [CI, 1.02 to 1.23] for quintile 2) and high body fat percentage (HR, 1.19 [CI, 1.08 to 1.32] for quintile 5) were associated with higher mortality in women. In men, low BMI (HR, 1.45 [CI, 1.17 to 1.79] for quintile 1) and high body fat percentage (HR, 1.59 [CI, 1.28 to 1.96] for quintile 5) were associated with increased mortality.

Limitations: All participants were referred for BMD testing, which may limit generalizability. Serial measures of BMD and weight were not used. Some measures, such as physical activity and smoking, were unavailable.

Conclusion: Low BMI and high body fat percentage are independently associated with increased mortality. These findings may help explain the counterintuitive relationship between BMI and mortality.

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Polypharmacy and effects of apixaban versus warfarin in patients with atrial fibrillation: post hoc analysis of the ARISTOTLE trial

Jeroen Jaspers Focks, Marc A Brouwer, Daniel M Wojdyla, et al

Objective: To determine whether the treatment effect of apixaban versus warfarin differs with increasing numbers of concomitant drugs used by patients with atrial fibrillation. Design: Post hoc analysis performed in 2015 of results from ARISTOTLE (apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation)—a multicentre, double blind, double dummy trial that started in 2006 and ended in 2011. Participants: 18201 ARISTOTLE trial participants. Interventions: In the ARISTOTLE trial, patients were randomised to either 5 mg apixaban twice daily (n=9120) or warfarin (target international normalised ratio range 2.0-3.0; n=9081). In the post hoc analysis, patients were divided into groups according to the number of concomitant drug treatments used at baseline (0-5, 6-8, ≥9 drugs) with a median follow-up of 1.8 years. Main outcome measures: Clinical outcomes and treatment effects of apixaban versus warfarin (adjusted for age, sex, and country). Results : Each patient used a median of six drugs (interquartile range 5-9); polypharmacy (≥5 drugs) was seen in 13932 (76.5%) patients. Greater numbers of concomitant drugs were used in older patients, women, and patients in the United States. The number of comorbidities increased across groups of increasing numbers of drugs (0-5, 6-8, ≥9 drugs), as did the proportions of patients treated with drugs that interact with warfarin or apixaban. Mortality also rose significantly with the number of drug treatments (P<0.001), as did rates of stroke or systemic embolism (1.29, 1.48, and 1.57 per 100 patient years, for 0-5, 6-8, and ≥9 drugs, respectively) and major bleeding (1.91, 2.46, and 3.88 per 100 patient years, respectively). Relative risk reductions in stroke or systemic embolism for apixaban versus warfarin were consistent, regardless of the number of concomitant drugs (Pinteraction=0.82). A smaller reduction in major bleeding was seen with apixaban versus warfarin with increasing numbers of concomitant drugs (Pinteraction=0.017). Patients with interacting (potentiating) drugs for warfarin or apixaban had similar outcomes and consistent treatment effects of apixaban versus warfarin. Conclusions: In the ARISTOTLE trial, three quarters of patients had polypharmacy; this subgroup had an increased comorbidity, more interacting drugs, increased mortality, and higher rates of thromboembolic and bleeding complications. In terms of a potential differential response to anticoagulation therapy in patients with atrial fibrillation and polypharmacy, apixaban was more effective than warfarin, and is at least just as safe

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Whole grain consumption and risk of cardiovascular disease, cancer, and all cause and cause specific mortality: systematic review and dose-response meta-analysis of prospective studies

Dagfinn Aune, NaNa Keum, Edward Giovannucci,et al

Objective: To quantify the dose-response relation between consumption of whole grain and specific types of grains and the risk of cardiovascular disease, total cancer, and all cause and cause specific mortality. Data sources: PubMed and Embase searched up to 3 April 2016.

Study selection: Prospective studies reporting adjusted relative risk estimates for the association between intake of whole grains or specific types of grains and cardiovascular disease, total cancer, all cause or cause specific mortality. Data synthesis Summary: relative risks and 95% confidence intervals calculated with a random effects model.

Results 45 studies (64 publications) were included. The summary relative risks per 90 g/day increase in whole grain intake (90 g is equivalent to three servings—for example, two slices of bread and one bowl of cereal or one and a half pieces of pita bread made from whole grains) was 0.81 (95% confidence interval 0.75 to 0.87; I2=9%, n=7 studies) for coronary heart disease, 0.88 (0.75 to 1.03; I2=56%, n=6) for stroke, and 0.78 (0.73 to 0.85; I2=40%, n=10) for cardiovascular disease, with similar results when studies were stratified by whether the outcome was incidence or mortality. The relative risks for morality were 0.85 (0.80 to 0.91; I2=37%, n=6) for total cancer, 0.83 (0.77 to 0.90; I2=83%, n=11) for all causes, 0.78 (0.70 to 0.87; I2=0%, n=4) for respiratory disease, 0.49 (0.23 to 1.05; I2=85%, n=4) for diabetes, 0.74 (0.56 to 0.96; I2=0%, n=3) for infectious diseases, 1.15 (0.66 to 2.02; I2=79%, n=2) for diseases of the nervous system disease, and 0.78 (0.75 to 0.82; I2=0%, n=5) for all non-cardiovascular, non-cancer causes. Reductions in risk were observed up to an intake of 210-225 g/day (seven to seven and a half servings per day) for most of the outcomes. Intakes of specific types of whole grains including whole grain bread, whole grain breakfast cereals, and added bran, as well as total bread and total breakfast cereals were also associated with reduced risks of cardiovascular disease and/or all cause mortality, but there was little evidence of an association with refined grains, white rice, total rice, or total grains.

Conclusions This meta-analysis provides further evidence that whole grain intake is associated with a reduced risk of coronary heart disease, cardiovascular disease, and total cancer, and mortality from all causes, respiratory diseases, infectious diseases, diabetes, and all non-cardiovascular, non-cancer causes. These findings support dietary guidelines that recommend increased intake of whole grain to reduce the risk of chronic diseases and premature mortality.

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Low dose oestrogen combined oral contraception and risk of pulmonary embolism, stroke, and myocardial infarction in five million French women: cohort study

Alain Weill, Marie Dalichampt, Fanny Raguideau, Philippe Ricordeau, et al

Objective: To assess the risk of pulmonary embolism, ischaemic stroke, and myocardial infarction associated with combined oral contraceptives according to dose of oestrogen (ethinylestradiol) and progestogen.

Design: Observational cohort study.

Setting Data from the French national health insurance database linked with data from the French national hospital discharge database.

Participants: 4945088 women aged 15-49 years, living in France, with at least one reimbursement for oral contraceptives and no previous hospital admission for cancer, pulmonary embolism, ischaemic stroke, or myocardial infarction, between July 2010 and September 2012.

Main outcome measures: Relative and absolute risks of first pulmonary embolism, ischaemic stroke, and myocardial infarction.

Results: The cohort generated 5443916 women years of oral contraceptive use, and 3253 events were observed: 1800 pulmonary embolisms (33 per 100000 women years), 1046 ischaemic strokes (19 per 100000 women years), and 407 myocardial infarctions (7 per 100000 women years). After adjustment for progestogen and risk factors, the relative risks for women using low dose oestrogen (20 µg v 30-40 µg) were 0.75 (95% confidence interval 0.67 to 0.85) for pulmonary embolism, 0.82 (0.70 to 0.96) for ischaemic stroke, and 0.56 (0.39 to 0.79) for myocardial infarction. After adjustment for oestrogen dose and risk factors, desogestrel and gestodene were associated with statistically significantly higher relative risks for pulmonary embolism (2.16, 1.93 to 2.41 and 1.63, 1.34 to 1.97, respectively) compared with levonorgestrel. Levonorgestrel combined with 20 µg oestrogen was associated with a statistically significantly lower risk than levonorgestrel with 30-40 µg oestrogen for each of the three serious adverse events.

Conclusions: For the same dose of oestrogen, desogestrel and gestodene were associated with statistically significantly higher risks of pulmonary embolism but not arterial thromboembolism compared with levonorgestrel. For the same type of progestogen, an oestrogen dose of 20 µg versus 30-40 µg was associated with lower risks of pulmonary embolism, ischaemic stroke, and myocardial infarction.

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Re-evaluation of the traditional diet-heart hypothesis: analysis of recovered data from Minnesota Coronary Experiment (1968-73)

Christopher E Ramsden, Daisy Zamora, Sharon Majchrzak-Hong, et al

Objective: To examine the traditional diet-heart hypothesis through recovery and analysis of previously unpublished data from the Minnesota Coronary Experiment (MCE) and to put findings in the context of existing diet-heart randomized controlled trials through a systematic review and meta-analysis.

Design: The MCE (1968-73) is a double blind randomized controlled trial designed to test whether replacement of saturated fat with vegetable oil rich in linoleic acid reduces coronary heart disease and death by lowering serum cholesterol. Recovered MCE unpublished documents and raw data were analyzed according to hypotheses prespecified by original investigators. Further, a systematic review and meta-analyses of randomized controlled trials that lowered serum cholesterol by providing vegetable oil rich in linoleic acid in place of saturated fat without confounding by concomitant interventions was conducted.

Setting: One nursing home and six state mental hospitals in Minnesota, United States.

Participants: Unpublished documents with completed analyses for the randomized cohort of 9423 women and men aged 20-97; longitudinal data on serum cholesterol for the 2355 participants exposed to the study diets for a year or more; 149 completed autopsy files.

Interventions Serum cholesterol lowering diet that replaced saturated fat with linoleic acid (from corn oil and corn oil polyunsaturated margarine). Control diet was high in saturated fat from animal fats, common margarines, and shortenings.

Main outcome measures: Death from all causes; association between changes in serum cholesterol and death; and coronary atherosclerosis and myocardial infarcts detected at autopsy.

Results: The intervention group had significant reduction in serum cholesterol compared with controls (mean change from baseline −13.8% v −1.0%; P<0.001). Kaplan Meier graphs showed no mortality benefit for the intervention group in the full randomized cohort or for any prespecified subgroup. There was a 22% higher risk of death for each 30 mg/dL (0.78 mmol/L) reduction in serum cholesterol in covariate adjusted Cox regression models (hazard ratio 1.22, 95% confidence interval 1.14 to 1.32; P<0.001). There was no evidence of benefit in the intervention group for coronary atherosclerosis or myocardial infarcts. Systematic review identified five randomized controlled trials for inclusion (n=10808). In meta-analyses, these

cholesterol lowering interventions showed no evidence of benefit on mortality from coronary heart disease (1.13, 0.83 to 1.54) or all cause mortality (1.07, 0.90 to 1.27).

Conclusions Available evidence from randomized controlled trials shows that replacement of saturated fat in the diet with linoleic acid effectively lowers serum cholesterol but does not support the hypothesis that this translates to a lower risk of death from coronary heart disease or all causes. Findings from the Minnesota Coronary Experiment add to growing evidence that incomplete publication has contributed to overestimation of the benefits of replacing saturated fat with vegetable oils rich in linoleic acid.

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Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged ≥75 Years A Randomized Clinical Trial

Jeff D. Williamson, Mark A. Supiano, William B. Applegate, for the SPRINT Research Group

Importance: The appropriate treatment target for systolic blood pressure (SBP) in older patients with hypertension remains uncertain. Objective: To evaluate the effects of intensive (<120 mm Hg) compared with standard (<140 mm Hg) SBP targets in persons aged 75 years or older with hypertension but without diabetes. Design, Setting, and Participants: A multicenter, randomized clinical trial of patients aged 75 years or older who participated in the Systolic Blood Pressure Intervention Trial (SPRINT). Recruitment began on October 20, 2010, and follow-up ended on August 20, 2015. Interventions: Participants were randomized to an SBP target of less than 120 mm Hg (intensive treatment group, n=1317) or an SBP target of less than 140 mm Hg (standard treatment group, n=1319). Main Outcomes and Measures: The primary cardiovascular disease outcome was a composite of nonfatal myocardial infarction, acute coronary syndrome not resulting in a myocardial infarction, nonfatal stroke, nonfatal acute decompensated heart failure, and death from cardiovascular causes. All-cause mortality was a secondary outcome. Results: Among 2636 participants (mean age, 79.9 years; 37.9% women), 2510 (95.2%) provided complete follow-up data. At a median follow-up of 3.14 years, there was a significantly lower rate of the primary composite outcome (102 events in the intensive treatment group vs 148 events in the standard treatment group; hazard ratio [HR], 0.66 [95% CI, 0.51-0.85]) and all-cause mortality (73 deaths vs 107 deaths, respectively; HR, 0.67 [95% CI, 0.49-0.91]). The overall rate of serious adverse events was not different between treatment groups (48.4% in the intensive treatment group vs 48.3% in the standard treatment group; HR, 0.99 [95% CI, 0.89-1.11]). Absolute rates of hypotension were 2.4% in the intensive treatment group vs 1.4% in the standard treatment group (HR, 1.71 [95% CI, 0.97-3.09]), 3.0% vs 2.4%, respectively, for syncope (HR, 1.23 [95% CI, 0.76-2.00]), 4.0% vs 2.7% for electrolyte abnormalities (HR, 1.51 [95% CI, 0.99-2.33]), 5.5% vs 4.0% for acute kidney injury (HR, 1.41 [95% CI, 0.98-2.04]), and 4.9% vs 5.5% for injurious falls (HR, 0.91 [95% CI, 0.65-1.29]).
Conclusions and Relevance: Among ambulatory adults aged 75 years or older, treating to an SBP target of less than 120 mm Hg compared with an SBP target of less than 140 mm Hg resulted in significantly lower rates of fatal and nonfatal major cardiovascular events and death from any cause.

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Sodium Excretion and the Risk of Cardiovascular Disease in Patients With Chronic Kidney Disease

Katherine T. Mills; Jing Chen, Wei Yang, Lawrence J. Appel,; for the Chronic Renal Insufficiency Cohort (CRIC) Study Investigators

Importance: Patients with chronic kidney disease (CKD) are at an increased risk of cardiovascular disease (CVD) compared with the general population. Prior studies have produced contradictory results on the association of dietary sodium intake with risk of CVD, and this relationship has not been investigated in patients with CKD. Objective: To evaluate the association between urinary sodium excretion and clinical CVD events among patients with CKD. Design, Setting, and Participants: A prospective cohort study of patients with CKD from 7 locations in the United States enrolled in the Chronic Renal Insufficiency Cohort Study and followed up from May 2003 to March 2013. Exposures: The cumulative mean of urinary sodium excretion from three 24-hour urinary measurements and calibrated to sex-specific mean 24-hour urinary creatinine excretion. Main Outcomes and Measures: A composite of CVD events defined as congestive heart failure, stroke, or myocardial infarction. Events were reported every 6 months and confirmed by medical record adjudication. Results: Among 3757 participants (mean age, 58 years; 45% women), 804 composite CVD events (575 heart failure, 305 myocardial infarction, and 148 stroke) occurred during a median 6.8 years of follow-up. From lowest (<2894 mg/24 hours) to highest (≥4548 mg/24 hours) quartile of calibrated sodium excretion, 174, 159, 198, and 273 composite CVD events occurred, and the cumulative incidence was 18.4%, 16.5%, 20.6%, and 29.8% at median follow-up. In addition, the cumulative incidence of CVD events in the highest quartile of calibrated sodium excretion compared with the lowest was 23.2% vs 13.3% for heart failure, 10.9% vs 7.8% for myocardial infarction, and 6.4% vs 2.7% for stroke at median follow-up. Hazard ratios of the highest quartile compared with the lowest quartile were 1.36 (95% CI, 1.09-1.70; P = .007) for composite CVD events, 1.34 (95% CI, 1.03-1.74; P = .03) for heart failure, and 1.81 (95% CI, 1.08-3.02; P = .02) for stroke after multivariable adjustment. Restricted cubic spline analyses of the association between sodium excretion and composite CVD provided no evidence of a nonlinear association (P = .11) and indicated a significant linear association (P < .001). Conclusions and Relevance: Among patients with CKD, higher urinary sodium excretion was associated with increased risk of CVD

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Efficacy and Tolerability of Evolocumab vs Ezetimibe in Patients With Muscle-Related Statin Intolerance, The GAUSS-3 Randomized Clinical Trial

Steven E. Nissen,; Erik Stroes,; Ricardo E. Dent-Acosta,; for the GAUSS-3 Investigators

Importance: Muscle-related statin intolerance is reported by 5% to 20% of patients. Objective To identify patients with muscle symptoms confirmed by statin rechallenge and compare lipid-lowering efficacy for 2 nonstatin therapies, ezetimibe and evolocumab. Design, Setting, and Participants: Two-stage randomized clinical trial including 511 adult patients with uncontrolled low-density lipoprotein cholesterol (LDL-C) levels and history of intolerance to 2 or more statins enrolled in 2013 and 2014 globally. Phase A used a 24-week crossover procedure with atorvastatin or placebo to identify patients having symptoms only with atorvastatin but not placebo. In phase B, after a 2-week washout, patients were randomized to ezetimibe or evolocumab for 24 weeks. Interventions: Phase A: atorvastatin (20 mg) vs placebo. Phase B: randomization 2:1 to subcutaneous evolocumab (420 mg monthly) or oral ezetimibe (10 mg daily). Main Outcome and Measures: Coprimary end points were the mean percent change in LDL-C level from baseline to the mean of weeks 22 and 24 levels and from baseline to week 24 levels. Results: Of the 491 patients who entered phase A (mean age, 60.7 [SD, 10.2] years; 246 women [50.1%]; 170 with coronary heart disease [34.6%]; entry mean LDL-C level, 212.3 [SD, 67.9] mg/dL), muscle symptoms occurred in 209 of 491 (42.6%) while taking atorvastatin but not while taking placebo. Of these, 199 entered phase B, along with 19 who proceeded directly to phase B for elevated creatine kinase (N = 218, with 73 randomized to ezetimibe and 145 to evolocumab; entry mean LDL-C level, 219.9 [SD, 72] mg/dL). For the mean of weeks 22 and 24, LDL-C level with ezetimibe was 183.0 mg/dL; mean percent LDL-C change, −16.7% (95% CI, −20.5% to −12.9%), absolute change, −31.0 mg/dL and with evolocumab was 103.6 mg/dL; mean percent change, −54.5% (95% CI, −57.2% to −51.8%); absolute change, −106.8 mg/dL (P < .001). LDL-C level at week 24 with ezetimibe was 181.5 mg/dL; mean percent change, −16.7% (95% CI, −20.8% to −12.5%); absolute change, −31.2 mg/dL and with evolocumab was 104.1 mg/dL; mean percent change, −52.8% (95% CI, −55.8% to −49.8%); absolute change, −102.9 mg/dL (P < .001). For the mean of weeks 22 and 24, between-group difference in LDL-C was −37.8%; absolute difference, −75.8 mg/dL. For week 24, between-group difference in LDL-C was −36.1%; absolute difference, –71.7 mg/dL. Muscle symptoms were reported in 28.8% of ezetimibe-treated patients and 20.7% of evolocumab-treated patients (log-rank P = .17). Active study drug was stopped for muscle symptoms in 5 of 73 ezetimibe-

treated patients (6.8%) and 1 of 145 evolocumab-treated patients (0.7%). Conclusions and Relevance: Among patients with statin intolerance related to muscle-related adverse effects, the use of evolocumab compared with ezetimibe resulted in a significantly greater reduction in LDL-C levels after 24 weeks. Further studies are needed to assess long-term efficacy and safety.

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Effect of Losmapimod on Cardiovascular Outcomes in Patients Hospitalized With Acute Myocardial Infarction A Randomized Clinical Trial

Michelle L. O'Donoghue, Ruchira Glaser, Matthew A. Cavender, for the LATITUDE-TIMI 60 Investigators

Importance: p38 Mitogen-activated protein kinase (MAPK)–stimulated inflammation is implicated in atherogenesis, plaque destabilization, and maladaptive processes in myocardial infarction (MI). Pilot data in a phase 2 trial in non–ST elevation MI indicated that the p38 MAPK inhibitor losmapimod attenuates inflammation and may improve outcomes.

Objective: To evaluate the efficacy and safety of losmapimod on cardiovascular outcomes in patients hospitalized with an acute myocardial infarction.

Design, Setting, and Patients: LATITUDE-TIMI 60, a randomized, placebo-controlled, double-blind, parallel-group trial conducted at 322 sites in 34 countries from June 3, 2014, until December 8, 2015. Part A consisted of a leading cohort (n=3503) to provide an initial assessment of safety and exploratory efficacy before considering progression to part B (approximately 22 000 patients). Patients were considered potentially eligible for enrollment if they had been hospitalized with an acute MI and had at least 1 additional predictor of cardiovascular risk.

Interventions: Patients were randomized to either twice-daily losmapimod (7.5 mg; n=1738) or matching placebo (n=1765) on a background of guideline-recommended therapy. Patients were treated for 12 weeks and followed up for an additional 12 weeks.

Main Outcomes and Measures The primary end point was the composite of cardiovascular death, MI, or severe recurrent ischemia requiring urgent coronary revascularization with the principal analysis specified at week 12.

Results In part A, among the 3503 patients randomized (median age, 66 years; 1036 [29.6%] were women), 99.1% had complete ascertainment for the primary outcome. The primary end point occurred by 12 weeks in 123 patients treated with placebo (7.0%) and 139 patients treated with losmapimod (8.1%; hazard ratio, 1.16; 95% CI, 0.91-1.47; P=.24). The on-treatment rates of serious adverse events were 16.0% with losmapimod and 14.2% with placebo.

Conclusions and Relevance: Among patients with acute MI, use of losmapimod compared with placebo did not reduce the risk of major ischemic cardiovascular events. The results of this exploratory efficacy study did not justify proceeding to a larger efficacy trial in the existing patient population.

Eur Heart J (2016) 37 (17): 1373-1379

Percent reduction in LDL cholesterol following high-intensity statin therapy: potential implications for guidelines and for the prescription of emerging lipid-lowering agents

Paul M Ridker, Samia Mora, Lynda Rose on behalf of the JUPITER Study Group

Aims: Current statin guidelines in Europe and Canada advocate achieving a fixed LDL target or the attainment of a ≥50% reduction in low-density lipoprotein cholesterol (LDLC), while current US guidelines advocate the use of statin therapies that reduce LDLC by <50% (moderate intensity) or ≥50% (high intensity). Data are limited, however, linking the achievement of these % reduction thresholds to subsequent cardiovascular outcomes particularly for contemporary high-intensity regimens.

Methods and results: In a randomized trial of 17 082 initially healthy men and women with median baseline LDLC of 108 mg/dL (interquartile range 94–119), we (i) used waterfall plots to assess the variability in LDLC response to rosuvastatin 20 mg daily and (ii) evaluated the impact of reaching ≥50% reductions in LDLC on risk of developing the first cardiovascular events. Among rosuvastatin allocated participants, 3640 individuals (46.3%) experienced an LDLC reduction ≥50%; 3365 individuals (42.8%) experienced an LDLC reduction >0 but <50%; and 851 individuals (10.8%) experienced no reduction or an increase in LDLC compared with baseline. These % LDLC reductions directly related to the risks of first cardiovascular events; at trial completion, incidence rates for the primary endpoint were 11.2, 9.2, 6.7, and 4.8 per 1000 person-years for those in the placebo, no LDLC reduction, LDLC reduction <50%, and LDLC reduction ≥50% groups, respectively. Compared with placebo, the multivariable adjusted hazard ratios for sequentially greater on-treatment per cent reductions in LDLC were 0.91 (95%CI 0.54–1.53), 0.61 (95%CI 0.44–0.83), and 0.43 (95%CI 0.30–0.60) ($P < 0.00001$). Similar relationships between % reduction and clinical outcomes were observed in analyses focusing on non-HDLC or apolipoprotein B.

Conclusions: As documented for low- and moderate-intensity regimens, variability in % LDLC reduction following high-intensity statin therapy is wide yet the magnitude of this % reduction directly relates to efficacy. These data support guideline approaches that incorporate % reduction targets for statin therapy as well as absolute targets, and might provide a structure for the allocation of emerging adjunctive lipid-lowering therapies such as PCSK9 inhibitors should these agents prove broadly effective for cardiovascular event reduction.

Eur Heart J (2016) 37 (17): 1384-1394

Mutations causative of familial hypercholesterolaemia: screening of 98 098 individuals from the Copenhagen General Population Study estimated a prevalence of 1 in 217

Marianne Benn, Gerald F. Watts, Anne Tybjærg-Hansen, Børge G. Nordestgaard

Aims: Ideally, familial hypercholesterolaemia (FH) is diagnosed by testing for mutations that decrease the catabolism of low-density lipoprotein (LDL) cholesterol; however, genetic testing is not universally available. The aim of the present study was to assess the frequency and predictors of FH causing mutations in 98 098 participants from the general population, the Copenhagen General Population Study.

Methods and results: We genotyped for LDLR[W23X;W66G;W556S] and APOB[R3500Q] accounting for 38.7% of pathogenic FH mutations in Copenhagen. Clinical FH assessment excluded mutation information. The prevalence of the four FH mutations was 0.18% (1:565), suggesting a total prevalence of FH mutations of 0.46% (1:217). Using the Dutch Lipid Clinic Network (DLCN) criteria, odds ratios for an FH mutation were 439 (95% CI: 170–1 138) for definite FH, 90 (53–152) for probable FH, and 18 (13–25) for possible FH vs. unlikely FH. Using the Simon Broome criteria, the odds ratio was 27 (20–36) for possible vs. unlikely FH, and using the Make Early Diagnosis to Prevent Early Death (MEDPED) criteria, 40 (28–58) for probable vs. unlikely FH. Odds ratios for an FH mutation were 17 (9–31) for LDL-cholesterol of 4–4.9 mmol/L, 69 (37–126) for LDL-cholesterol of 5–5.9 mmol/L, 132 (66–263) for LDL-cholesterol of 6–6.9 mmol/L, 264 (109–637) for LDL-cholesterol of 7–7.9 mmol/L, and 320 (129–798) for LDL-cholesterol above 7.9 mmol/L vs. LDL-cholesterol below 4 mmol/L. The most optimal threshold for LDL-cholesterol concentration to discriminate between mutation carriers and non-carriers was 4.4 mmol/L.

Conclusion: Familial hypercholesterolaemia-causing mutations are estimated to occur in 1:217 in the general population and are best identified by a definite or probable phenotypic diagnosis of FH based on the DLCN criteria or an LDL-cholesterol above 4.4 mmol/L

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Diagnostic Yield and Clinical Utility of Sequencing Familial Hypercholesterolemia Genes in Patients With Severe Hypercholesterolemia

Amit V. Khera, MDa,b; Hong-Hee Won, PhDc; Gina M. Peloso, et al

Background: Approximately 7% of American adults have severe hypercholesterolemia (untreated low-density lipoprotein [LDL] cholesterol ≥190 mg/dl), which may be due to familial hypercholesterolemia (FH). Lifelong LDL cholesterol elevations in FH mutation carriers may confer coronary artery disease (CAD) risk beyond that captured by a single LDL cholesterol measurement.

Objectives: This study assessed the prevalence of an FH mutation among those with severe hypercholesterolemia and determined whether CAD risk varies according to mutation status beyond the observed LDL cholesterol level.

Methods: Three genes causative for FH (LDLR, APOB, and PCSK9) were sequenced in 26,025 participants from 7 case-control studies (5,540 CAD case subjects, 8,577 CAD-free control subjects) and 5 prospective cohort studies (11,908 participants). FH mutations included loss-of-function variants in LDLR, missense mutations in LDLR predicted to be damaging, and variants linked to FH in ClinVar, a clinical genetics database.

Results: Among 20,485 CAD-free control and prospective cohort participants, 1,386 (6.7%) had LDL cholesterol ≥190 mg/dl; of these, only 24 (1.7%) carried an FH mutation. Within any stratum of observed LDL cholesterol, risk of CAD was higher among FH mutation carriers than noncarriers. Compared with a reference group with LDL cholesterol <130 mg/dl and no mutation, participants with LDL cholesterol ≥190 mg/dl and no FH mutation had a 6-fold higher risk for CAD (odds ratio: 6.0; 95% confidence interval: 5.2 to 6.9), whereas those with both LDL cholesterol ≥190 mg/dl and an FH mutation demonstrated a 22-fold increased risk (odds ratio: 22.3; 95% confidence interval: 10.7 to 53.2). In an analysis of participants with serial lipid measurements over many years, FH mutation carriers had higher cumulative exposure to LDL cholesterol than noncarriers.

Conclusions: Among participants with LDL cholesterol ≥190 mg/dl, gene sequencing identified an FH mutation in <2%. However, for any observed LDL cholesterol, FH mutation carriers had substantially increased risk for CAD.

J Am Coll Cardiol. 2016;67(22):2593-2603.

Effects of Vitamin D on Cardiac Function in Patients With Chronic HF: The VINDICATE Study

Klaus K. Witte, Rowena Byrom, John Gierula, Maria F. Paton, et al

Background: Patients with chronic heart failure (HF) secondary to left ventricular systolic dysfunction (LVSD) are

Objectives: The VINDICATE (VitamIN D treatIng patients with Chronic heArT failurE) study was undertaken to establish safety and efficacy of high-dose 25 (OH) vitamin D3 (cholecalciferol) supplementation in patients with chronic HF due to LVSD.

Methods: We enrolled 229 patients (179 men) with chronic HF due to LVSD and vitamin D deficiency (cholecalciferol <50 nmol/l [<20 ng/ml]). Participants were allocated to 1 year of vitamin D3 supplementation (4,000 IU [100 μg] daily) or matching non−calcium-based placebo. The primary endpoint was change in 6-minute walk distance between baseline and 12 months. Secondary endpoints included change in LV ejection fraction at 1 year, and safety measures of renal function and serum calcium concentration assessed every 3 months.

Results: One year of high-dose vitamin D3 supplementation did not improve 6-min walk distance at 1 year, but was associated with a significant improvement in cardiac function (LV ejection fraction +6.07% [95% confidence interval (CI): 3.20 to 8.95; p < 0.0001]); and a reversal of LV remodeling (LV end diastolic diameter -2.49 mm [95% CI: -4.09 to -0.90; p = 0.002] and LV end systolic diameter -2.09 mm [95% CI: -4.11 to -0.06 p = 0.043]).

Conclusions: One year of 100 μg daily vitamin D3 supplementation does not improve 6-min walk distance but has beneficial effects on LV structure and function in patients on contemporary optimal medical therapy. Further studies are necessary to determine whether these translate to improvements in outcomes.

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Short Telomere Load, Telomere Length, and Subclinical Atherosclerosis, The PESA Study

Juan M. Fernández-Alvira, Valentin Fuster, Beatriz Dorado,; et al

Background: Leucocyte telomere length (LTL) shortening is associated with cardiovascular ischemic events and mortality in humans, but data on its association with subclinical atherosclerosis are scarce. Whether the incidence and severity of subclinical atherosclerosis are associated with the abundance of critically short telomeres, a major trigger of cellular senescence, remains unknown.

Objectives: The authors conducted a cross-sectional exploration of the association between subclinical atherosclerosis burden and both average LTL and the abundance of short telomeres (%LTL<3 kb).

Methods: Telomere length was assessed by high-throughput quantitative fluorescence in situ hybridization in circulating leukocytes from 1,459 volunteers without established cardiovascular disease (58% men, 40 to 54 years of age) from the PESA (Progression of Early Subclinical Atherosclerosis) study. Subclinical atherosclerosis was evaluated by coronary artery calcium scan and 2-dimensional/3-dimensional ultrasound in different aortic territories. Statistical significance of differences among multiple covariates was assessed with linear regression models. Independent associations of telomere parameters with plaque presence were evaluated using general linear models.

Results: In men and women, age was inversely associated with LTL (Pearson's $r = -0.127$, $p < 0.001$) and directly with %LTL<3 kb (Pearson's $r = 0.085$; $p = 0.001$). Short LTL reached statistical significance as a determinant of total and femoral plaque in men, but not in women. However, this association was not sustained after adjustment for age or additional adjustment for cardiovascular risk factors. No significant independent association was found between %LTL<3 kb and plaque burden. Serum-oxidized low-density lipoprotein levels were directly associated with %LTL<3 kb in men ($p = 0.008$) and women ($p < 0.001$).

Conclusions: In a cross-sectional study of a middle-aged population, average LTL and short telomere load are not significant independent determinants of subclinical atherosclerosis. Longitudinal follow-up of PESA participants will assess long-term associations between telomere length and progression of subclinical atherosclerosis.

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Beyond Coronary Calcification, Family History, and C-Reactive Protein: Cholesterol Efflux Capacity and Cardiovascular Risk Prediction

Purav Mody, Parag H. Joshi, Amit Khera, et al

Background: Cholesterol efflux capacity (CEC), which is a key step in the reverse cholesterol transport pathway, is independently associated with atherosclerotic cardiovascular disease (ASCVD). However, whether it predicts ASCVD beyond validated novel risk markers is unknown.

Objectives : This study assessed if CEC improved ACSVD risk prediction beyond using coronary artery calcium (CAC), family history (FH), and high-sensitivity C-reactive protein (hs-CRP).

Methods: CEC, CAC, self-reported FH, and hs-CRP were assessed among participants without baseline ASCVD who were enrolled in the Dallas Heart Study (DHS). ASCVD was defined as a first nonfatal myocardial infarction (MI) or stroke, coronary revascularization, or cardiovascular death, assessed over a median 9.4 years. Risk prediction was assessed using various modeling techniques and improvements in the c-statistic, the integrated discrimination index (IDI), and the net reclassification index (NRI).

Results: The mean age of the population (N = 1,972) was 45 years, 52% had CAC (>0), 31% had FH, and 58% had elevated hs-CRP (≥2 mg/l). CEC greater than the median was associated with a 50% reduced incidence of ASCVD in those with CAC (5.4% vs. 10.5%; p = 0.003), FH (5.8% vs. 10%; p = 0.05), and elevated hs-CRP (3.8% vs. 7.9%; p = 0.004). CEC improved all metrics of discrimination and reclassification when added to CAC (c-statistic, p = 0.004; IDI, p = 0.02; NRI: 0.38; 95% confidence interval [CI]: 0.13 to 0.53), FH (c-statistic, p = 0.006; IDI, p = 0.008; NRI: 0.38; 95% CI: 0.13 to 0.55), or elevated hs-CRP (c-statistic p = 0.008; IDI p = 0.02; NRI: 0.36; 95% CI 0.12 to 0.52).

Conclusions: CEC improves ASCVD risk prediction beyond using CAC, FH, and hs-CRP and warrants consideration as a novel ASCVD risk marker

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Effect of Statin Treatment on Modifying Plaque Composition: A Double-Blind, Randomized Study

Seung-Jung Park, Soo-Jin Kang, , Jung-Min Ahn, et al

Background: How statins alter the natural course of coronary atherosclerosis with compositional changes remains unclear.

Objectives: This study aimed to determine the effect of statin therapy on modifying plaque composition.

Methods: The STABLE (Statin and Atheroma Vulnerability Evaluation) prospective, single-center, double-blind, randomized study evaluated the effect of statins on functionally insignificant coronary stenoses. We randomly assigned 312 patients with a virtual histology (VH) intravascular ultrasound–defined fibroatheroma-containing index lesion to rosuvastatin 40 mg versus 10 mg (2:1 ratio). In 225 (72%) patients, grayscale- and VH-intravascular ultrasound were completed at baseline and 12 months. The primary endpoint was the change in VH-defined percent compositional volume within the target segment from baseline to follow-up in the per-protocol analysis set.

Results: Percent necrotic core (NC) volume within the target segment significantly decreased from 21.3 ± 6.8% to 18.0 ± 7.5% during 1-year follow-up, whereas the percent fibrofatty volume increased (11.7 ± 5.8% vs. 14.8 ± 9.3%; all $p < 0.001$). Percent fibrous (59.4 ± 7.8% vs. 59.2 ± 8.6%) and dense calcium (7.6 ± 5.1% vs. 7.8 ± 5.6%) volumes were unchanged. Frequencies of VH (55% vs. 29%) decreased significantly. Normalized total (202.9 ± 72.3 mm3 vs. 188.5 ± 67.8 mm3; $p = 0.001$) and percent (51.4 ± 8.3% vs. 50.4 ± 8.8%; $p = 0.018$) atheroma volumes decreased. Independent predictors of percent NC volume change were body mass index ($\beta = 0.37$; 95% confidence interval [CI]: 0.05 to 0.70), high sensitivity C-reactive protein ($\beta = -3.16$; 95% CI: −5.64 to −0.69), and baseline percent NC volume ($\beta = -0.44$; 95% CI: −0.68 to −0.19; all $p < 0.05$). VH-defined percent compositional volume changes in the rosuvastatin 40- and 10-mg groups were similar.

Conclusions: Rosuvastatin reduced NC and plaque volume and decreased thin-cap fibroatheroma rate. There were no significant differences between high- versus moderate-intensity rosuvastatin. (Statin and Atheroma Vulnerability Evaluation [STABLE]

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Poor Adherence to Statin and Antihypertensive Therapies as Risk Factors for Fatal Stroke

Kimmo Herttua, Pekka Martikainen, G. David Batty, and Mika Kivimäki,

Background: Poor adherence to medication regimens is common, potentially contributing to the occurrence of related disease.

Objectives: The authors sought to assess the risk of fatal stroke associated with nonadherence to statin and/or antihypertensive therapy.

Methods: We conducted a population-based study using electronic medical and prescription records from Finnish national registers in 1995 to 2007. Of the 58,266 hypercholesterolemia patients age 30+ years without pre-existing stroke or cardiovascular disease, 532 patients died of stroke (cases), and 57,734 remained free of incident stroke (controls) during the mean follow-up of 5.5 years. We captured year-by-year adherence to statin and antihypertensive therapy in both study groups and estimated the excess risk of stroke death associated with nonadherence.

Results: In all hypercholesterolemia patients, the adjusted odds ratio for stroke death for nonadherent compared with adherent statin users was 1.35 (95% confidence interval [CI] 1.04 to 1.74) 4 years before and 2.04 (95% CI: 1.72 to 2.43) at the year of stroke death or the end of the follow-up. In hypercholesterolemia patients with hypertension, relative to those who adhered to statins and antihypertensive therapy, the odds ratio at the year of stroke death was 7.43 (95% CI: 5.22 to 10.59) for those nonadherent both to statin and antihypertensive therapy, 1.82 (95% CI: 1.43 to 2.33) for those non-adherent to statin but adherent to antihypertensive therapy, and 1.30 (95% CI: 0.53 to 3.20) for those adherent to statin, but nonadherent to antihypertensive, therapy.

Conclusions: Individuals with hypercholesterolemia and hypertension who fail to take their prescribed statin and antihypertensive medication experience a substantially increased risk of fatal stroke. The risk is lower if the patient is adherent to either one of these therapies.

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Ischemic cardiac outcomes and hospitalizations according to prior macrovascular disease status in patients with type 2 diabetes and recent acute coronary syndrome from the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care trial

Yuichi J. Shimada, Christopher P. Cannon, Yuyin Liu, for the EXAMINE Investigators

Concerns raised regarding adverse cardiovascular (CV) outcomes with new therapies for type 2 diabetes mellitus (T2DM) have led to several large-scale CV outcome trials. The EXAMINE trial confirmed noninferiority of the dipeptidyl dipeptidase 4 inhibitor alogliptin to placebo on major adverse cardiac event rates in a post–acute coronary syndrome (ACS) T2DM population. We present data on additional ischemic cardiac events and CV hospitalizations in EXAMINE.

Methods- Patients with T2DM and an ACS event in the previous 15 to 90 days were randomly assigned to aloglipti-n or placebo on a background of standard treatment for diabetes. The incident rates of a 5-component composite end point of CV death, stroke, myocardial infarction, unstable angina, and coronary revascularization as well as CV hospitalization were calculated in all participants and according to macrovascular disease at baseline.

Results- There were no significant differences between alogliptin (n = 2,701) and placebo (n = 2,679) in the event rate of the 5-component composite endpoint with median follow-up 533 days (21.0% vs 21.5%, hazard ratio [HR] 0.98 [0.87-1.10], P = .72). No differences were observed in terms of CV hospitalization (25.0% vs 25.4%, HR 0.98 [0.88-1.09], P = .70) or coronary revascularization (10.6% vs 10.2%, HR 1.05 [0.88-1.09], P = .60). No interactions were observed for treatment and prior macrovascular disease.

Conclusions - EXAMINE demonstrates that there was no increase in the risk of cardiac ischemic events and CV hospitalizations with alogliptin in a high-risk post-ACS patient population. Because these are major driver of overall health care costs, these data suggest that there would be no adverse impact on health care resource utilization.

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Cardiovascular Risk Factor Targets and Cardiovascular Disease Event Risk in Diabetes: A Pooling Project of the Atherosclerosis Risk in Communities Study, Multi-Ethnic Study of Atherosclerosis, and Jackson Heart Study

Nathan D. Wong, Yanglu Zhao, Rohini Patel, et al

OBJECTIVE Controlling cardiovascular disease (CVD) risk factors in diabetes mellitus (DM) reduces the number of CVD events, but the effects of multifactorial risk factor control are not well quantified. We examined whether being at targets for blood pressure (BP), LDL cholesterol (LDL-C), and glycated hemoglobin (HbA1c) together are associated with lower risks for CVD events in U.S. adults with DM.

RESEARCH DESIGN AND METHODS We studied 2,018 adults, 28–86 years of age with DM but without known CVD, from the Atherosclerosis Risk in Communities (ARIC) study, Multi-Ethnic Study of Atherosclerosis (MESA), and Jackson Heart Study (JHS). Cox regression examined coronary heart disease (CHD) and CVD events over a mean 11-year follow-up in those individuals at BP, LDL-C, and HbA1c target levels, and by the number of controlled risk factors.

RESULTS Of 2,018 DM subjects (43% male, 55% African American), 41.8%, 32.1%, and 41.9% were at target levels for BP, LDL-C, and HbA1c, respectively; 41.1%, 26.5%, and 7.2% were at target levels for any one, two, or all three factors, respectively. Being at BP, LDL-C, or HbA1c target levels related to 17%, 33%, and 37% lower CVD risks and 17%, 41%, and 36% lower CHD risks, respectively ($P < 0.05$ to $P < 0.0001$, except for BP in CHD risk); those subjects with one, two, or all three risk factors at target levels (vs. none) had incrementally lower adjusted risks of CVD events of 36%, 52%, and 62%, respectively, and incrementally lower adjusted risks of CHD events of 41%, 56%, and 60%, respectively ($P < 0.001$ to $P < 0.0001$). Propensity score adjustment showed similar findings.

CONCLUSIONS Optimal levels of BP, LDL-C, and HbA1c occurring together in individuals with DM are uncommon, but are associated with substantially lower risk of CHD and CVD.

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Intensive Diabetes Treatment and Cardiovascular Outcomes in Type 1 Diabetes: The DCCT/EDIC Study 30-Year Follow-up

The Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group

OBJECTIVE Early initiation of intensive diabetes therapy aimed at achieving near-normal glycemia reduces the early development of vascular complications in type 1 diabetes. We now assess whether intensive therapy compared with conventional therapy during the Diabetes Control and Complications Trial (DCCT) affected the incidence of cardiovascular disease over 30 years of follow-up.

RESEARCH DESIGN AND METHODS The DCCT randomly assigned 1,441 patients with type 1 diabetes to intensive versus conventional therapy for a mean of 6.5 years, after which 93% were subsequently monitored during the observational Epidemiology of Diabetes Interventions and Complications (EDIC) study. Cardiovascular disease (nonfatal myocardial infarction and stroke, cardiovascular death, confirmed angina, congestive heart failure, and coronary artery revascularization) was adjudicated using standardized measures.

RESULTS During 30 years of follow-up in DCCT and EDIC, 149 cardiovascular disease events occurred in 82 former intensive treatment group subjects versus 217 events in 102 former conventional treatment group subjects. Intensive therapy reduced the incidence of any cardiovascular disease by 30% (95% CI 7, 48; P = 0.016), and the incidence of major cardiovascular events (nonfatal myocardial infarction, stroke, or cardiovascular death) by 32% (95% CI −3, 56; P = 0.07). The lower HbA1c levels during the DCCT/EDIC statistically account for all of the observed treatment effect on cardiovascular disease risk. Increased albuminuria was also independently associated with cardiovascular disease risk.

CONCLUSIONS Intensive diabetes therapy during the DCCT (6.5 years) has long-term beneficial effects on the incidence of cardiovascular disease in type 1 diabetes that persist for up to 30 years.

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Long-term Benefits of Intensive Glucose Control for Preventing End-Stage Kidney Disease: ADVANCE-ON

Muh Geot Wong, Vlado Perkovic, John Chalmers, for the ADVANCE-ON Collaborative Group

OBJECTIVE The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial reported that intensive glucose control prevents end-stage kidney disease (ESKD) in patients with type 2 diabetes, but uncertainty about the balance between risks and benefits exists. Here, we examine the long-term effects of intensive glucose control on risk of ESKD and other outcomes.

RESEARCH DESIGN AND METHODS Survivors, previously randomized to intensive or standard glucose control, were invited to participate in post-trial follow-up. ESKD, defined as the need for dialysis or kidney transplantation, or death due to kidney disease, was documented overall and by baseline CKD stage, along with hypoglycemic episodes, major cardiovascular events, and death from other causes.

RESULTS A total of 8,494 ADVANCE participants were followed for a median of 5.4 additional years. In-trial HbA1c differences disappeared by the first post-trial visit. The in-trial reductions in the risk of ESKD (7 vs. 20 events, hazard ratio [HR] 0.35, P = 0.02) persisted after 9.9 years of overall follow-up (29 vs. 53 events, HR 0.54, P < 0.01). These effects were greater in earlier-stage CKD (P = 0.04) and at lower baseline systolic blood pressure levels (P = 0.01). The effects of glucose lowering on the risks of death, cardiovascular death, or major cardiovascular events did not differ by levels of kidney function (P > 0.26).

CONCLUSIONS Intensive glucose control was associated with a long-term reduction in ESKD, without evidence of any increased risk of cardiovascular events or death. These benefits were greater with preserved kidney function and with well-controlled blood pressure.

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Nine-Year Effects of 3.7 Years of Intensive Glycemic Control on Cardiovascular Outcomes

The ACCORD Study Group

OBJECTIVE In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, ~4 years of intensive versus standard glycemic control in participants with type 2 diabetes and other cardiovascular risk factors had a neutral effect on the composite cardiovascular outcome, increased cardiovascular and total mortality, and reduced nonfatal myocardial infarction. Effects of the intervention during prolonged follow-up were analyzed.

RESEARCH DESIGN AND METHODS All surviving ACCORD participants were invited to participate in the ACCORD Follow-on (ACCORDION) study, during which participants were treated according to their health care provider's judgment. Cardiovascular and other health-related outcomes were prospectively collected and analyzed using an intention-to-treat approach according to the group to which participants were originally allocated.

RESULTS A total of 8,601 people, representing 98% of those who did not suffer a primary outcome or death during the ACCORD trial, were monitored for a median of 8.8 years and a mean of 7.7 years from randomization. Intensive glucose lowering for a mean of 3.7 years had a neutral long-term effect on the primary composite outcome (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death), death from any cause, and an expanded composite outcome that included all-cause death. Moreover, the risk of cardiovascular mortality noted during the active phase (hazard ratio 1.49; 95% CI 1.19, 1.87; $P < 0.0001$) decreased (HR 1.20; 95% CI 1.03, 1.39; $P = 0.02$).

CONCLUSIONS In high-risk people with type 2 diabetes monitored for 9 years, a mean of 3.7 years of intensive glycemic control had a neutral effect on death and nonfatal cardiovascular events but increased cardiovascular-related death.

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Cardiovascular and Other Outcomes Postintervention With Insulin Glargine and Omega-3 Fatty Acids (ORIGINALE)

ORIGIN Trial Investigators

OBJECTIVE The Outcome Reduction With Initial Glargine Intervention (ORIGIN) trial reported neutral effects of insulin glargine on cardiovascular outcomes and cancers and reduced incident diabetes in high–cardiovascular risk adults with dysglycemia after 6.2 years of active treatment. Omega-3 fatty acids had neutral effects on cardiovascular outcomes. The ORIGIN and Legacy Effects (ORIGINALE) study measured posttrial effects of these interventions during an additional 2.7 years.

RESEARCH DESIGN AND METHODS Surviving ORIGIN participants attended up to two additional visits. The hazard of clinical outcomes during the entire follow-up period from randomization was calculated.

RESULTS Of 12,537 participants randomized, posttrial data were analyzed for 4,718 originally allocated to insulin glargine (2,351) versus standard care (2,367), and 4,771 originally allocated to omega-3 fatty acid supplements (2,368) versus placebo (2,403). Posttrial, small differences in median HbA1c persisted (glargine 6.6% [49 mmol/mol], standard care 6.7% [50 mmol/mol], P = 0.025). From randomization to the end of posttrial follow-up, no differences were found between the glargine and standard care groups in myocardial infarction, stroke, or cardiovascular death (1,185 vs. 1,165 events; hazard ratio 1.01 [95% CI 0.94–1.10]; P = 0.72); myocardial infarction, stroke, cardiovascular death, revascularization, or hospitalization for heart failure (1,958 vs. 1,910 events; 1.03 [0.97–1.10]; P = 0.38); or any cancer (524 vs. 529 events; 0.99 [0.88–1.12]; P = 0.91) or between omega-3 and placebo groups in cardiovascular death (688 vs. 700; 0.98 [0.88–1.09]; P = 0.68) or other outcomes.

CONCLUSIONS During >6 years of treatment followed by >2.5 years of observation, insulin glargine had neutral effects on health outcomes and salutary effects on metabolic control, whereas omega-3 fatty acid supplementation had no effect