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Improving Mortality Prediction Using Biosocial Surveys

Noreen Goldman, Dana A. Gleib, Yu-Hsuan Lin and Maxine Weinstein

The authors used data from a nationally representative survey of 933 adults aged 54 years or older (mean age = 66.2 years; standard deviation, 8.0) in Taiwan to explore whether mortality prediction at older ages is improved by the use of 3 clusters of biomarkers: 1) standard cardiovascular and metabolic risk factors; 2) markers of disease progression; and 3) nonclinical (neuroendocrine and immune) markers. They also evaluated the extent to which these biomarkers account for the female advantage in survival. Estimates from logistic regression models of the probability of dying between 2000 and 2006 (162 deaths; mean length of follow-up = 5.8 years) showed that inclusion of each of the 3 sets of markers significantly ($P = 0.024$, $P = 0.002$ and $P = 0.003$, respectively) improved discriminatory power in comparison with a base model that adjusted for demographic characteristics, smoking and baseline health status. The set of disease progression markers and the set of nonclinical markers each provided more discriminatory power than standard risk factors. Most of the excess male mortality resulted from the men being more likely than women to smoke, but each of 3 markers related to disease progression or inflammation (albumin, neutrophils and interleukin-6) explained more than 10% of excess male mortality. (*American Journal of Epidemiology* 2009 169(6):769-779; doi:10.1093/aje/kwn389)

Intersecting Birth Weight-specific Mortality Curves: Solving the Riddle

Olga Basso and Allen J. Wilcox

Small babies from a population with higher infant mortality often have better survival than small babies from a lower-risk population. This phenomenon can in principle be explained entirely by the presence of unmeasured confounding factors that increase mortality and decrease birth weight. Using a previously developed model for birth weight-specific mortality, the authors demonstrate specifically how strong unmeasured confounders can cause mortality curves stratified by known risk factors to intersect. In this model, the addition of a simple exposure (one that reduces birth weight and independently increases mortality) will produce the familiar reversal of risk among small babies. Furthermore, the model explicitly shows how the mix of high- and low-risk babies within a given stratum of birth weight produces lower mortality for high-risk babies at low birth weights. If unmeasured confounders are, in fact, responsible for the intersection of weight-specific mortality curves, then they must also (by virtue of being confounders) contribute to the strength of the observed gradient of mortality by birth weight. It

follows that the true gradient of mortality with birth weight would be weaker than what is observed, if indeed there is any true gradient at all. (American Journal of Epidemiology 2009 169(7):787-797; doi:10.1093/aje/kwp024)

Invited Commentary: Crossing Curves-It's Time to Focus on Gestational Age-specific Mortality

Jennifer D. Parker and Mark A. Klebanoff

For decades, epidemiologists have observed that, among lower birth weight infants, higher risk infants have lower mortality rates than do lower risk infants. However, among higher birth weight infants, the pattern reverses, leading to a riddle of crossing birth weight-specific mortality curves. The riddle has been considered from different perspectives, including relative z scores, directed acyclic graphs and, most recently, simulated mathematical models of underlying causal factors that produce the observed curves; similarly paradoxical gestational age-specific mortality curves uncross when calculations include all fetuses-at-risk rather than just infants delivered at a particular gestational age. However, researchers have generally focused on birth weight rather than gestational age, likely because birth weight is accurately measured and, if one assumes that birth weight is an intermediate variable between the underlying causal factors and mortality, is easier to model. Within the framework of existing analytical approaches, adding the complexity of a direct relation between gestational age and mortality and possibly more complex relations among the casual factors, may be difficult. Nevertheless, duration of pregnancy seems a better proxy for the true construct of interest, whether the baby is mature enough to survive, so shifting attention to understanding the riddle of gestational age-specific mortality is encouraged. (American Journal of Epidemiology 2009 169(7):798-801; doi:10.1093/aje/kwp025)

Meta- and Pooled Analysis of *GSTP1* Polymorphism and Lung Cancer: A HuGE-GSEC Review

Michele L. Cote, Wei Chen, Daryn W. Smith, Simone Benhamou, Christine Bouchardy, Dorota Butkiewicz, Kwun M. Fong, Manuel Gené, Ari Hirvonen, Chikako Kiyohara, Jill E. Larsen, Pinpin Lin, Ole Raaschou-Nielsen, Andrew C. Povey, Edyta Reszka, Angela Risch, Joachim Schneider, Ann G. Schwartz, Mette Sorensen, Jordi To-Figueras, Shinkan Tokudome, Yuepu Pu, Ping Yang, Angela S. Wenzlaff, Harriet Wikman and Emanuela Taioli

Lung cancer is the most common cancer worldwide. Polymorphisms in genes associated with carcinogen metabolism may modulate risk of disease. Glutathione S-transferase pi (*GSTP1*) detoxifies polycyclic aromatic hydrocarbons found in

cigarette smoke and is the most highly expressed glutathione *S*-transferase in lung tissue. A polymorphism in the *GSTP1* gene, an A-to-G transition in exon 5 (Ile105Val, 313A →313G), results in lower activity among individuals who carry the valine allele. The authors present a meta- and a pooled analysis of case-control studies that examined the association between this polymorphism in *GSTP1* and lung cancer risk (27 studies, 8,322 cases and 8,844 controls and 15 studies, 4,282 cases and 5,032 controls, respectively). Overall, the meta-analysis found no significant association between lung cancer risk and the *GSTP1* exon 5 polymorphism. In the pooled analysis, there was an overall association (odds ratio = 1.11, 95% confidence interval: 1.03, 1.21) between lung cancer and carriage of the *GSTP1* Val/Val or Ile/Val genotype compared with those carrying the Ile/Ile genotype. Increased risk varied by histologic type in Asians. There appears to be evidence for interaction between amount of smoking, the *GSTP1* exon 5 polymorphism and risk of lung cancer in whites. (American Journal of Epidemiology 2009 169(7):802-814; doi:10.1093/aje/kwn417)

Long-term Use of β -Carotene, Retinol, Lycopene and Lutein Supplements and Lung Cancer Risk: Results From the VITamins And Lifestyle (VITAL) Study

Jessie A. Satia, Alyson Littman, Christopher G. Slatore, Joseph A. Galanko and Emily White

High-dose β -carotene supplementation in high-risk persons has been linked to increased lung cancer risk in clinical trials; whether effects are similar in the general population is unclear. The authors examined associations of supplemental β -carotene, retinol, vitamin A, lutein and lycopene with lung cancer risk among participants, aged 50-76 years, in the VITamins And Lifestyle (VITAL) cohort Study in Washington State. In 2000-2002, eligible persons ($n = 77,126$) completed a 24-page baseline questionnaire, including detailed questions about supplement use (duration, frequency, dose) during the previous 10 years from multivitamins and individual supplements/mixtures. Incident lung cancers ($n = 521$) through December 2005 were identified by linkage to the Surveillance, Epidemiology and End Results cancer registry. Longer duration of use of individual β -carotene, retinol and lutein supplements (but not total 10-year average dose) was associated with statistically significantly elevated risk of total lung cancer and histologic cell types; for example, hazard ratio = 2.02, 95% confidence interval: 1.28, 3.17 for individual supplemental lutein with total lung cancer and hazard ratio = 3.22, 95% confidence interval: 1.29, 8.07 for individual β -carotene with small-cell lung cancer for >4 years versus no use. There was little evidence for effect

modification by gender or smoking status. Long-term use of individual β -carotene, retinol and lutein supplements should not be recommended for lung cancer prevention, particularly among smokers. (*American Journal of Epidemiology* 2009 169(7):815-828; doi:10.1093/aje/kwn409)

Life-Course Socioeconomic Position and Incidence of Coronary Heart Disease

Eric B. Loucks, John W. Lynch, Louise Pilote, Rebecca Fuhrer, Nisha D. Almeida, Hugues Richard, Golareh Agha, Joanne M. Murabito and Emelia J. Benjamin

Cumulative exposure to socioeconomic disadvantage across the life course may be inversely associated with coronary heart disease (CHD); the mechanisms are not fully clear. An objective of this study was to determine whether cumulative life-course socioeconomic position (SEP) is associated with CHD incidence in a well-characterized US cohort that had directly assessed childhood and adulthood measures of SEP and prospectively measured CHD incidence. Furthermore, analyses aimed to evaluate whether adjustment for CHD risk factors reduces the association between cumulative life-course SEP and CHD. The authors examined 1,835 subjects who participated in the Framingham Heart Study Offspring Cohort from 1971 through 2003 (mean age, 35.0 years; 52.4% women). Childhood SEP was measured as father's education; adulthood SEP was assessed as own education and occupation. CHD incidence included myocardial infarction, coronary insufficiency and coronary death. Cox proportional hazards analyses indicated that cumulative SEP was associated with incident CHD after adjustment for age and sex (hazard ratio = 1.82, 95% confidence interval: 1.17, 2.85 for low vs. high cumulative SEP score). Adjustment for CHD risk factors reduced that magnitude of association (hazard ratio = 1.29, 95% confidence interval: 0.78, 2.13). These findings underscore the potential importance of CHD prevention and treatment efforts for those whose backgrounds include low SEP throughout life. (*American Journal of Epidemiology* 2009 169(7):829-836; doi:10.1093/aje/kwn403)

Association of Hip Circumference With Incident Diabetes and Coronary Heart Disease

Emily D. Parker, Mark A. Pereira, June Stevens and Aaron R. Folsom

When waist circumference is taken into account, larger hip circumference is associated with reduced risk factors for diabetes and cardiovascular disease. The

authors investigated the prospective association of hip circumference with type 2 diabetes and coronary heart disease (CHD) incidence in a biracial cohort of men and women in 4 US communities. A total of 10,767 participants from the Atherosclerosis Risk in Communities (ARIC) study were followed from 1987 to 1998. Hip and waist circumferences and body mass index (BMI) were modeled separately and mutually in association with incident diabetes and CHD by using proportional hazards regression. After adjustment for age, race, sex and clinical center, hip circumference was positively associated with incident diabetes. However, after further controlling for waist circumference, BMI and confounding variables, successive quintiles of hip circumference were associated with a statistically significant reduced hazard of incident diabetes (hazard ratios = 1.00, 0.79, 0.60, 0.44, 0.41). Similarly, successive quintiles of hip circumference were associated with a statistically significant reduced hazard of CHD after controlling for waist circumference, BMI and confounding variables (hazard ratios = 1.00, 0.92, 0.75, 0.63, 0.50). Although excess adiposity is a general risk factor for diabetes and CHD, for a given BMI and waist circumference, greater hip circumference appears to lessen the risk of diabetes and CHD. (*American Journal of Epidemiology* 2009 169(7):837-847; doi:10.1093/aje/kwn395)

Vascular Function, Inflammation and Variations in Cardiac Autonomic Responses to Particulate Matter Among Welders

Shona C. Fang, Jennifer M. Cavallari, Ellen A. Eisen, Jiu-Chiuan Chen, Murray A. Mittleman and David C. Christiani

Patients with health conditions associated with impaired vascular function and inflammation may be more susceptible to the adverse health effects of fine particulate (particulate matter with a mass median aerodynamic diameter of $\leq 2.5 \mu\text{m}$ ($\text{PM}_{2.5}$)) exposure. In 2006, the authors conducted a panel study to investigate directly whether vascular function and inflammation (assessed by C-reactive protein) modify $\text{PM}_{2.5}$ -associated reductions in heart rate variability among 23 young male workers (mean age, 40 years) from Massachusetts. Concurrent 24-hour ambulatory electrocardiogram and personal $\text{PM}_{2.5}$ exposure information was collected over a total of 36 person-days, including either or both welding and nonwelding days. Linear mixed models were used to examine the 5-minute standard deviation of normal-to-normal intervals (SDNN) in relation to the moving $\text{PM}_{2.5}$ averages in the preceding 1-4 hours. C-reactive protein levels and 3 measures of vascular function (augmentation index, mean arterial pressure and pulse pressure) were determined at baseline. The authors observed an inverse association between the 1-hour $\text{PM}_{2.5}$ and 5-minute SDNN. Greater SDNN

declines were observed among those with C-reactive protein ($P_{\text{interaction}} < 0.001$) and augmentation index ($P = 0.06$) values at or above the 75th percentile and pulse pressure values below the 75th percentile ($P < 0.001$). Systemic inflammation and poorer vascular function appear to aggravate particle-related declines in heart rate variability among workers. (American Journal of Epidemiology 2009 169(7):848-856; doi:10.1093/aje/kwn405)

The Relation Between Body Size Perception and Change in Body Mass Index Over 13 Years

Elizabeth Lynch, Kiang Liu, Gina S. Wei, Bonnie Spring, Catarina Kiefe and Philip Greenland

The authors assessed associations of body size perception and weight change over 13 years in black men and women and white men and women from the Coronary Artery Risk Development in Young Adults (CARDIA) Study (1992-2005). The perceptions of self and ideal body size were measured by using the Stunkard 9-figure scale at the year 7 examination (1992-1993). Figures were classified into underweight, normal weight, overweight and obese. Self-ideal discrepancy yielded 4 body size satisfaction categories. Body mass index (BMI) (measured at years 7, 10, 15 and 20) was the dependent variable in gender-specific adjusted multiple regression models stratified by year 7 BMI. Obese women who perceived themselves as obese lost 0.09 BMI units annually, while those who perceived themselves as normal weight gained 0.31 units annually ($P = 0.0005$); obese women who considered their body size much too large had less annual weight gain than did those who considered their body size a bit too large (0.21 vs. 0.38 BMI units; $P = 0.009$). Obese women with overweight ideal body size gained less weight annually than did those with normal weight ideal body size (0.12 vs. 0.27 BMI units; $P = 0.04$). Results for men showed fewer and weaker associations. When obese women perceive themselves as obese and feel that their body size is too large, they gain less weight over time. (American Journal of Epidemiology 2009 169(7):857-866; doi:10.1093/aje/kwn412)

Red Meat and Chicken Consumption and Its Association With Age-related Macular Degeneration

Elaine W.-T. Chong, Julie A. Simpson, Luibov D. Robman, Allison M. Hodge, Khin Zaw Aung, Dallas R. English, Graham G. Giles and Robyn H. Guymer

Age-related macular degeneration (AMD) is the leading cause of blindness among older people and diet has been postulated to alter risk of AMD. To evaluate

associations between red meat and chicken intake and AMD, the authors conducted a cohort study of 6,734 persons aged 58-69 years in 1990-1994 in Melbourne, Australia. Meat intake was estimated from a food frequency questionnaire at baseline. At follow-up (2003-2006), bilateral digital macular photographs were taken and evaluated for AMD (1,680 cases of early AMD, 77 cases of late AMD). Logistic regression was used to estimate odds ratios, adjusted for age, smoking and other potential confounders. Higher red meat intake was positively associated with early AMD; the odds ratio for consumption of red meat ≥ 10 times/week versus < 5 times/week was 1.47 (95% confidence interval: 1.21, 1.79; P -trend < 0.001). Similar trends toward increasing prevalence of early AMD were seen with higher intakes of fresh and processed red meat. Conversely, consumption of chicken ≥ 3.5 times/week versus < 1.5 times/week was inversely associated with late AMD (odds ratio = 0.43, 95% confidence interval: 0.20, 0.91; P -trend = 0.007). These results suggest that different meats may differently affect AMD risk and may be a target for lifestyle modification. (American Journal of Epidemiology 2009 169(7):867-876; doi:10.1093/aje/kwn393)

Lifestyle Impact on Lifetime Bone Loss in Women and Men

Tom Wilsgaard, Nina Emaus, Luai Awad Ahmed, Guri Grimnes, Ragnar Martin Joakimsen, Tone Kristin Omsland and Gro Rosvold Berntsen

A physically active, nonsmoking lifestyle with weight maintenance positively influences bone health. The authors estimated the effect of lifestyles on peak bone mass and lifetime bone loss in the Tromsø Study, Norway. Bone mineral density (BMD) was measured at distal and ultradistal forearm sites with single x-ray absorptiometric devices in 7,948 men and women aged 24-84 years in 1994-1995 and repeated in 2001 in 6,182 subjects. BMD was significantly higher at peak than at old age. However, the difference, estimated as lifetime loss, varied between lifestyle groups. Lifetime loss in nonsmoking, physically active men with a body mass index of 25 kg/m^2 compared with smoking, inactive and lean men was 15.9% and 25.9% at the distal site and 17.5% and 29.7% at the ultradistal site, respectively. In women, the corresponding loss estimates were 34.4% and 45.7% and 35.6% and 55.7%, respectively. The differences in BMD at the age of 80 years correspond to an increased forearm fracture risk of 69% in men and 85% in women with greatest bone loss. A lifestyle including nonsmoking, a high physical activity level and a high body weight reduces bone loss and fracture risk in both sexes, with increasing effect from peak bone mass to old age. (American Journal of Epidemiology 2009 169(7):877-886; doi:10.1093/aje/kwn407)

Trends in Dietary Supplement Use in a Cohort of Postmenopausal Women From Iowa

Kyong Park, Lisa Harnack and David R. Jacobs, Jr.

Although it is widely known that use of dietary supplements is common in the United States, little is known about use patterns among older Americans. The authors examined trends in dietary supplement use and its contribution to total nutrient intake in the Iowa Women's Health Study cohort in 1986 (baseline) and 2004 (follow-up). The proportion of women who reported using dietary supplements increased substantially between baseline (66%) and follow-up (85%). Moreover, a substantial proportion of women reported using multiple dietary supplements, with 27% using 4 or more products in 2004. Dietary supplements contributed substantially to total intake of many nutrients at baseline and their contribution became relatively greater at follow-up for most nutrients examined. For most nutrients, no decline in intake was observed, as might have been expected in an aging cohort. Rather, intake of many nutrients increased, primarily because of the rising use of dietary supplements. Use of dietary supplements by older individuals is of particular importance because of the potential benefits of maintaining nutrient intake levels despite potentially declining food intake. However, possible risks from obtaining a large proportion of purified nutrients from dietary supplements rather than deriving them from foods should be studied. (American Journal of Epidemiology 2009 169(7):887-892; doi:10.1093/aje/kwn410)

Associations Between Macronutrient Intake and Self-reported Appetite and Fasting Levels of Appetite Hormones: Results From the Optimal Macronutrient Intake Trial to Prevent Heart Disease

Jeannette M. Beasley, Brett A. Ange, Cheryl A. M. Anderson, Edgar R. Miller, III, Thomas P. Erlinger, Janet T. Holbrook, Frank M. Sacks and Lawrence J. Appel

The authors compared effects of macronutrients on self-reported appetite and selected fasting hormone levels. The Optimal Macronutrient Intake Trial to Prevent Heart Disease (OMNI-Heart) (2003-2005) was a randomized, 3-period, crossover feeding trial ($n = 164$) comparing the effects of 3 diets, each rich in a different macronutrient. Percentages of kilocalories of carbohydrate, fat and protein were 48, 27 and 25, respectively, for the protein-rich diet; 58, 27 and 15,

for the carbohydrate-rich diet; and 48, 37 and 15 for the diet rich in unsaturated fat. Food and drink were provided for each isocaloric 6-week period. Appetite was measured by visual analog scales. Pairwise differences between diets were estimated using generalized estimating equations. Compared with the protein diet, premeal appetite was 14% higher on the carbohydrate ($P = 0.01$) and unsaturated-fat ($P = 0.003$) diets. Geometric mean leptin was 8% lower on the protein diet than on the carbohydrate diet ($P = 0.003$). Obestatin levels were 7% and 6% lower on the protein diet than on the carbohydrate ($P = 0.02$) and unsaturated-fat ($P = 0.004$) diets, respectively. There were no between-diet differences for ghrelin. A diet rich in protein from lean meat and vegetables reduces self-reported appetite compared with diets rich in carbohydrate and unsaturated fat and can be recommended in a weight-stable setting. The observed pattern of hormone changes does not explain the inverse association between protein intake and appetite. (American Journal of Epidemiology 2009 169(7):893-900; doi:10.1093/aje/kwn415)

The Impact on National Death Index Ascertainment of Limiting Submissions to Social Security Administration Death Master File Matches in Epidemiologic Studies of Mortality

Sigurd W. Hermansen, Michael F. Leitzmann and Arthur Schatzkin

Although many epidemiologists use the National Death Index (NDI) as the "gold standard" for ascertainment of US mortality, high search costs per year and per subject for large cohorts warrant consideration of less costly alternatives. In this study, for 1995-2001 deaths, the authors compared matches of a random sample of 11,968 National Institutes of Health (NIH)-AARP Diet and Health Study subjects to the Social Security Administration's Death Master File (DMF) and commercial list updates (CLU) with matches of those subjects to the NDI. They examined how varying the lower limits of estimated DMF match probabilities (m scores of 0.60, 0.20 and 0.05) altered the benefits and costs of mortality ascertainment. Observed DMF/CLU ascertainment of NDI-identified decedents increased from 89.8% to 95.1% as m decreased from 0.60 (stringent) to 0.20 (less stringent) and increased further to 96.4% as m decreased to 0.05 (least stringent). At these same cutpoints, the false-match probability increased from 0.4% of the sample to 0.6% and then 2.3%. Limiting NDI cause-of-death searches to subjects found in DMF searches using less stringent match criteria, further supplemented by CLU vital status updates, improves vital status assessment while increasing substantially the cost-effectiveness of ascertaining mortality in large prospective cohort studies. (American Journal of Epidemiology 2009 169(7):901-908; doi:10.1093/aje/kwn404)

Different Methods of Balancing Covariates Leading to Different Effect Estimates in the Presence of Effect Modification

Mark Lunt, Daniel Solomon, Kenneth Rothman, Robert Glynn, Kimme Hyrich, Deborah P. M. Symmons, Til Stürmer and the British Society for Rheumatology Biologics Register, the British Society for Rheumatology Biologics Register Control Centre Consortium

A number of covariate-balancing methods, based on the propensity score, are widely used to estimate treatment effects in observational studies. If the treatment effect varies with the propensity score, however, different methods can give very different answers. The authors illustrate this effect by using data from a United Kingdom-based registry of subjects treated with anti-tumor necrosis factor drugs for rheumatoid arthritis. Estimates of the effect of these drugs on mortality varied from a relative risk of 0.4 (95% confidence interval: 0.16, 0.91) to a relative risk of 1.3 (95% confidence interval: 0.8, 2.25), depending on the balancing method chosen. The authors show that these differences were due to a combination of an interaction between propensity score and treatment effect and to differences in weighting subjects with different propensity scores. Thus, the methods are being used to calculate average treatment effects in populations with very different distributions of effect-modifying variables, resulting in different overall estimates. This phenomenon highlights the importance of careful selection of the covariate-balancing method so that the overall estimate has a meaningful interpretation. (American Journal of Epidemiology 2009 169(7):909-917; doi:10.1093/aje/kwn391)

Parkinson's Disease and Residential Exposure to Maneb and Paraquat From Agricultural Applications in the Central Valley of California

Sadie Costello, Myles Cockburn, Jeff Bronstein, Xinbo Zhang and Beate Ritz

Evidence from animal and cell models suggests that pesticides cause a neurodegenerative process leading to Parkinson's disease (PD). Human data are insufficient to support this claim for any specific pesticide, largely because of challenges in exposure assessment. The authors developed and validated an exposure assessment tool based on geographic information systems that integrated information from California Pesticide Use Reports and land-use maps to estimate historical exposure to agricultural pesticides in the residential environment. In

1998-2007, the authors enrolled 368 incident PD cases and 341 population controls from the Central Valley of California in a case-control study. They generated estimates for maneb and paraquat exposures incurred between 1974 and 1999. Exposure to both pesticides within 500 m of the home increased PD risk by 75% (95% confidence interval (CI): 1.13, 2.73). Persons aged ≤ 60 years at the time of diagnosis were at much higher risk when exposed to either maneb or paraquat alone (odds ratio = 2.27, 95% CI: 0.91, 5.70) or to both pesticides in combination (odds ratio = 4.17, 95% CI: 1.15, 15.16) in 1974-1989. This study provides evidence that exposure to a combination of maneb and paraquat increases PD risk, particularly in younger subjects and/or when exposure occurs at younger ages. (American Journal of Epidemiology 2009 169(8):919-926; doi:10.1093/aje/kwp006)

Overweight and Obesity Over the Adult Life Course and Incident Mobility Limitation in Older Adults

Denise K. Houston, Jingzhong Ding, Barbara J. Nicklas, Tamara B. Harris, Jung Sun Lee, Michael C. Nevitt, Susan M. Rubin, Frances A. Tylavsky, Stephen B. Kritchevsky

Obesity in middle and old age predicts mobility limitation; however, the cumulative effect of overweight and/or obesity over the adult life course is unknown. The association between overweight and/or obesity in young, middle and late adulthood and its cumulative effect on incident mobility limitation was examined among community-dwelling US adults aged 70-79 years at baseline (1997-1998) in the Health, Aging and Body Composition Study ($n = 2,845$). Body mass index was calculated by using recalled weight at ages 25 and 50 years and measured weight at ages 70-79 years. Mobility limitation (difficulty walking 1/4 mile (0.4 km) or climbing 10 steps) was assessed semiannually over 7 years of follow-up and was reported by 43.0% of men and 53.7% of women. Men and women who were overweight or obese at all 3 time points had an increased risk of mobility limitation (hazard ratio = 1.61, 95% confidence interval: 1.25, 2.06 and hazard ratio = 2.85, 95% confidence interval: 2.15, 3.78, respectively) compared with those who were normal weight throughout. Furthermore, there was a significant graded response ($P < 0.0001$) on risk of mobility limitation for the cumulative effect of obesity in men and overweight and/or obesity in women. Onset of overweight and obesity in earlier life contributes to an increased risk of mobility limitation in old age. (American Journal of Epidemiology 2009 169(8):927-936; doi:10.1093/aje/kwp007)

Association of Diabetes With Prostate Cancer Risk in the Multiethnic Cohort

Kevin M. Waters, Brian E. Henderson, Daniel O. Stram, Peggy Wan, Laurence N. Kolonel and Christopher A. Haiman

Among men of European ancestry, diabetics have a lower risk of prostate cancer than do nondiabetics. The biologic basis of this association is unknown. The authors have examined whether the association is robust across populations in a population-based prospective study. The analysis included 5,941 prostate cancer cases identified over a 12-year period (1993-2005) among 86,303 European-American, African-American, Latino, Japanese-American and Native Hawaiian men from the Multiethnic Cohort. The association between diabetes and prostate-specific antigen (PSA) levels ($n = 2,874$) and PSA screening frequencies ($n = 46,970$) was also examined. Diabetics had significantly lower risk of prostate cancer than did nondiabetics (relative risk = 0.81, 95% confidence interval (CI): 0.74, 0.87; $P < 0.001$), with relative risks ranging from 0.65 (95% CI: 0.50, 0.84; $P = 0.001$) among European Americans to 0.89 (95% CI: 0.77, 1.03; $P = 0.13$) among African Americans. Mean PSA levels were significantly lower in diabetics than in nondiabetics (mean PSA levels, 1.07 and 1.28, respectively; $P = 0.003$) as were PSA screening frequencies (44.7% vs. 48.6%; $P < 0.001$); however, this difference could explain only a small portion (~20%) of the inverse association between these diseases. Diabetes is a protective factor for prostate cancer across populations, suggesting shared risk factors that influence a common mechanism. (American Journal of Epidemiology 2009 169(8):937-945; doi:10.1093/aje/kwp003)

Modification of the Effect of Vitamin E Supplementation on the Mortality of Male Smokers by Age and Dietary Vitamin C

Harri Hemilä and Jaakko Kaprio

The Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study (1985-1993) recruited 29,133 Finnish male cigarette smokers, finding that vitamin E supplementation had no overall effect on mortality. The authors of this paper found that the effect of vitamin E on respiratory infections in ATBC Study participants was modified by age, smoking and dietary vitamin C intake; therefore, they examined whether the effect of vitamin E supplementation on mortality is modified by the same variables. During a median follow-up time of 6.1 years,

3,571 deaths occurred. Age and dietary vitamin C intake had a second-order interaction with vitamin E supplementation of 50 mg/day. Among participants with a dietary vitamin C intake above the median of 90 mg/day, vitamin E increased mortality among those aged 50-62 years by 19% (95% confidence interval: 5, 35), whereas vitamin E decreased mortality among those aged 66-69 years by 41% (95% CI: -56, -21). Vitamin E had no effect on participants who had a dietary vitamin C intake below the median. Smoking quantity did not modify the effect of vitamin E. This study provides strong evidence that the effect of vitamin E supplementation on mortality varies between different population groups. Further study is needed to confirm this heterogeneity. (American Journal of Epidemiology 2009 169(8):946-953; doi:10.1093/aje/kwn413)

Dietary Acrylamide Intake and Risk of Premenopausal Breast Cancer

Kathryn M. Wilson, Lorelei A. Mucci, Eunyoung Cho, David J. Hunter, Wendy Y. Chen and Walter C. Willett

Acrylamide, a probable human carcinogen, is formed during high-temperature cooking of many commonly consumed foods. It is widespread; approximately 30% of calories consumed in the United States are from foods containing acrylamide. In animal studies, acrylamide causes mammary tumors, but it is unknown whether the level of acrylamide in foods affects human breast cancer risk. The authors studied the association between acrylamide intake and breast cancer risk among 90,628 premenopausal women in the Nurses' Health Study II. They calculated acrylamide intake from food frequency questionnaires in 1991, 1995, 1999 and 2003. From 1991 through 2005, they documented 1,179 cases of invasive breast cancer. They used Cox proportional hazards models to assess the association between acrylamide and breast cancer risk. The multivariable-adjusted relative risk of premenopausal breast cancer was 0.92 (95% confidence interval: 0.76, 1.11) for the highest versus the lowest quintile of acrylamide intake ($P_{\text{trend}} = 0.61$). Results were similar regardless of smoking status or estrogen and progesterone receptor status of the tumors. The authors found no associations between intakes of foods high in acrylamide, including French fries, coffee, cereal, potato chips, potatoes and baked goods and breast cancer risk. They found no evidence that acrylamide intake, within the range of US diets, is associated with increased risk of premenopausal breast cancer. (American Journal of Epidemiology 2009 169(8):954-961; doi:10.1093/aje/kwn421)

Alcohol Intake and Cigarette Smoking and Risk of a Contralateral Breast Cancer

Julia A. Knight, Leslie Bernstein, Joan Largent, Marinela Capanu, Colin B. Begg, Lene Mellekjær, Charles F. Lynch, Kathleen E. Malone, Anne S. Reiner, Xiaolin Liang, Robert W. Haile, John D. Boice, Jr., WECARE Study Collaborative Group and Jonine L. Bernstein

Women with primary breast cancer are at increased risk of developing second primary breast cancer. Few studies have evaluated risk factors for the development of asynchronous contralateral breast cancer in women with breast cancer. In the Women's Environmental Cancer and Radiation Epidemiology Study (1985-2001), the roles of alcohol and smoking were examined in 708 women with asynchronous contralateral breast cancer (cases) compared with 1,399 women with unilateral breast cancer (controls). Cases and controls aged less than 55 years at first breast cancer diagnosis were identified from 5 population-based cancer registries in the United States and Denmark. Controls were matched to cases on birth year, diagnosis year, registry region and race and countermatched on radiation treatment. Risk factor information was collected by telephone interview. Rate ratios and 95% confidence intervals were estimated by using conditional logistic regression. Ever regular drinking was associated with an increased risk of asynchronous contralateral breast cancer (rate ratio = 1.3, 95% confidence interval: 1.0, 1.6) and the risk increased with increasing duration ($P = 0.03$). Smoking was not related to asynchronous contralateral breast cancer. In this, the largest study of asynchronous contralateral breast cancer to date, alcohol is a risk factor for the disease, as it is for a first primary breast cancer. (*American Journal of Epidemiology* 2009 169(8):962-968; doi:10.1093/aje/kwn422)

Positive Associations Between Ionizing Radiation and Lymphoma Mortality Among Men

David B. Richardson, Hiromi Sugiyama, Steve Wing, Ritsu Sakata, Eric Grant, Yukiko Shimizu, Nobuo Nishi, Susan Geyer, Midori Soda, Akihiko Suyama, Fumiyoshi Kasagi and Kazunori Kodama

The authors investigated the relation between ionizing radiation and lymphoma mortality in 2 cohorts: 1) 20,940 men in the Life Span Study, a study of Japanese atomic bomb survivors who were aged 15-64 years at the time of the bombings of Hiroshima and Nagasaki and 2) 15,264 male nuclear weapons workers who were hired at the Savannah River Site in South Carolina between 1950 and 1986.

Radiation dose-mortality trends were evaluated for all malignant lymphomas and for non-Hodgkin's lymphoma. Positive associations between lymphoma mortality and radiation dose under a 5-year lag assumption were observed in both cohorts (excess relative rates per sievert were 0.79 (90% confidence interval: 0.10, 1.88) and 6.99 (90% confidence interval: 0.96, 18.39), respectively). Exclusion of deaths due to Hodgkin's disease led to small changes in the estimates of association. In each cohort, evidence of a dose-response association was primarily observed more than 35 years after irradiation. These findings suggest a protracted induction and latency period for radiation-induced lymphoma mortality. (American Journal of Epidemiology 2009 169(8):969-976; doi:10.1093/aje/kwp018)

Biomarker-calibrated Energy and Protein Consumption and Increased Cancer Risk Among Postmenopausal Women

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The authors previously reported equations, derived from the Nutrient Biomarker Study within the Women's Health Initiative, that produce calibrated estimates of energy, protein and percentage of energy from protein consumption from corresponding food frequency questionnaire estimates and data on other factors, such as body mass index, age and ethnicity. Here, these equations were applied to yield calibrated consumption estimates for 21,711 women enrolled in the Women's Health Initiative dietary modification trial comparison group and 59,105 women enrolled in the observational study. These estimates were related prospectively to total and site-specific invasive cancer incidence (1993-2005). In combined cohort analyses that do not control for body mass, uncalibrated energy was not associated with total cancer incidence or site-specific cancer incidence for most sites, whereas biomarker-calibrated energy was positively associated with total cancer (hazard ratio = 1.18, 95% confidence interval: 1.10, 1.27, for 20% consumption increase), as well as with breast, colon, endometrial and kidney cancer (respective hazard ratios of 1.24, 1.35, 1.83 and 1.47). Calibrated protein was weakly associated and calibrated percentage of energy from protein was inversely associated, with total cancer. Calibrated energy and body mass index associations were highly interdependent. Implications for the interpretation of nutritional epidemiology studies are described. (American Journal of Epidemiology 2009 169(8):977-989; doi:10.1093/aje/kwp008)

Sex-Modified Effect of Hepatitis B Virus Infection on Mortality From Primary Liver Cancer

Na Wang, Yingjie Zheng, Xinsen Yu, Wenyao Lin, Yue Chen and Qingwu Jiang

Sex and hepatitis B virus (HBV) infection are both important risk factors for primary liver cancer. However, their possible biologic interaction has not been well studied. The authors examined data from 89,789 subjects aged 25-69 years who participated in a 14-year cohort study (1992-2006) conducted in Haimen, China. An age-stratified Cox proportional hazards model was used for multivariate analysis. The authors assessed the combined effect of sex and HBV infection on liver cancer mortality by calculating 3 interaction measures: the relative risk due to interaction, the attributable proportion of interaction and the synergy index. There was a greater risk difference between hepatitis B surface antigen carriers and noncarriers among men than among women. After adjustment for potential confounders, the relative risk due to interaction, the attributable proportion of interaction and the synergy index were 33.27 (95% confidence interval (CI): 22.54, 43.99), 0.59 (95% CI: 0.55, 0.63) and 2.49 (95% CI: 2.13, 2.90), respectively, suggesting a significant synergistic effect of the interaction between sex and HBV infection on liver cancer mortality. HBV infection had a larger impact on liver cancer mortality in men than in women, which may explain at least part of the sex difference in liver cancer risk. (*American Journal of Epidemiology* 2009 169(8):990-995; doi:10.1093/aje/kwn418)

Serum Selenium and Peripheral Arterial Disease: Results From the National Health and Nutrition Examination Survey, 2003-2004

Joachim Bleys, Ana Navas-Acien, Martin Laclaustra, Roberto Pastor-Barriuso andy Menke, Jose Ordovas, Saverio Stranges and Eliseo Guallar

The authors conducted a cross-sectional study of the association of serum selenium with the prevalence of peripheral arterial disease among 2,062 US men and women 40 years of age or older participating in the National Health and Nutrition Examination Survey, 2003-2004. Serum selenium was measured by using inductively coupled plasma-dynamic reaction cell-mass spectrometry. Peripheral arterial disease was defined as an ankle-brachial blood pressure index <0.90. The age-, sex- and race-adjusted prevalence of peripheral arterial disease decreased with increasing serum selenium (P for linear trend = 0.02), but there was an indication of an upturn in risk in the highest quartile of serum selenium. The

fully adjusted odds ratios for peripheral arterial disease comparing selenium quartiles 2, 3 and 4 with the lowest quartile were 0.75 (95% confidence interval: 0.37, 1.52), 0.58 (95% confidence interval: 0.28, 1.19) and 0.67 (95% confidence interval: 0.34, 1.31), respectively. In spline regression models, peripheral arterial disease prevalence decreased with increasing serum selenium levels up to 150-160 ng/mL, followed by a gradual increase at higher selenium levels. The association between serum selenium levels and the prevalence of peripheral arterial disease was not statistically significant, although a U-shaped relation was suggested. (*American Journal of Epidemiology* 2009 169(8):996-1003; doi:10.1093/aje/kwn414)

Ambient Air Pollution and Cardiovascular Malformations in Atlanta, Georgia, 1986-2003

Matthew J. Strickland, Mitchel Klein, Adolfo Correa, Mark D. Reller, William T. Mahle, Tiffany J. Riehle-Colarusso, Lorenzo D. Botto, W. Dana Flanders, James A. Mulholland, Csaba Siffel, Michele Marcus and Paige E. Tolbert

Associations between ambient air pollution levels during weeks 3-7 of pregnancy and risks of cardiovascular malformations were investigated among the cohort of pregnancies reaching at least 20 weeks' gestation that were conceived during January 1, 1986-March 12, 2003, in Atlanta, Georgia. Surveillance records obtained from the Metropolitan Atlanta Congenital Defects Program, which conducts active, population-based surveillance on this cohort, were reviewed to classify cardiovascular malformations. Ambient 8-hour maximum ozone and 24-hour average carbon monoxide, nitrogen dioxide, particulate matter with an average aerodynamic diameter of $<10 \mu\text{m}$ (PM_{10}) and sulfur dioxide measurements were obtained from centrally located stationary monitors. Temporal associations between these pollutants and daily risks of secundum atrial septal defect, aortic coarctation, hypoplastic left heart syndrome, patent ductus arteriosus, valvar pulmonary stenosis, tetralogy of Fallot, transposition of the great arteries, muscular ventricular septal defect, perimembranous ventricular septal defect, conotruncal defects, left ventricular outflow tract defect and right ventricular outflow defect were modeled by using Poisson generalized linear models. A statistically significant association was observed between PM_{10} and patent ductus arteriosus (for an interquartile range increase in PM_{10} levels, risk ratio = 1.60, 95% confidence interval: 1.11, 2.31). Of the 60 associations examined in the primary analysis, no other significant associations were observed. (*American Journal of Epidemiology* 2009 169(8):1004-1014; doi:10.1093/aje/kwp011)

Maternal Urinary Metabolites of Di-(2-Ethylhexyl) Phthalate in Relation to the Timing of Labor in a US Multicenter Pregnancy Cohort Study

Jennifer J. Adibi, Russ Hauser, Paige L. Williams, Robin M. Whyatt, Antonia M. Calafat, Heather Nelson, Robert Herrick and Shanna H. Swan

Di-(2-ethylhexyl) phthalate (DEHP) is a plasticizer used in consumer and medical products that can cross the placenta, disrupt steroid hormone synthesis and activate peroxisome proliferator-activated receptor γ . The authors examined DEHP exposure in relation to the timing of labor in a pregnancy cohort study of 283 women recruited in 4 US states (California, Iowa, Minnesota and Missouri) between 2000 and 2004. The authors estimated associations between concentrations of DEHP metabolites and gestational age at delivery using linear regression models and associations between DEHP metabolites and clinical outcomes using logistic regression models. After covariate adjustment, women at the 75th percentile of DEHP metabolite concentrations had a 2-day-longer mean length of gestation than women at the 25th percentile (95% confidence interval: 1.4, 3.3). Log-unit increases in mono-2-ethylhexyl phthalate and mono-2-ethyl-5-oxohexyl phthalate concentrations were associated with increased odds of cesarean section delivery (30% and 50% increased odds, respectively), increased odds of delivering at 41 weeks or later (100% and 120% increased odds) and reduced odds of preterm delivery (50% and 60% decreased odds). These data suggest that DEHP may interfere with signaling related to the timing of parturition. (American Journal of Epidemiology 2009 169(8):1015-1024; doi:10.1093/aje/kwp001)

Longitudinal Trends in Hazardous Alcohol Consumption Among Women With Human Immunodeficiency Virus Infection, 1995-2006

Robert L. Cook, Fang Zhu, Bea Herbeck Belnap, Kathleen Weber, Judith A. Cook, David Vlahov, Tracey E. Wilson, Nancy A. Hessol, Michael Plankey andrea A. Howard, Stephen R. Cole, Gerald B. Sharp, Jean L. Richardson and Mardge H. Cohen

Hazardous alcohol consumption among women with human immunodeficiency virus (HIV) infection is associated with several adverse health and behavioral outcomes, but the proportion of HIV-positive women who engage in hazardous drinking over time is unclear. The authors sought to determine rates of hazardous alcohol consumption among these women over time and to identify factors

associated with this behavior. Subjects were 2,770 HIV-positive women recruited from 6 US cities who participated in semiannual follow-up visits in the Women's Interagency HIV Study from 1995 to 2006. Hazardous alcohol consumption was defined as exceeding daily (≥ 4 drinks) or weekly (>7 drinks) consumption recommendations. Over the 11-year follow-up period, 14%-24% of the women reported past-year hazardous drinking, with a slight decrease in hazardous drinking over time. Women were significantly more likely to report hazardous drinking if they were unemployed, were not high school graduates, had been enrolled in the original cohort (1994-1995), had a CD4 cell count of 200-500 cells/mL, were hepatitis C-seropositive, or had symptoms of depression. Approximately 1 in 5 of the women met criteria for hazardous drinking. Interventions to identify and address hazardous drinking among HIV-positive women are urgently needed. (*American Journal of Epidemiology* 2009 169(8):1025-1032; doi:10.1093/aje/kwp004)

Suicide Mortality Among Patients Receiving Care in the Veterans Health Administration Health System

John F. McCarthy, Marcia Valenstein, H. Myra Kim, Mark Ilgen, Kara Zivin and Frederic C. Blow

Understanding and reducing mortality from suicide among veterans is a national priority, particularly for individuals receiving care from the US Veterans Health Administration (VHA). This report examines suicide rates among VHA patients and compares them with rates in the general population. Suicide mortality was assessed in fiscal year 2001 for patients alive at the start of that fiscal year and with VHA use in fiscal years 2000-2001 ($n = 4,692,034$). Deaths from suicide were identified by using National Death Index data. General population rates were identified by use of the Web-based Injury Statistics Query and Reporting System. VHA rates were 43.13/100,000 person-years for men and 10.41/100,000 person-years for women. For male patients, the age-adjusted standardized mortality ratio was 1.66; for females, it was 1.87. Male patients aged 30-79 years had increased risks relative to men in the general population; standardized mortality ratios ranged from 2.56 (ages 30-39 years) to 1.33 (ages 70-79 years). Female patients aged 40-59 years had greater risks than did women in the general population, with standardized mortality ratios of 2.15 (ages 40-49 years) and 2.36 (ages 50-59 years). Findings offer heretofore unavailable comparison points for health systems. Prior to the conflicts in Afghanistan and Iraq and before recent VHA initiatives, rates were higher among VHA patients than in the general population. Female patients had particularly high relative risks. (*American Journal of Epidemiology* 2009 169(8):1033-1038; doi:10.1093/aje/kwp010)

Alcohol Use and Risk of Pancreatic Cancer

Li Jiao, Debra T. Silverman, Catherine Schairer, Anne C. M. Thiébaud, Albert R. Hollenbeck, Michael F. Leitzmann, Arthur Schatzkin and Rachael Z. Stolzenberg-Solomon

The epidemiologic evidence for the role of alcohol use in pancreatic cancer development is equivocal. The authors prospectively examined the relation between alcohol use and risk of pancreatic cancer among 470,681 participants who were aged 50-71 years in 1995-1996 in the US National Institutes of Health-AARP Diet and Health Study. The authors identified 1,149 eligible exocrine pancreatic cancer cases through December 2003. Multivariate Cox proportional hazards regression models were used to calculate relative risks and 95% confidence intervals with the referent group being light drinkers (<1 drink/day). The relative risks of developing pancreatic cancer were 1.45 (95% confidence interval (CI): 1.17, 1.80; $P_{\text{trend}} = 0.002$) for heavy total alcohol use (≥ 3 drinks/day, ~ 40 g of alcohol/day) and 1.62 (95% CI: 1.24, 2.10; $P_{\text{trend}}=0.001$) for heavy liquor use, compared with the respective referent group. The increased risk with heavy total alcohol use was seen in never smokers (relative risk = 1.35, 95% CI: 0.79, 2.30) and participants who quit smoking 10 or more years ago before baseline (relative risk = 1.41, 95% CI: 1.01, 2.00). These findings suggest a moderately increased pancreatic cancer risk with heavy alcohol use, particularly liquor; however, residual confounding by cigarette smoking cannot be completely excluded. (American Journal of Epidemiology 2009 169(9):1043-1051; doi:10.1093/aje/kwp034)

Sleep Duration in the United States: A Cross-sectional Population-based Study

Patrick M. Krueger and Elliot M. Friedman

Sleep duration is associated with cardiovascular disease and diabetes risk factors, depression, automobile and workplace accidents and prospective mortality. Little is known, however, about sleep patterns in the US population. The 2004-2007 National Health Interview Survey-Sample Adult Files provide nationally representative data for 110,441 noninstitutionalized US adults aged 18 years or older and multinomial logistic regression examines whether variables in 5 domains-demographic, family structure, socioeconomic, health behavior and health status-are associated with long or short sleep duration. Being older, non-Hispanic black, or a current or former smoker; having low levels of education, income, or few income sources; consuming few or numerous drinks in a week; or reporting cardiovascular disease, diabetes, depression, underweight, or activity limitations

is associated with increased odds of both long and short sleep duration. Other variables are associated with shorter (e.g., living with young children, being unmarried, working long hours, more frequent binge drinking) or longer (e.g., being younger, Mexican American, pregnant, or having low levels of physical activity) sleep hours. The authors identify numerous risk factors for long and short sleep; many of those variables are potential confounders of the relation between sleep hours and other health outcomes. (*American Journal of Epidemiology* 2009 169(9):1052-1063; doi:10.1093/aje/kwp023)

Plasma Urate and Parkinson's Disease in the Atherosclerosis Risk in Communities (ARIC) Study

Honglei Chen, Thomas H. Mosley, Alvaro Alonso and Xuemei Huang

Higher plasma urate concentration has been linked to lower risk of Parkinson's disease in men, but data are lacking on women and African Americans. The authors examined plasma urate in relation to Parkinson's disease in the biracial, population-based Atherosclerosis Risk in Communities (ARIC) cohort. Between 1987 and 1989, 15,792 participants, aged 45-64 years, were recruited from 4 US communities and have since been followed with 3 triennial visits and annual surveillance. Plasma urate was measured at visits 1 and 2 and the concentrations were highly correlated. From visit 1 through 2004, 95 potential cases of Parkinson's disease were identified from multiple sources. Odds ratios and 95% confidence intervals were calculated from multivariate logistic regression models. Plasma urate concentration was inversely associated with Parkinson's disease occurrence. The odds ratios between extreme quartiles of plasma urate were 0.4 (95% confidence interval: 0.2, 0.8) in the overall analysis, 0.3 (95% confidence interval: 0.1, 0.7) for men and 0.4 (95% confidence interval: 0.2, 1.0) for Caucasians. Such an association was also suggested among women and African Americans but was not statistically significant because of small sample sizes. These data support the previous finding that urate may be a protective factor against Parkinson's disease. (*American Journal of Epidemiology* 2009 169(9):1064-1069; doi:10.1093/aje/kwp033)

Stroke Rates: 1980-2000

Kamakshi Lakshminarayan, David C. Anderson, David R. Jacobs, Jr., Cheryl A. Barber and Russell V. Luepker

In this paper, the authors report trends in hospitalized stroke rates among Minneapolis-St. Paul, Minnesota (population 2.6 million) metropolitan area

residents aged 30-74 years from 1980 to 2000. Cases were identified from lists of discharge diagnoses provided by hospitals serving the target population. Age-adjusted, sex-specific stroke attack rates were computed for each survey year by using 5 different diagnostic definitions: 2 based purely on *International Classification of Diseases*, Ninth Revision (ICD-9) codes and 3 including clinical and neuroimaging criteria. Stroke rates, as measured by a highly specific clinical definition, remained stable from 1980 to 2000 for women. For men, these rates declined modestly from 1980 to 1990 and leveled off during 1990-2000. In contrast, use of stroke-related ICD-9 discharge codes declined significantly from 1980 to 2000: 35% among men and 16% among women. Neuroimaging use increased significantly from 75% of cases in 1980 to 98% in 2000. Short-term (28-day) stroke survival improved significantly, by 16% for women and 12% for men, from 1980 to 2000. The decline in stroke ICD-9 code usage reflects the influence of increased neuroimaging on discharge coding. The improved short-term survival in the face of stable, clinically defined stroke rates may imply treatment advances or ascertainment of less severe strokes, possibly masking a true decline in stroke rates. (*American Journal of Epidemiology* 2009 169(9):1070-1078; doi:10.1093/aje/kwp029)

Antibiotic Use and Type 1 Diabetes in Childhood

Anders Hviid and Henrik Svanström

Indirect evidence is accumulating for an association between antibiotic use, especially in early childhood and long-term immunologic health. The authors evaluated the association between antibiotic use in childhood and subsequent development of type 1 diabetes. A nationwide cohort study of all Danish singleton children born during 1995-2003 ($n = 606,420$) was conducted. Incidence rate ratios for type 1 diabetes comparing children according to antibiotic use were estimated. Antibiotic use was classified according to class, number of uses and age at use. Use of any antibiotic was not associated with type 1 diabetes (rate ratio = 1.16, 95% confidence interval: 0.91, 1.50). Evaluation of type 1 diabetes risk according to number of courses of any antibiotic yielded no association between antibiotic use and type 1 diabetes, with an increase in rate ratio per course of 1.02 (95% confidence interval: 0.97, 1.07). No specific class of antibiotics was associated with type 1 diabetes, no specific age of use was associated with type 1 diabetes and no specific age at onset of type 1 diabetes was associated with antibiotics. In a large nationwide prospective study, no association between antibiotic use and type 1 diabetes was found among Danish children. (*American Journal of Epidemiology* 2009 169(9):1079-1084; doi:10.1093/aje/kwp038)

Changes in Perceived Job Strain and the Risk of Major Depression: Results From a Population-based Longitudinal Study

JianLi Wang, Norbert Schmitz, Carolyn Dewa and Stephen Stansfeld

Major depression is a prevalent mental disorder in the working population. Improving the work environment may reduce the risk of major depression. The authors examined data from the longitudinal cohort of the Canadian National Population Health Survey from 1994-1995 to 2004-2005. Survey participants were classified into 4 groups by changes in job strain status from 1994-1995 to 2000-2001 (no change in low job strain, no change in high job strain, changing from high to low job strain and changing from low to high job strain). The incidence proportion of major depressive episodes in each of the 4 groups was 4.0%, 8.0%, 4.4% and 6.9%, respectively. Participants who reported a change from high to low job strain had a risk of major depression similar to those exposed to persistently low job strain. Among those exposed to persistent high job strain, only participants who reported good or excellent health at baseline had a higher risk of major depression, but those who reported fair or poor health did not. Reducing job strain may have positive impacts on the risk of depression. Self-rated health is a strong predictor of depression and plays an important role in the relation between job strain and depression. (*American Journal of Epidemiology* 2009 169(9):1085-1091; doi:10.1093/aje/kwp037)

Neighborhood Context and Cognitive Decline in Older Mexican Americans: Results From the Hispanic Established Populations for Epidemiologic Studies of the Elderly

Kristin M. Sheffield and M. Kristen Peek

In previous research on cognitive decline among older adults, investigators have not considered the potential impact of contextual variables, such as neighborhood-level conditions. In the present investigation, the authors examined the association between 2 neighborhood-context variables—socioeconomic status and percentage of Mexican-American residents—and individual-level cognitive function over a 5-year follow-up period (1993-1998). Data were obtained from the Hispanic Established Populations for Epidemiologic Studies of the Elderly, a longitudinal study of community-dwelling older Mexican Americans ($n = 3,050$) residing in the southwestern United States. Individual records were linked with 1990 US Census tract data, which provided information on neighborhood characteristics.

Hierarchical linear growth-curve models and hierarchical logistic models were used to examine relations between individual- and neighborhood-level variables and the rate and incidence of cognitive decline. Results showed that baseline cognitive function and rates of cognitive decline varied significantly across US Census tracts. Respondents living in economically disadvantaged neighborhoods experienced significantly faster rates of cognitive decline than those in more advantaged neighborhoods. Odds of incident cognitive decline decreased as a function of neighborhood percentage of Mexican-American residents and increased with neighborhood economic disadvantage. The authors conclude that neighborhood context is associated with late-life cognitive function and that the effects are independent of individual-level risk factors. (*American Journal of Epidemiology* 2009 169(9):1092-1101; doi:10.1093/aje/kwp005)

Do Socioeconomic Gradients in Body Mass Index Vary by Race/Ethnicity, Gender and Birthplace?

Emma V. Sánchez-Vaznaugh, Ichiro Kawachi, S. V. Subramanian, Brisa N. Sánchez and Dolores Acevedo-Garcia

Despite the well-documented negative socioeconomic status (SES) gradient in body mass index (BMI; weight (kg)/height (m)²) among women in developed societies, the presence and strength of the gradient is less consistent among men. Far less clear is the SES patterning of BMI among racial/ethnic minorities and immigrants. Using data from the 2001 California Health Interview Survey, a cross-sectional representative sample of California adults, the authors examined whether the SES patterning of BMI varied across 4 major US racial/ethnic groups ($n = 37,150$) by gender and birthplace. The shape and strength of the relation between SES and BMI differed markedly by race/ethnicity; and within racial/ethnic groups, it varied by gender. Irrespective of race/ethnicity, there were negative income and education gradients in BMI among women; however, there was considerable variation among men. The effect of education on BMI differed by birthplace in some groups. A clear education gradient in BMI was found among all US-born participants, a quadratic education pattern in BMI was found among foreign-born Asian men, a flat pattern was found among foreign-born Asian women and no clear pattern was found in the remaining foreign-born groups. There is substantial heterogeneity in the contemporaneous SES gradient in BMI. US social disparities in BMI require simultaneous consideration of race/ethnicity and SES, but also birthplace. (*American Journal of Epidemiology* 2009 169(9):1102-1112; doi:10.1093/aje/kwp027)

Is House-Dust Nicotine a Good Surrogate for Household Smoking?

Todd Whitehead, Catherine Metayer, Mary H. Ward, Marcia G. Nishioka, Robert Gunier, Joanne S. Colt, Peggy Reynolds, Steve Selvin, Patricia Buffler and Stephen M. Rappaport

The literature is inconsistent regarding associations between parental smoking and childhood leukemia, possibly because previous studies used self-reported smoking habits as surrogates for children's true exposures to cigarette smoke. Here, the authors investigated the use of nicotine concentrations in house dust as measures of children's exposure to cigarette smoke in 469 households from the Northern California Childhood Leukemia Study (1999-2007). House dust was collected by using high-volume surface samplers and household vacuum cleaners and was analyzed for nicotine via gas chromatography-mass spectrometry. Using multivariable linear regression, the authors evaluated the effects of self-reported parental smoking, parental demographics, house characteristics and other covariates on house-dust nicotine concentrations. They observed that nicotine concentrations in house dust were associated with self-reported smoking for periods of months and years before dust collection. Furthermore, the authors found that the relation between nicotine dust levels and self-reported smoking varied by parental age and socioeconomic status. These findings suggest that house-dust nicotine concentrations reflect long-term exposures to cigarette smoke in the home and that they may be less biased surrogates for children's exposures to cigarette smoke than self-reported smoking habits. (*American Journal of Epidemiology* 2009 169(9):1113-1123; doi:10.1093/aje/kwp021)

Effect of Highly Active Antiretroviral Therapy on Incident AIDS Using Calendar Period as an Instrumental Variable

Lauren E. Cain, Stephen R. Cole, Sander Greenland, Todd T. Brown, Joan S. Chmiel, Lawrence Kingsley and Roger Detels

Human immunodeficiency virus (HIV) researchers often use calendar periods as an imperfect proxy for highly active antiretroviral therapy (HAART) when estimating the effect of HAART on HIV disease progression. The authors report on 614 HIV-positive homosexual men followed from 1984 to 2007 in 4 US cities. During 5,321 person-years, 268 of 614 men incurred acquired immunodeficiency

syndrome, 49 died and 90 were lost to follow-up. Comparing the pre-HAART calendar period (<1996) with the HAART calendar period (\geq 1996) resulted in a naive rate ratio of 3.62 (95% confidence limits: 2.67, 4.92). However, this estimate is likely biased because of misclassification of HAART use by calendar period. Simple calendar period approaches may circumvent confounding by indication at the cost of inducing exposure misclassification. To correct this misclassification, the authors propose an instrumental-variable estimator analogous to ones previously used for noncompliance corrections in randomized clinical trials. When the pre-HAART calendar period was compared with the HAART calendar period, the instrumental-variable rate ratio was 5.02 (95% confidence limits: 3.45, 7.31), 39% higher than the naive result. Weighting by the inverse probability of calendar period given age at seroconversion, race/ethnicity and time since seroconversion did not appreciably alter the results. These methods may help resolve discrepancies between observational and randomized evidence. (*American Journal of Epidemiology* 2009 169(9):1124-1132; doi:10.1093/aje/kwp002)

Multiple Imputation With Large Data Sets: A Case Study of the Children's Mental Health Initiative

Elizabeth A. Stuart, Melissa Azur, Constantine Frangakis and Philip Leaf

Multiple imputation is an effective method for dealing with missing data and it is becoming increasingly common in many fields. However, the method is still relatively rarely used in epidemiology, perhaps in part because relatively few studies have looked at practical questions about how to implement multiple imputation in large data sets used for diverse purposes. This paper addresses this gap by focusing on the practicalities and diagnostics for multiple imputation in large data sets. It primarily discusses the method of multiple imputation by chained equations, which iterates through the data, imputing one variable at a time conditional on the others. Illustrative data were derived from 9,186 youths participating in the national evaluation of the Community Mental Health Services for Children and Their Families Program, a US federally funded program designed to develop and enhance community-based systems of care to meet the needs of children with serious emotional disturbances and their families. Multiple imputation was used to ensure that data analysis samples reflect the full population of youth participating in this program. This case study provides an illustration to assist researchers in implementing multiple imputation in their own data. (*American Journal of Epidemiology* 2009 169(9):1133-1139; doi:10.1093/aje/kwp026)

Estimating the Effects of Potential Public Health Interventions on Population Disease Burden: A Step-by-Step Illustration of Causal Inference Methods

Jennifer Ahern, Alan Hubbard and Sandro Galea

Causal inference methods allow estimation of the effects of potential public health interventions on the population burden of disease. Motivated by calls for epidemiologic research to be presented in ways that are more informative for intervention, the authors present a didactic discussion of the steps required to estimate the population effect of a potential intervention using an imputation-based causal inference method and discuss the assumptions of and limitations to its use. An analysis of neighborhood smoking norms and individual smoking behavior is used as an illustration. The implementation steps include the following: 1) modeling the adjusted exposure and outcome association, 2) imputing the outcome probability for each individual while manipulating the exposure by "setting" it to different values, 3) averaging these probabilities across the population and 4) bootstrapping confidence intervals. Imputed probabilities represent counterfactual estimates of the population smoking prevalence if neighborhood smoking norms could be manipulated through intervention. The degree to which temporal ordering, randomization, stability and experimental treatment assignment assumptions are met in the illustrative example is discussed, along with ways that future studies could be designed to better meet the assumptions. With this approach, the potential effects of an intervention targeting neighborhoods, individuals, or other units can be estimated. (*American Journal of Epidemiology* 2009 169(9):1140-1147; doi:10.1093/aje/kwp015)

Validity of Maternal Recall of Preschool Diet After 43 Years

Jorge E. Chavarro, Karin B. Michels, Sheherazadh Isaq, Bernard A. Rosner, Laura Sampson, Carol Willey, Paula Tocco, Walter C. Willett and William Cameron Chumlea

Validation of early childhood diet recalls by surrogate responders decades later has not been possible because of a lack of diet records from the distant past. Between 1948 and 1970, parents of children participating in the Fels Longitudinal Study (Kettering, Ohio) completed a 7-day diet record for their children every year from birth to age 18 years. In 2005-2006, all surviving women ($n = 59$) with a child aged 3-5 years when diet records had been collected were asked to complete a 42-item food frequency questionnaire (FFQ) pertaining to 1 of their

children's diets at age 3-5 years. One or more diet records were available for 48 children. The authors calculated Spearman correlation coefficients for correlations between food, food-group and nutrient intakes from the diet records and the FFQ and deattenuated them to account for the effects of within-person variation in the diet records on the association. For foods, the median deattenuated correlation coefficient was 0.19 (range, -0.31 to 0.85); moderate-to-high correlations were found for some specific foods. Correlations for food groups were slightly higher (median, 0.27; range, -0.14 to 0.85). Correlations for nutrient intakes were consistently low (median, 0.06; range, -0.35 to 0.27). Overall, the FFQ did not validly reflect overall preschool diet when completed by mothers 4 decades later. (*American Journal of Epidemiology* 2009 169(9):1148-1157; doi:10.1093/aje/kwp012)

Mixed Treatment Comparison Meta-Analysis of Complex Interventions: Psychological Interventions in Coronary Heart Disease

Nicky J. Welton, D. M. Caldwell, E. Adamopoulos and K. Vedhara

Meta-analyses of psychological interventions typically find a pooled effect of "psychological intervention" compared with usual care. This answers the research question, "Are psychological interventions in general effective?" In fact, psychological interventions are usually complex with several different components. The authors propose that mixed treatment comparison meta-analysis methods may be a valuable tool when exploring the efficacy of interventions with different components and combinations of components, as this allows one to answer the research question, "Are interventions with a particular component (or combination of components) effective?" The authors illustrate the methods using a meta-analysis of psychological interventions for patients with coronary heart disease for a variety of outcomes. The authors carried out systematic literature searches to update an earlier Cochrane review and classified components of interventions into 6 types: usual care, educational, behavioral, cognitive, relaxation and support. Most interventions were a combination of these components. There was some evidence that psychological interventions were effective in reducing total cholesterol and standardized mean anxiety scores, that interventions with behavioral components were effective in reducing the odds of all-cause mortality and nonfatal myocardial infarction and that interventions with behavioral and/or cognitive components were associated with reduced standardized mean depression scores. (*American Journal of Epidemiology* 2009 169(9):1158-1165; doi:10.1093/aje/kwp014)

Life Course Path Analysis of Birth Weight, Childhood Growth and Adult Systolic Blood Pressure

Michael Gamborg, Per Kragh Andersen, Jennifer L. Baker, Esben Budtz-Jørgensen, Torben Jørgensen, Gorm Jensen and Thorkild I. A. Sørensen

The inverse associations between birth weight and later adverse health outcomes and the positive associations between adult body size and poor health imply that increases in relative body size between birth and adulthood may be undesirable. In this paper, the authors describe life course path analysis, a method that can be used to jointly estimate associations between body sizes at different time points and associations of body sizes throughout life with health outcomes. Additionally, this method makes it possible to assess both the direct effect and the indirect effect mediated through later body size and thereby the total effect, of size and changes in size on later outcomes. Using data on childhood body size and adult systolic blood pressure from a sample of 1,284 Danish men born between 1936 and 1970, the authors compared results from path analysis with results from 3 standard regression methods. Path analysis produced easily interpretable results and compared with standard regression methods it produced a noteworthy gain in statistical power. The effect of change in relative body size on adult blood pressure was more pronounced after age 11 years than in earlier childhood. These results suggest that increases in body size prior to age 11 years are less harmful to adult blood pressure than increases occurring after this age. (*American Journal of Epidemiology* 2009 169(10):1167-1178; doi:10.1093/aje/kwp047)

Invited Commentary: Coming Out of the Box

Pam Factor-Litvak and Arnold Sher

The authors apply the analogy of a "black box" from systems theory to epidemiologic problems. They highlight this process using the example of associations between sequential measures of body size and systolic blood pressure. Several other examples of the use of structural equation modeling or path analysis are described. Finally, the authors highlight several requirements for using these methods to "come out of the box." (*American Journal of Epidemiology* 2009 169(10):1179-1181; doi:10.1093/aje/kwp066)

Methods of Covariate Selection: Directed Acyclic Graphs and the Change-in-Estimate Procedure

Hsin-Yi Weng, Ya-Hui Hsueh, Locksley L. McV. Messam and Irva Hertz-Picciotto

Four covariate selection approaches were compared: a directed acyclic graph (DAG) full model and 3 DAG and change-in-estimate combined procedures. Twenty-five scenarios with case-control samples were generated from 10 simulated populations in order to address the performance of these covariate selection procedures in the presence of confounders of various strengths and under DAG misspecification with omission of confounders or inclusion of nonconfounders. Performance was evaluated by standard error, bias, square root of the mean-squared error and 95% confidence interval coverage. In most scenarios, the DAG full model without further covariate selection performed as well as or better than the other procedures when the DAGs were correctly specified, as well as when confounders were omitted. Model reduction by using change-in-estimate procedures showed potential gains in precision when the DAGs included nonconfounders, but underestimation of regression-based standard error might cause reduction in 95% confidence interval coverage. For modeling binary outcomes in a case-control study, the authors recommend construction of a "conservative" DAG, determination of all potential confounders and then change-in-estimate procedures to simplify this full model. The authors advocate that, under the conditions investigated, the selection of final model should be based on changes in precision: Adopt the reduced model if its standard error (derived from logistic regression) is substantially smaller; otherwise, the full DAG-based model is appropriate. (*American Journal of Epidemiology* 2009 169(10):1182-1190; doi:10.1093/aje/kwp035)

Physical Activity, Mortality and Cardiovascular Disease: Is Domestic Physical Activity Beneficial?

Emmanuel Stamatakis, Mark Hamer and Debbie A. Lawlor

Intense domestic physical activity (IDPA) is promoted by preventive health campaigns, but this recommendation is not supported by evidence. The authors used data from the 1995, 1998 and 2003 Scottish Health Survey samples and the associated mortality and hospital episode records to determine the independent effects of IDPA on cardiovascular disease (CVD) events and all-cause mortality. The sample comprised 13,726 (6,102 men) CVD-free respondents (≥ 35 years).

Multivariable survival analysis assessed the relation between IDPA and the risk for CVD (fatal/nonfatal combined) or all-cause mortality. During 8.4 (standard deviation, 3.4) years of follow-up, there were 1,103 deaths (573 among men) and 890 CVD events (521 among men). Participation in IDPA was associated with lower all-cause mortality (men: relative risk = 0.68, 95% confidence interval: 0.50, 0.91; women: relative risk = 0.70, 95% confidence interval: 0.52, 0.93). In both sexes, IDPA was unrelated to the risk for CVD. Total physical activity (including IDPA) was unrelated to fatal/nonfatal CVD, but when domestic activity was excluded from the calculations there was an association (men: relative risk = 0.76, 95% confidence interval: 0.58, 0.98; women: relative risk = 0.68, 95% confidence interval: 0.50, 0.93). These results indicate that IDPA may not offer protection against CVD, but it may protect against all-cause mortality. CVD preventive efforts may need to focus on moderate-to-vigorous-intensity physical activities other than those performed in and around the household. (*American Journal of Epidemiology* 2009 169(10):1191-1200; doi:10.1093/aje/kwp042)

Are the Short-term Effects of Air Pollution Restricted to Cardiorespiratory Diseases?

Sophie Larrieu, Agnès Lefranc, Gaëlle Gault, Edouard Chatignoux, Franck Couves, Bernard Jouves and Laurent Filleul

Short-term effects of air pollution on common morbidity are largely unknown. The authors explored links between daily levels of air pollution (nitrogen dioxide, ozone and particulate matter less than 10 μm in diameter (PM_{10})) and medical home visits made for diverse reasons in Bordeaux, France, during 2000-2006. Daily numbers of visits were obtained from a network of general practitioners. The excess relative risk (ERR) of a visit for each indicator associated with increased pollutant levels was estimated by fitting a Poisson regression model, controlling for well-known confounding factors and temporal trends. Positive and significant associations were found between air pollution and most health indicators. A 10- $\mu\text{g}/\text{m}^3$ increase in PM_{10} levels was associated with increases in visits for upper and lower respiratory diseases (ERRs were 1.5% (95% confidence interval (CI): 0.3, 2.7) and 2.5% (95% CI: 0.5, 4.4), respectively), headache and asthenia (ERR = 3.5%, 95% CI: 1.3, 5.9) and skin rash and conjunctivitis (ERR = 3.2%, 95% CI: -0.2, 6.8). Significant associations were also found between nitrogen dioxide and ozone and several health indicators. Distributed-lag models showed no harvesting effect and some effects persisted up to 15 days after exposure increased. These results suggest that considering only the most severe effects of air pollution leads to underestimation of its impact on public health. (*American Journal of Epidemiology* 2009 169(10):1201-1208; doi:10.1093/aje/kwp032)

Adolescent Manifestations of Metabolic Syndrome Among Children Born to Women With Gestational Diabetes in a General-Population Birth Cohort

Marja Väärasmäki, Anneli Pouta, Paul Elliot, Päivi Tapanainen, Ulla Sovio, Aimo Ruokonen, Anna-Liisa Hartikainen, Mark McCarthy and Marjo-Riitta Järvelin

The association between maternal gestational diabetes (GDM) and manifestations of metabolic syndrome among Caucasian adolescents was studied with data from the population-based Northern Finland 1986 Birth Cohort. This is a longitudinal cohort study from early pregnancy until offspring age 16 years and includes data from a risk group-based GDM screen of pregnant mothers by an oral glucose tolerance test. Metabolic outcomes were compared between the offspring of women with GDM (OGDM; $n = 95$) and reference group offspring ($n = 3,909$). The prevalence of overweight was significantly higher in the OGDM group (18.8 vs. 8.4%; $P < 0.001$) than in the reference group. The median body mass index (20.8 vs. 20.2 kg/m², 95% confidence interval (CI) for the percentage difference adjusted for sex: 3.5%, 9.5%), waist circumference (73.3 vs. 71.5 cm, 95% CI: 3.2%, 7.5%) and fasting insulin (10.20 vs. 9.30 milliunits/L, 95% CI: 5.9%, 26.0%) were higher and homeostatic model assessment-insulin sensitivity (74.7 vs. 82.3, 95% CI: -20.6%, -5.4%) was lower in the OGDM group. These differences were similar after an additional adjustment for birth weight and gestational age. The differences in waist circumference, insulin and homeostatic model assessment-insulin sensitivity were attenuated but remained statistically significant after additional adjustment for body mass index at 16 years. These findings highlight the importance of prevention strategies among children born to women with GDM. (*American Journal of Epidemiology* 2009 169(10):1209-1215; doi:10.1093/aje/kwp020)

Maternal Consumption of Coffee and Caffeine-containing Beverages and Oral Clefts: A Population-based Case-Control Study in Norway

Anne Marte W. Johansen, Allen J. Wilcox, Rolv T. Lie, Lene F. Andersen and Christian A. Drevon

A large, population-based case-control study of facial clefts was carried out in Norway between 1996 and 2001. The study included 573 cases—377 with cleft lip with or without cleft palate and 196 with cleft palate only—and 763 randomly selected controls. Maternal consumption of coffee and other caffeine-containing

beverages in early pregnancy was recorded shortly after birth. Compared with that for no coffee consumption, the adjusted odds ratios for cleft lip with or without cleft palate were 1.39 (95% confidence interval: 1.01, 1.92) for less than 3 cups a day and 1.59 (95% confidence interval: 1.05, 2.39) for 3 cups or more. Coffee consumption was not associated with risk of cleft palate only (for ≥ 3 cups vs. none, adjusted odds ratio = 0.96, 95% confidence interval: 0.55, 1.67). Tea consumption was associated with a reduced odds ratio of both cleft lip with or without cleft palate and cleft palate only. There was little evidence of an association between caffeine exposure and clefts when all sources of caffeine were considered. Adjustment for known confounding factors in general had minor effects on risk estimates. Still, the authors could not rule out the possibility of uncontrolled confounding by factors associated with the habit of drinking coffee. (*American Journal of Epidemiology* 2009 169(10):1216-1222; doi:10.1093/aje/kwp040)

Serum Vitamin D and Risk of Prostate Cancer in a Case-Control Analysis Nested Within the European Prospective Investigation into Cancer and Nutrition (EPIC)

Ruth C. Travis, Francesca L. Crowe, Naomi E. Allen, Paul N. Appleby, Andrew W. Roddam, Anne Tjønneland, Anja Olsen, Jakob Linseisen, Rudolf Kaaks, Heiner Boeing, Janine Kröger, Antonia Trichopoulou, Vardis Dilis, Dimitrios Trichopoulos, Paolo Vineis, Domenico Palli, Rosario Tumino, Sabina Sieri, H. Bas Bueno-de-Mesquita, Fränzel J. B. van Duijnhoven, María-Dolores Chirlaque, Aurelio Barricarte, Nerea Larrañaga, Carlos A. González, Marcial V. Argüelles, Maria-José Sánchez, Pär Stattin, Göran Hallmans, Kay-Tee Khaw, Sheila Bingham, Sabina Rinaldi, Nadia Slimani, Mazda Jenab, Elio Riboli and Timothy J. Key

Results from the majority of studies show little association between circulating concentrations of vitamin D and prostate cancer risk, a finding that has not been demonstrated in a wider European population, however. The authors examined whether vitamin D concentrations were associated with prostate cancer risk in a case-control study nested within the European Prospective Investigation into Cancer and Nutrition (1994-2000). Serum concentrations of 25-hydroxyvitamin D were measured in 652 prostate cancer cases matched to 752 controls from 7 European countries after a median follow-up time of 4.1 years. Conditional logistic regression models were used to calculate odds ratios for prostate cancer risk in relation to serum 25-hydroxyvitamin D after standardizing for month of blood collection and adjusting for covariates. No significant association was found

between 25-hydroxyvitamin D and risk of prostate cancer (highest vs. lowest quintile: odds ratio = 1.28, 95% confidence interval: 0.88, 1.88; P for trend = 0.188). Subgroup analyses showed no significant heterogeneity by cancer stage or grade, age at diagnosis, body mass index, time from blood collection to diagnosis, or calcium intake. In summary, the results of this large nested case-control study provide no evidence in support of a protective effect of circulating concentrations of vitamin D on the risk of prostate cancer. (*American Journal of Epidemiology* 2009 169(10):1223-1232; doi:10.1093/aje/kwp022)

Alcohol Consumption and Risk of Pancreatic Cancer in the Netherlands Cohort Study

Mirjam M. Heinen, Bas A. J. Verhage, Ton A. W. Ambergen, R. Alexandra Goldbohm and Piet A. van den Brandt

To examine prospectively the relation between alcohol consumption and pancreatic cancer risk, the authors analyzed data from the Netherlands Cohort Study. Participants were 120,852 persons who completed a baseline questionnaire in 1986. After 13.3 years of follow-up, 350 cases of pancreatic cancer (67% microscopically confirmed) were available for analysis. Compared with abstention, the highest category of alcohol consumption (≥ 30 g/day of ethanol) was positively associated with pancreatic cancer risk (for all cases, rate ratio = 1.57, 95% confidence interval: 1.03, 2.39; $P_{\text{trend}} = 0.12$; for microscopically confirmed cases, rate ratio = 1.54, 95% confidence interval: 0.94, 2.54; $P_{\text{trend}} = 0.22$). In a subgroup of stable alcohol users (no change during the 5 years before baseline), a similarly increased risk of pancreatic cancer was found. This increased risk was limited to the first 7 years of follow-up. No associations were observed between consumption of specific alcoholic beverages and risk of pancreatic cancer. The associations were not modified by folate intake or smoking. Overall, these findings suggest an increased pancreatic cancer risk for persons with a high ethanol intake (30 g/day). However, this increased risk was observed only during the first 7 years of follow-up. (*American Journal of Epidemiology* 2009 169(10):1233-1242; doi:10.1093/aje/kwp028)

Reproductive Factors and Risk of Renal Cell Cancer

Jung Eun Lee, Susan E. Hankinson and Eunyoung Cho

Few prospective studies have examined associations between reproductive factors and risk of renal cell cancer (RCC). The authors prospectively examined whether

postmenopausal hormone (PMH) use, oral contraceptive use, parity and other reproductive factors were associated with RCC risk among 118,219 US women in the Nurses' Health Study. A total of 247 RCC cases were confirmed between 1976 and 2004. Multivariate relative risks, adjusted for known risk factors, were calculated using Cox proportional hazards models. Compared with 1 or 2 childbirths, the multivariate relative risks were 1.75 (95% confidence interval (CI): 1.21, 2.53) for 4 childbirths and 1.50 (95% CI: 1.00, 2.23) for ≥ 5 childbirths ($P_{\text{trend}} = 0.02$). Comparing an age at first birth of ≥ 28 years with an age at first birth of ≤ 22 years, the multivariate relative risk was 0.66 (95% CI: 0.43, 1.01; $P_{\text{trend}} = 0.01$). Compared with 1-3 childbirths and an age at first birth of ≥ 26 years, the multivariate relative risk was 2.17 (95% CI: 1.49, 3.14) for ≥ 4 childbirths and an age at first birth of < 26 years. No clear associations were observed for PMH use or duration, time since last PMH use, oral contraceptive use or duration, age at menarche, age at menopause, or history of hysterectomy or oophorectomy. (American Journal of Epidemiology 2009 169(10):1243-1250; doi:10.1093/aje/kwp030)

Breast Cancer Risk Factors Defined by Estrogen and Progesterone Receptor Status

Veronica Wendy Setiawan, Kristine R. Monroe, Lynne R. Wilkens, Laurence N. Kolonel, Malcolm C. Pike and Brian E. Henderson

Prospective data on ethnic differences in hormone receptor-defined subtypes of breast cancer and their risk factor profiles are scarce. The authors examined the joint distributions of estrogen receptor (ER) and progesterone receptor (PR) status across 5 ethnic groups and the associations of established risk factors with ER/PR status in the Multiethnic Cohort Study (Hawaii and Los Angeles, California). During an average of 10.4 years of follow-up of 84,427 women between 1993-1996 and 2004/2005, 2,543 breast cancer cases with data on ER/PR status were identified: 1,672 estrogen receptor-positive (ER+)/progesterone receptor-positive (PR+); 303 ER+/progesterone receptor-negative (PR-); 77 estrogen receptor-negative (ER-)/PR+; and 491 ER-/PR-. ER/PR status varied significantly across racial/ethnic groups even within the same tumor stage (for localized tumors, $P < 0.0001$; for advanced tumors, $P = 0.01$). The highest fraction of ER-/PR- tumors was observed in African Americans (31%), followed by Latinas (25%), Whites (18%), Japanese (14%) and Native Hawaiians (14%). Associations differed between ER+/PR+ and ER-/PR- cases for postmenopausal obesity ($P = 0.02$), age at menarche ($P = 0.05$), age at first birth ($P = 0.04$) and postmenopausal hormone use ($P < 0.0001$). African Americans are more likely

to be diagnosed with ER-/PR- tumors independently of stage at diagnosis and there are disparate risk factor profiles across the ER/PR subtypes of breast cancer. (American Journal of Epidemiology 2009 169(10):1251-1259; doi:10.1093/aje/kwp036)

Clinically Observed Chickenpox and the Risk of Childhood-onset Multiple Sclerosis

Yann Mikaeloff, Guillaume Caridade, Samy Suissa, Marc Tardieu on Behalf of the KIDSEP Study Group

The authors conducted a population-based case-control study to investigate whether clinically observed chickenpox, linked with a level of intensity for clinical expression, increases the risk of multiple sclerosis (MS) in childhood. The cases were MS patients whose disease onset occurred between 1994 and 2003, before age 16 years, in France. Each case was matched for age, sex and geographic origin with as many as 12 controls randomly selected from the general population. Information about clinically observed chickenpox in cases and controls before the index date regarding onset of MS was collected with a standardized questionnaire and was checked against health certificates. Conditional logistic regression was used to estimate the odds ratio for an association between MS and chickenpox. The 137 MS cases were matched with 1,061 controls. Clinically observed chickenpox had occurred in 76.6% of the cases and 84.9% of their matched controls. The adjusted odds ratio of MS onset associated with chickenpox occurrence was 0.58 (95% confidence interval: 0.36, 0.92). The authors concluded that clinically observed chickenpox was associated with a lower risk of childhood-onset MS in a French population. (American Journal of Epidemiology 2009 169(10):1260-1266; doi:10.1093/aje/kwp039)

Relation of Age-related Cataract With Obesity and Obesity Genes in an Asian Population

Laurence S. Lim, E-Shyong Tai, Tin Aung, Wan Ting Tay, Seang Mei Saw, Mark Seielstad and Tien Yin Wong

Obesity shows an inconsistent association with cataract. Causality has not been established. Polymorphisms at the fat mass- and obesity-associated (*FTO*) locus are associated with obesity and offer an opportunity to examine the obesity-cataract association using a mendelian randomization approach. The authors conducted a population-based study among Singaporean Malay adults

(2004-2006) in which nuclear, cortical and posterior subcapsular (PSC) cataracts were assessed and defined by slit-lamp examination using Lens Opacity Classification System III. Obesity was defined as body mass index (weight (kg)/height (m)²) ≥ 30 . The study included 3,000 subjects, of whom 1,339 (44.6%) had cataract (848 (28.3%) nuclear, 939 (31.3%) cortical and 285 (9.5%) PSC). After multivariable adjustment for age, gender, diabetes, hypertension, smoking and education, obesity was significantly associated with cortical (odds ratio (OR) = 1.31, 95% confidence interval (CI): 1.01, 1.71) and PSC (OR = 1.60, 95% CI: 1.10, 2.32) cataracts but not nuclear cataract. *FTO* single nucleotide polymorphisms known to be associated with obesity in this study population were not associated with cortical or PSC cataract but were associated with nuclear cataract (OR = 1.33, 95% CI: 1.11, 1.58), even in multivariate analyses controlling additionally for body mass index, diabetes, hypertension and smoking (OR = 1.30, 95% CI: 1.08, 1.55). These results do not support a causal association between obesity and cortical or PSC cataract. The *FTO* gene may be involved in the pathogenesis of nuclear cataract. (American Journal of Epidemiology 2009 169(10):1267-1274; doi:10.1093/aje/kwp045)

Associations Between C-Reactive Protein and Benign Prostatic Hyperplasia/Lower Urinary Tract Symptom Outcomes in a Population-based Cohort

Jennifer L. St. Sauver, Aruna V. Sarma, Debra J. Jacobson, Michaela E. McGree, Michael M. Lieber, Cynthia J. Girman, Ajay Nehra and Steven J. Jacobsen

Inflammation may play a role in the development of benign prostatic hyperplasia and/or lower urinary tract symptoms (LUTS). Higher levels of C-reactive protein (CRP) may therefore be associated with the development of these outcomes. The authors examined the association of CRP levels measured in 1996 with rapid increases in prostate volume, prostate-specific antigen levels and LUTS as well as rapid decreases in peak flow rates (through 2005) in a population-based cohort of men residing in Olmsted County, Minnesota. Men with CRP levels of ≥ 3.0 mg/L were more likely to have rapid increases in irritative LUTS (odds ratio (OR) = 2.14, 95% confidence interval (CI): 1.18, 3.85) and rapid decreases in peak flow rates (OR = 2.54, 95% CI: 1.09, 5.92) compared with men with CRP levels of < 3.0 mg/L. CRP levels were not significantly associated with rapid increases in prostate volume, obstructive LUTS, or prostate-specific antigen levels. Associations were attenuated after adjusting for age, body mass index, hypertension and smoking history (irritative LUTS: OR = 2.00, 95% CI: 1.04,

3.82; peak flow rate: OR = 2.45, 95% CI: 0.73, 8.25). These results suggest that rapid increases in irritative LUTS and rapid decreases in peak flow rates may be due to inflammatory processes. (*American Journal of Epidemiology* 2009 169(11):1281-1290; doi:10.1093/aje/kwp085)

Invited Commentary: Lower Urinary Tract Symptoms and Inflammation-Weighing the Evidence

Stephen J. Freedland and William J. Aronson

Lower urinary tract symptoms (LUTS) are a common condition, particularly among older men. The etiology of these symptoms is often obscure and not always clearly related to prostatic enlargement or benign prostatic hyperplasia. St. Sauver et al. (*Am J Epidemiol.* 2009;169(11):1281-1290) hypothesized that systemic inflammation may be associated with LUTS and benign prostatic hyperplasia. Using a well-defined cohort, they found that, in general, inflammation was not related to LUTS or to benign prostatic hyperplasia progression. However, men with the highest amount of systemic inflammation, as measured by C-reactive protein levels, were at increased risk of a rapid change in irritative voiding symptoms and decreased urinary flow but not obstructive voiding symptoms or prostate size. To what degree systemic inflammation relates to inflammation within the urinary system and specifically the bladder and/or prostate is unclear. Furthermore, to what degree inflammation within the urinary system contributes to LUTS is unclear. Given that clinical trials of antiinflammatory drugs for LUTS have been largely unsuccessful, the role of inflammation as a contributor to LUTS remains an interesting hypothesis that requires further study. (*American Journal of Epidemiology* 2009 169(11):1291-1293; doi:10.1093/aje/kwp084)

Birth Defects in Children With Autism Spectrum Disorders: A Population-based, Nested Case-Control Study

Somer Dawson, Emma J. Glasson, Glenys Dixon and Carol Bower

The causes of autism spectrum disorders (ASDs) are unknown, although genetic and environmental influences have been implicated. Previous studies have suggested an association with birth defects, but most investigators have not addressed associations with specific diagnostic categories of ASD. In this study, the authors investigated the associations between birth defects and autism, Asperger syndrome and pervasive developmental disorder not otherwise specified. Using Western Australian population-based linked data, the authors

compared all children with ASD born in Western Australia during 1980-1995 ($n = 465$) with their siblings ($n = 481$) and population controls ($n = 1,313$) in a nested case-control study. The prevalence of birth defects was significantly higher in ASD cases than in population controls; this difference remained significant after adjustment for confounding factors. Odds ratios for birth defects were similar for autism (odds ratio (OR) = 2.0, 95% confidence interval (CI): 1.3, 3.0) and pervasive developmental disorder not otherwise specified (OR = 2.2, 95% CI: 1.1, 4.3) but not for Asperger syndrome (OR = 0.5, 95% CI: 0.1, 1.9). Birth defects in case siblings were not significantly different from those in cases and population controls. The association between birth defects and ASD may be due to underlying genetic and/or environmental factors common to both ASD and birth defects, or birth defects may predispose a child to ASD. (American Journal of Epidemiology 2009 169(11):1296-1303; doi:10.1093/aje/kwp059)

Association of Periconceptional Multivitamin Use With Reduced Risk of Preeclampsia Among Normal-Weight Women in the Danish National Birth Cohort

Janet M. Catov, Ellen A. Nohr, Lisa M. Bodnar, Vibeke K. Knudson, Sjurdur F. Olsen and Jorn Olsen

The timing and frequency of periconceptional multivitamin use may be related to the risk of preeclampsia. Women in the Danish National Birth Cohort (1997-2003) reported multivitamin or folate-only supplement use during a 12-week periconceptional period (from 4 weeks prior to 8 weeks after the last menstrual period). Preeclampsia cases were identified by using *International Classification of Diseases*, Tenth Revision, codes. Cox regression was used to estimate the association of frequency (weeks of use) and timing (preconception and postconception) of use with preeclampsia risk. Overall, there were 668 cases of preeclampsia (2.3%) and 18,551 women (65%) reported periconceptional multivitamin use. After adjustment, regular use (12 of 12 weeks) was related to a reduced risk of preeclampsia among normal-weight women. Compared with nonusers with a body mass index of 22 kg/m^2 , regular multivitamin users with the same body mass index had a 20% reduced risk of preeclampsia (hazard ratio = 0.78, 95% confidence interval: 0.60, 0.99). In addition, regular use in the postconception period only was associated with reduced risk, a relation that also appeared to be limited to women with a body mass index of $<25 \text{ kg/m}^2$ (hazard ratio = 0.63, 95% confidence interval: 0.42, 0.93). Folate-only supplement use was unrelated to preeclampsia risk. Regular periconceptional multivitamin use was associated with a reduced risk of preeclampsia among normal-weight women and

the immediate postconception period appeared to be the relevant exposure window. (*American Journal of Epidemiology* 2009 169(11):1304-1311; doi:10.1093/aje/kwp052)

Self-reported Vitamin Supplementation in Early Pregnancy and Risk of Miscarriage

Reem Hasan, Andrew F. Olshan, Amy H. Herring, David A. Savitz, Anna Maria Siega-Riz and Katherine E. Hartmann

Miscarriage is a common and poorly understood adverse pregnancy outcome. In this study, the authors sought to evaluate the relation between self-reported use of prenatal vitamins in early pregnancy and the risk of miscarriage. Between 2000 and 2008, 4,752 US women were prospectively enrolled in Right From the Start. Information about vitamin use was obtained from a first-trimester interview. Discrete-time hazard models were used, candidate confounders were assessed and the following variables were included in the model: study site, maternal age, gravidity, marital status, education, race/ethnicity, smoking and use of progesterone in early pregnancy. Approximately 95% of participants reported use of vitamins during early pregnancy. A total of 524 women had a miscarriage. In the final adjusted model, any use of vitamins during pregnancy was associated with decreased odds of miscarriage (odds ratio = 0.43, 95% confidence interval: 0.30, 0.60) in comparison with no exposure. These results should be viewed in the context of a potentially preventive biologic mechanism mitigated by possible confounding by healthy behaviors and practices that are also associated with vitamin supplement use during pregnancy. (*American Journal of Epidemiology* 2009 169(11):1312-1318; doi:10.1093/aje/kwp050)

Stress Pathways to Spontaneous Preterm Birth: The Role of Stressors, Psychological Distress and Stress Hormones

Michael S. Kramer, John Lydon, Louise Séguin, Lise Goulet, Susan R. Kahn, Helen McNamara, Jacques Genest, Clément Dassa, Moy Fong Chen, Shakti Sharma, Michael J. Meaney, Steven Thomson, Stan Van Uum, Gideon Koren, Mourad Dahhou, Julie Lamoureux and Robert W. Platt

The authors investigated a large number of stressors and measures of psychological distress in a multicenter, prospective cohort study of spontaneous preterm birth among 5,337 Montreal (Canada)-area women who delivered from October 1999 to April 2004. In addition, a nested case-control analysis (207 cases, 444 controls) was used to explore potential biologic pathways by analyzing

maternal plasma corticotrophin-releasing hormone (CRH), placental histopathology and (in a subset) maternal hair cortisol. Among the large number of stress and distress measures studied, only pregnancy-related anxiety was consistently and independently associated with spontaneous preterm birth (for values above the median, adjusted odds ratio = 1.8 (95% confidence interval: 1.3, 2.4)), with a dose-response relation across quartiles. The maternal plasma CRH concentration was significantly higher in cases than in controls in crude analyses but not after adjustment (for concentrations above the median, adjusted odds ratio = 1.1 (95% confidence interval: 0.8, 1.6)). In the subgroup ($n = 117$) of participants with a sufficient maternal hair sample, hair cortisol was positively associated with gestational age. Neither maternal plasma CRH, hair cortisol, nor placental histopathologic features of infection/inflammation, infarction, or maternal vasculopathy were significantly associated with pregnancy-related anxiety or any other stress or distress measure. The biologic pathways underlying stress-induced preterm birth remain poorly understood. (American Journal of Epidemiology 2009 169(11):1319-1326; doi:10.1093/aje/kwp061)

Association of Early-life Exposure to Household Gas Appliances and Indoor Nitrogen Dioxide With Cognition and Attention Behavior in Preschoolers

Eva Morales, Jordi Julvez, Maties Torrent, Rafael de Cid, Mònica Guxens, Mariona Bustamante, Nino Künzli and Jordi Sunyer

The authors investigated the association of early-life exposure to indoor air pollution with neuropsychological development in preschoolers and assessed whether this association differs by glutathione-*S*-transferase gene (*GSTP1*) polymorphisms. A prospective, population-based birth cohort was set up in Menorca, Spain, in 1997-1999 ($n = 482$). Children were assessed for cognitive functioning (McCarthy Scales of Children's Abilities) and attention-hyperactivity behaviors (*Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition) at age 4 years. During the first 3 months of life, information about gas appliances at home and indoor nitrogen dioxide concentration was collected at each participant's home ($n = 398$, 83%). Genotyping was conducted for the *GSTP1* coding variant Ile105Val. Use of gas appliances was inversely associated with cognitive outcomes (β coefficient for general cognition = -5.10, 95% confidence interval (CI): -9.92, -0.28; odds ratio for inattention symptoms = 3.59, 95% CI: 1.14, 11.33), independent of social class and other confounders. Nitrogen dioxide concentrations were associated with cognitive function (a decrease of 0.27 point per 1 ppb, 95% CI: -0.48, -0.07) and inattention symptoms (odds ratio = 1.06, 95% CI: 1.01, 1.12). The deleterious effect of indoor pollution from gas

appliances on neuropsychological outcomes was stronger in children with the *GSTP1* Val-105 allele. Early-life exposure to air pollution from indoor gas appliances may be negatively associated with neuropsychological development through the first 4 years of life, particularly among genetically susceptible children. (American Journal of Epidemiology 2009 169(11):1327-1336; doi:10.1093/aje/kwp067)

Is the Association Between Low Birth Weight and Asthma Independent of Genetic and Shared Environmental Factors?

Eduardo Villamor, Anastasia Iliadou and Sven Cnattingius

Epidemiologic evidence linking birth weight and asthma is inconsistent. The authors examined the association between birth weight and asthma during childhood and adult life in twins. Using prospectively collected data on 21,588 like-sexed Swedish twins of known zygosity born in 1928-1952, they first conducted a cohort study to examine the risk of asthma in relation to birth weight. Next, they conducted nested co-twin control analyses among 643 dizygotic and 365 monozygotic twin pairs discordant for asthma to ascertain whether the association between birth weight and asthma could be confounded by genetic and shared environmental exposures. In the cohort analysis, birth weight of <2,500 g was associated with significantly greater risk of asthma independent of perinatal characteristics and within-twin-pair correlations. In the co-twin control analyses, birth weight of <2,500 g was significantly related to increased risk of asthma among monozygotic twins (relative risk for 2,000 g vs. 2,500 g = 1.58, 95% confidence interval: 1.06, 2.38). A negative association between birth weight and asthma, albeit not statistically significant, was also found among dizygotic twins. In conclusion, there is a negative association between birth weight and asthma in twins that is unlikely to be confounded by genetic or shared environmental factors. (American Journal of Epidemiology 2009 169(11):1337-1343; doi:10.1093/aje/kwp054)

Joint Associations of Adiposity and Physical Activity With Mortality

Annemarie Koster, Tamara B. Harris, Steven C. Moore, Arthur Schatzkin, Albert R. Hollenbeck, Jacques Th. M. van Eijk and Michael F. Leitzmann

The authors examined the joint associations of adiposity (assessed by body mass index (BMI; weight (kg)/height (m)²) and waist circumference) and physical

activity with mortality to evaluate whether physical activity protects against the adverse effects of high adiposity. Using data on 185,412 men and women aged 51-72 years participating in the National Institutes of Health-AARP Diet and Health Study, the authors assessed all-cause mortality over 10 years (1996-2006). Overweight (BMI 25-<30), obesity (BMI \geq 30), a large waist circumference (men: \geq 102 cm; women: \geq 88 cm) and low physical activity were each independent predictors of mortality. Compared with normal-weight persons (BMI 18.5-<25) who were physically active (>7 hours/week of moderate physical activity), mortality risks were 1.62 (95% confidence interval (CI): 1.50, 1.75) for inactive normal-weight persons, 1.79 (95% CI: 1.37, 2.33) for active morbidly obese (BMI \geq 35) persons and 3.45 (95% CI: 2.79, 4.00) for inactive morbidly obese persons. Similar results were found for the combined relation of BMI and vigorous physical activity. Inactive persons with a large waist circumference had 2 times' greater mortality risk than active persons with a normal waist circumference. High physical activity attenuated but did not eliminate the increased mortality risk associated with obesity. Preventing weight gain and promoting physical activity in older persons may lower mortality risk. (*American Journal of Epidemiology* 2009 169(11):1344-1351; doi:10.1093/aje/kwp053)

Lipid Changes During the Menopause Transition in Relation to Age and Weight

Carol A. Derby, Sybil L. Crawford, Richard C. Pasternak, MaryFran Sowers, Barbara Sternfeld and Karen A. Matthews

Few studies have prospectively examined lipid changes across the menopause transition or in relation to menopausal changes in endogenous hormones. The relative independent contributions of menopause and age to lipid changes are unclear. Lipid changes were examined in relation to changes in menopausal status and in levels of estradiol and follicle-stimulating hormone in 2,659 women followed in the Study of Women's Health Across the Nation (1995-2004). Baseline age was 42-52 years and all were initially pre- or perimenopausal. Women were followed annually for up to 7 years (average, 3.9 years). Lipid changes occurred primarily during the later phases of menopause, with menopause-related changes similar in magnitude to changes attributable to aging. Total cholesterol, low density lipoprotein cholesterol, triglycerides and lipoprotein(a) peaked during late peri- and early postmenopause, while changes in the early stages of menopause were minimal. The relative odds of low density lipoprotein cholesterol (\geq 130 mg/dL) for early postmenopausal, compared with premenopausal, women were 2.1 (95% confidence interval: 1.5, 2.9). High density lipoprotein cholesterol also peaked in

late peri- and early postmenopause. Results for estradiol and follicle-stimulating hormone confirmed the results based on status defined by bleeding patterns. Increases in lipids were smallest in women who were heaviest at baseline. (American Journal of Epidemiology 2009 169(11):1352-1361; doi:10.1093/aje/kwp043)

Is Previous Psychological Health Associated With the Likelihood of Iraq War Deployment? An Investigation of the "Healthy Warrior Effect"

Jennifer Wilson, Margaret Jones, Nicola T. Fear, Lisa Hull, Matthew Hotopf, Simon Wessely and Roberto J. Rona

Using survey data, the authors assessed whether military personnel's prior mental health status would influence their likelihood of being deployed. None of the previous studies that assessed a possible "healthy warrior effect," in which persons selected for deployment have better predeployment health, were based on surveys. A sample of 2,820 United Kingdom military personnel studied in 2002, before the Iraq War, was contacted again between 2004 and 2006. The baseline questionnaire included a measure of psychological distress (the General Health Questionnaire), the PTSD [posttraumatic stress disorder] Checklist (PCL), physical symptoms and level of medical fitness. A total of 1,885 (67%) participants completed a follow-up questionnaire. General Health Questionnaire caseness in 2002 was associated with a reduction in risk of deployment later on (risk ratio = 0.81, 95% confidence interval: 0.67, 0.99). Scoring high on the PCL intrusiveness and avoidance domains also reduced the risk of deployment. These associations were slightly stronger when the comparison was made between persons who were deployed to Iraq and those who were not. Although risk ratios were well below 1.00, PCL categories were not significantly associated with being deployed. This study demonstrated a small "healthy warrior effect"; persons with better psychological health had a higher chance of being deployed, even after adjustment for predeployment medical fitness. (American Journal of Epidemiology 2009 169(11):1362-1369; doi:10.1093/aje/kwp044)

Rotating Night Shift Work and the Risk of Ischemic Stroke

Devin L. Brown, Diane Feskanich, Brisa N. Sánchez, Kathryn M. Rexrode, Eva S. Schernhammer and Lynda D. Lisabeth

Rotating night shift work disrupts circadian rhythms and is associated with coronary heart disease. The relation between rotating night shift work and ischemic

stroke is unclear. The Nurses' Health Study, an ongoing cohort study of registered female nurses, assessed in 1988 the total number of years the nurses had worked rotating night shifts. The majority (69%) of stroke outcomes from 1988 to 2004 were confirmed by physician chart review. The authors used Cox proportional hazards models to assess the relation between years of rotating night shift work and ischemic stroke, adjusting for multiple vascular risk factors. Of 80,108 subjects available for analysis, 60% reported at least 1 year of rotating night shift work. There were 1,660 ischemic strokes. Rotating night shift work was associated with a 4% increased risk of ischemic stroke for every 5 years (hazard ratio = 1.04, 95% confidence interval: 1.01, 1.07; $P_{\text{trend}} = 0.01$). This increase in risk was similar when limited to the 1,152 confirmed ischemic strokes (hazard ratio = 1.03, 95% confidence interval: 0.99, 1.07; $P_{\text{trend}} = 0.10$) and may be confined to women with a history of 15 or more years of rotating shift work. Women appear to have a modestly increased risk of stroke after extended periods of rotating night shift work. (*American Journal of Epidemiology* 2009 169(11):1370-1377; doi:10.1093/aje/kwp056)

Use of Nonsteroidal Antiinflammatory Agents and Incidence of Ovarian Cancer in 2 Large Prospective Cohorts

Simone P. Pinheiro, Shelley S. Tworoger, Daniel W. Cramer, Bernard A. Rosner and Susan E. Hankinson

Epidemiologic data on the association between nonsteroidal antiinflammatory drugs (NSAIDs) and ovarian cancer risk have been inconsistent. The authors prospectively examined the association between regular use of aspirin and nonaspirin NSAIDs and ovarian cancer incidence among 197,486 participants of the Nurses' Health Study (NHS) and the Nurses' Health Study-II (NHS-II) over 24 and 16 years of follow-up, respectively. Information on aspirin was initially assessed in 1980 (NHS) and 1989 (NHS-II) and on nonaspirin NSAIDs and acetaminophen in 1990 (NHS) and 1989 (NHS-II) and updated throughout follow-up. The authors used Cox proportional hazards models adjusting for ovarian cancer risk factors. A total of 666 confirmed cases of epithelial ovarian cancer were identified over 2,790,986 person-years of follow-up. The hazard ratios associated with regular use of aspirin, nonaspirin NSAIDs and acetaminophen were 1.11 (95% confidence interval (CI): 0.92, 1.33), 0.81 (95% CI: 0.64, 1.01) and 1.14 (95% CI: 0.92, 1.43), respectively. The authors did not observe a dose-response relation with increased frequency or duration of regular use of any of these medications and ovarian cancer incidence. The results did not differ substantially by tumor histology. In this large prospective study, the authors found no compelling evidence to support an association between regular use of

aspirin, nonaspirin NSAIDs, or acetaminophen and ovarian cancer incidence. (American Journal of Epidemiology 2009 169(11):1378-1387; doi:10.1093/aje/kwp062)

Truth or Consequences: The Intertemporal Consistency of Adolescent Self-report on the Youth Risk Behavior Survey

Janet E. Rosenbaum

Surveys are the primary information source about adolescents' health risk behaviors, but adolescents may not report their behaviors accurately. Survey data are used for formulating adolescent health policy and inaccurate data can cause mistakes in policy creation and evaluation. The author used test-retest data from the Youth Risk Behavior Survey (United States, 2000) to compare adolescents' responses to 72 questions about their risk behaviors at a 2-week interval. Each question was evaluated for prevalence change and 3 measures of unreliability: inconsistency (retraction and apparent initiation), agreement measured as tetrachoric correlation and estimated error due to inconsistency assessed with a Bayesian method. Results showed that adolescents report their sex, drug, alcohol and tobacco histories more consistently than other risk behaviors in a 2-week period, opposite their tendency over longer intervals. Compared with other Youth Risk Behavior Survey topics, most sex, drug, alcohol and tobacco items had stable prevalence estimates, higher average agreement and lower estimated measurement error. Adolescents reported their weight control behaviors more unreliably than other behaviors, particularly problematic because of the increased investment in adolescent obesity research and reliance on annual surveys for surveillance and policy evaluation. Most weight control items had unstable prevalence estimates, lower average agreement and greater estimated measurement error than other topics. (American Journal of Epidemiology 2009 169(11):1388-1397; doi:10.1093/aje/kwp049)

Using the Whole Cohort in the Analysis of Case-Cohort Data

Norman E. Breslow, Thomas Lumley, Christie M. Ballantyne, Lloyd E. Chambless and Michal Kulich

Case-cohort data analyses often ignore valuable information on cohort members not sampled as cases or controls. The Atherosclerosis Risk in Communities (ARIC) study investigators, for example, typically report data for just the 10%-15% of subjects sampled for substudies of their cohort of 15,972 participants. Remaining subjects contribute to stratified sampling weights only. Analysis

methods implemented in the freely available R statistical system (<http://cran.r-project.org/>) make better use of the data through adjustment of the sampling weights via calibration or estimation. By reanalyzing data from an ARIC study of coronary heart disease and simulations based on data from the National Wilms Tumor Study, the authors demonstrate that such adjustment can dramatically improve the precision of hazard ratios estimated for baseline covariates known for all subjects. Adjustment can also improve precision for partially missing covariates, those known for substudy participants only, when their values may be imputed with reasonable accuracy for the remaining cohort members. Links are provided to software, data sets and tutorials showing in detail the steps needed to carry out the adjusted analyses. Epidemiologists are encouraged to consider use of these methods to enhance the accuracy of results reported from case-cohort analyses. (*American Journal of Epidemiology* 2009 169(11):1398-1405; doi:10.1093/aje/kwp055)

Occupation as Socioeconomic Status or Environmental Exposure? A Survey of Practice Among Population-based Cardiovascular Studies in the United States

Leslie A. MacDonald, Alex Cohen, Sherry Baron and Cecil M. Burchfiel

Decisions about how occupation is used in epidemiologic research can affect conclusions about the importance of socioeconomic and environmental factors in explaining disparities for outcomes such as cardiovascular disease. A review of practices in the collection and use of occupational data was conducted among population-based cardiovascular studies in the United States. Studies were identified for review from the National Heart, Lung and Blood Institute website and the biomedical database, Computer Retrieval of Information on Scientific Projects, by use of selected criteria. Data collection instruments and study publications were retrieved and reviewed for 30 of 33 studies (91%). Most of the studies (83%) collected at least descriptive occupational data and more than half (60%) collected data on workplace hazards. The reviewed studies produced 80 publications in which occupational data were used in analyses, most often as an indicator of socioeconomic status. Authors rarely acknowledged known conceptual and empirical links among socioeconomic status, employment stability and working conditions. Underutilization of data on workplace conditions was found. Existing data could be used more effectively to examine the contribution of work-related social and environmental conditions to the development of modifiable cardiovascular disease through multiple pathways. (*American Journal of Epidemiology* 2009 169(12):1411-1421; doi:10.1093/aje/kwp082)

Invited Commentary: The Search for Preventable Causes of Cardiovascular Disease-Whither Work?

Mark R. Cullen

The incidence and mortality of the major cardiovascular disorders vary sharply by occupation, but this is usually attributed to broad socioeconomic factors; the contributions of physical and psychosocial stressors at work remain obscure or controversial. Review of the ongoing studies of cardiovascular disease in the United States in this issue of the *Journal* demonstrates that few have either collected sufficient occupational data or used these data in published analyses to address this issue. There are compelling reasons to study this issue, starting with the sheer magnitude of the occupational gradient and disease prevalence. If only 5%–15% prove causally linked to preventable factors, an enormous disease-control opportunity would present itself. Moreover, the most suspect work factors—job stress, fine particulate dust, heat, noise and shiftwork—are highly prevalent in the US workforce. Thankfully, there is evidence that many of the large ongoing studies are moving toward enhancing their occupational data and using what they have already collected. However, because of the complexity of studying these relations, the better solution is not retrofitting but designing studies in the future that combine *de novo* the conceptual frameworks and technical skills of occupational and social epidemiologists with those of more biologically focused investigators. (*American Journal of Epidemiology* 2009 169(12):1422-1425; doi:10.1093/aje/kwp078)

Birth Weight, Early Weight Gain and Subsequent Risk of Type 1 Diabetes: Systematic Review and Meta-Analysis

Thomas Harder, Katharina Roepke, Natasha Diller, Yvonne Stechling, Joachim W. Dudenhausen and Andreas Plagemann

Previous studies suggest that birth weight and weight gain during the first year of life are related to later risk of type 1 diabetes. The authors performed a systematic review and meta-analysis on these associations. Twelve studies involving 2,398,150 persons of whom 7,491 had type 1 diabetes provided odds ratios and 95% confidence intervals of type 1 diabetes associated with birth weight. Four studies provided data on weight and/or weight gain during the first year of life. High birth weight (>4,000 g) was associated with increased risk of type 1 diabetes (odds ratio = 1.17, 95% confidence interval (CI): 1.09, 1.26). According to sensitivity analysis, this result was not influenced by particular study characteristics.

The pooled confounder-adjusted estimate was 1.43 (95% CI: 1.11, 1.85). No heterogeneity was found ($I^2 = 0\%$) and no publication bias. Low birth weight (<2,500 g) was associated with a nonsignificantly decreased risk of type 1 diabetes (odds ratio = 0.82, 95% CI: 0.54, 1.23). Each 1,000-g increase in birth weight was associated with a 7% increase in type 1 diabetes risk. In all studies, patients with type 1 diabetes showed increased weight gain during the first year of life, compared with controls. This meta-analysis indicates that high birth weight and increased early weight gain are risk factors for type 1 diabetes. (American Journal of Epidemiology 2009 169(12):1428-1436; doi:10.1093/aje/kwp065)

Serum and Dietary Magnesium and Risk of Ischemic Stroke

Tetsuya Ohira, James M. Peacock, Hiroyasu Iso, Lloyd E. Chambless, Wayne D. Rosamond and Aaron R. Folsom

The authors sought to examine the relation between serum or dietary magnesium and the incidence of ischemic stroke among blacks and whites. Between 1987 and 1989, 14,221 men and women aged 45–64 years took part in the first examination of the Atherosclerosis Risk in Communities Study cohort. The incidence of stroke was ascertained from hospital records. Higher serum magnesium levels were associated with lower prevalence of hypertension and diabetes mellitus at baseline. During the 15-year follow-up, 577 ischemic strokes occurred. Serum magnesium was inversely associated with ischemic stroke incidence. The age-, sex- and race-adjusted rate ratios of ischemic stroke for those with serum magnesium levels of ≤ 1.5 , 1.6, 1.7 and ≥ 1.8 mEq/L were 1.0, 0.78 (95% confidence interval (CI): 0.62, 0.96), 0.70 (95% CI: 0.56, 0.88) and 0.75 (95% CI: 0.59, 0.95) ($P_{\text{trend}} = 0.005$). After adjustment for hypertension and diabetes, the rate ratios were attenuated to nonsignificant levels. Dietary magnesium intake was marginally inversely associated with the incidence of ischemic stroke ($P_{\text{trend}} = 0.09$). Low serum magnesium levels could be associated with increased risk of ischemic stroke, in part, via effects on hypertension and diabetes. (American Journal of Epidemiology 2009 169(12):1437-1444; doi:10.1093/aje/kwp071)

Coffee Intake, Smoking and Pulmonary Function in the Atherosclerosis Risk in Communities Study

Jennifer A. Nettleton, Jack L. Follis and Matthew B. Schabath

Coffee contains polyphenolic antioxidants and caffeine, which may favorably affect pulmonary function. Therefore, the authors studied cross-sectional associations (1987–1989) between coffee intake and pulmonary function in the Atherosclerosis

Risk in Communities Study, a population-based cohort study (analytic sample = 10,658). They also conducted analyses stratified by smoking status, since smoking is a strong risk factor for respiratory disease and could influence the effects of caffeine and antioxidants. Self-reported coffee intake was categorized as rare/never, <7 cups/week, 1 cup/day, 2–3 cups/day and ≥4 cups/day. Pulmonary function was characterized by the spirometric measures forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV₁). After adjustment for demographic factors, lifestyle characteristics and dietary factors, pulmonary function values increased across increasing categories of coffee consumption in never and former smokers but not in current smokers. In never or former smokers who consumed ≥4 cups of coffee daily, FVC and FEV₁ were 2%–3% greater than in never or former smokers who rarely/never consumed coffee (P_{trend} values: in never smokers, 0.04 for FVC and 0.07 for FEV₁; in former smokers, <0.001 for FVC and <0.001 for FEV₁). These data show a possible beneficial effect of coffee (or a coffee ingredient) on pulmonary function, but it appears to be limited to nonsmokers. (American Journal of Epidemiology 2009 169(12):1445-1453; doi:10.1093/aje/kwp068)

Is There a Clear Threshold for Fasting Plasma Glucose That Differentiates Between Those With and Without Neuropathy and Chronic Kidney Disease?

Ei Ei Khaing Nang, Chin Meng Khoo, E. Shyong Tai, Su Chi Lim, Subramaniam Tavintharan, Tien Yin Wong, Derrick Heng and Jeannette Lee

Recent studies suggest that no distinct glycemic threshold consistently differentiates individuals with or without retinopathy. The authors sought to determine whether the same was true for other microvascular complications. They studied 5,094 participants with fasting plasma glucose values and concurrent microvascular complications from 4 previous cross-sectional surveys carried out in Singapore (1982–1998) who attended a follow-up examination in 2004–2007. Peripheral neuropathy was diagnosed based on abnormal responses to a 10-g monofilament or neurothesiometer test. Chronic kidney disease was defined in various ways by using albuminuria (urine albumin:creatinine ratio >30 $\mu\text{g}/\text{mg}$) and estimated glomerular filtration rate, alone and in combination. Prevalence of peripheral neuropathy was 7.5%. For chronic kidney disease, prevalence of albuminuria only was 10.5%, estimated glomerular filtration rate of <60 mL/minute per 1.73 m² only was 4.1% and both was 2.1%. Prevalence of peripheral neuropathy and chronic kidney disease gradually increased in relation to fasting plasma glucose, beginning at levels below the existing diagnostic threshold for diabetes mellitus of 7.0 mmol/L (126 mg/dL). For chronic kidney disease, these associations persisted after

adjustment for age, gender, ethnic group and hypertension. Current diagnostic thresholds for diabetes mellitus have limited sensitivity for identifying individuals with these microvascular complications. Ascertaining these individuals may require development and application of novel screening strategies. (*American Journal of Epidemiology* 2009 169(12):1454-1462; doi:10.1093/aje/kwp076)

Time-Varying Effects of Prognostic Factors Associated With Disease-Free Survival in Breast Cancer

Loki Natarajan, Minya Pu, Barbara A. Parker, Cynthia A. Thomson, Bette J. Caan, Shirley W. Flatt, Lisa Madlensky, Richard A. Hajek, Wael K. Al-Delaimy, Nazmus Saquib, Ellen B. Gold and John P. Pierce

Early detection and effective treatments have dramatically improved breast cancer survivorship, yet the risk of relapse persists even 15 years after the initial diagnosis. It is important to identify prognostic factors for late breast cancer events. The authors investigated time-varying effects of tumor characteristics on breast-cancer-free survival using data on 3,088 breast cancer survivors from 4 US states who participated in a randomized dietary intervention trial in 1995–2006, with maximum follow-up through 15 years (median, 9 years). A piecewise constant penalized spline approach incorporating time-varying coefficients was adopted, allowing for deviations from the proportional hazards assumption. This method is more flexible than standard approaches, provides direct estimates of hazard ratios across time intervals and is computationally tractable. Having a stage II or III tumor was associated with a 3-fold higher hazard of breast cancer than having a stage I tumor during the first 2.5 years after diagnosis; this hazard ratio decreased to 2.1 after 7.7 years, but higher tumor stage remained a significant risk factor. Similar diminishing effects were found for poorly differentiated tumors. Interestingly, having a positive estrogen receptor status was protective up to 4 years after diagnosis but detrimental after 7.7 years (hazard ratio = 1.5). These results emphasize the importance of careful statistical modeling allowing for possibly time-dependent effects in long-term survivorship studies. (*American Journal of Epidemiology* 2009 169(12):1463-1470; doi:10.1093/aje/kwp077)

Quantitative Exposure to Metalworking Fluids and Bladder Cancer Incidence in a Cohort of Autoworkers

Melissa C. Friesen, Sadie Costello and Ellen A. Eisen

Occupations with mineral oil exposure have been associated with bladder cancer in population-based case-control studies. The authors report results from the first

cohort study to examine bladder cancer incidence in relation to quantitative exposures to metalworking fluids (MWFs), based on 21,999 male Michigan automotive workers, followed from 1985 through 2004. Cox regression was used to estimate hazard ratios based on categorical exposure variables for straight, soluble and synthetic MWFs, as well as duration of exposure to ethanalamines and nitrosamines. Penalized splines were also fit to estimate the functional form of the exposure-response relation. Increased bladder cancer risk was associated with straight MWFs but not with any other exposure. The hazard ratio increased with cumulative exposure to a maximum of 2-fold observed at 75 mg/m³-year straight MWF exposure (lagged 20 years). Calendar time windows relevant to polycyclic aromatic hydrocarbon exposure were examined but could not be distinguished from the lagged (10-, 20-year) metrics. No association was observed between any exposure and incident lung cancer, suggesting that smoking is unlikely to confound the associations observed here. The quantitative relation with straight MWFs strengthens the evidence for mineral oils as a bladder carcinogen. (American Journal of Epidemiology 2009 169(12):1471-1478; doi:10.1093/aje/kwp073)

Exposure to Farm Crops, Livestock and Farm Tasks and Risk of Glioma

Avima M. Ruder, Tania Carreón, Mary Ann Butler, Geoffrey M. Calvert, Karen E. Davis-King, Martha A. Waters, Paul A. Schulte, Jack S. Mandel, Roscoe F. Morton, Douglas J. Reding, Kenneth D. Rosenman and the Brain Cancer Collaborative Study Group

Some studies of brain cancer have found an excess risk for farmers. The National Institute for Occupational Safety and Health previously found no increased glioma risk for ever (vs. never) being exposed to pesticides on a farm among 798 cases and 1,175 population-based controls (adult (ages 18–80 years) nonmetropolitan residents of Iowa, Michigan, Minnesota and Wisconsin). For this analysis (1995–1998), 288 cases and 474 controls (or their proxies) who had lived on farms at age 18 years or after were asked about exposure to crops, livestock and farm tasks. Logistic regression was used to calculate odds ratios adjusted for age, age group, sex, state and education. Never immediately washing up (adjusted odds ratio (OR) = 3.08, 95% confidence interval (CI): 1.78, 5.34) or changing clothes (OR = 2.84, 95% CI: 1.04, 7.78) after applying pesticides was associated with increased glioma risk. Living on a farm on which corn, oats, soybeans, or hogs were raised was associated with decreased risk (corn—OR = 0.37, 95% CI: 0.20, 0.69; oats—OR = 0.63, 95% CI: 0.40, 1.00; soybeans—OR = 0.69, 95%

CI: 0.48, 0.98; hogs—OR = 0.63, 95% CI: 0.43, 0.93). Negative associations may be due to chance or a "healthy farmer" effect. Farmers' increased risk of glioma may be due to work practices, other activities, or an inverse association with allergies (reported by other investigators). (American Journal of Epidemiology 2009 169(12):1479-1491; doi:10.1093/aje/kwp075)

Obesity, Lifestyle Factors and Risk of Myelodysplastic Syndromes in a Large US Cohort

Xiaomei Ma, Unhee Lim, Yikyung Park, Susan T. Mayne, Rong Wang, Patricia Hartge, Albert R. Hollenbeck and Arthur Schatzkin

The etiology of myelodysplastic syndromes (MDS) is not well understood. The authors examined the relations of obesity and lifestyle factors to MDS in a cohort of 471,799 persons aged 50–71 years who were recruited into the National Institutes of Health-AARP Diet and Health Study, a large US prospective study, in 1995–1996. Incident MDS was diagnosed in 193 persons during 2001–2003. A significant positive association was observed between body mass index (BMI; weight (kg)/height (m)²) at baseline and MDS. Compared with persons with a BMI less than 25.0, the hazard ratios for persons with BMIs of 25.0–<30.0 and ≥30.0 were 1.15 (95% confidence interval (CI): 0.81, 1.64) and 2.18 (95% CI: 1.51, 3.17; *P* for trend < 0.001), respectively. The association was not affected by physical activity, cigarette smoking, or alcohol intake. As reported in previous studies, the risk of MDS was elevated among former smokers (hazard ratio = 1.68, 95% CI: 1.17, 2.41) and current smokers (hazard ratio = 3.17, 95% CI: 2.02, 4.98) as compared with never smokers. Physical activity, alcohol consumption, meat intake and fruit and vegetable intake did not appear to significantly influence the risk of MDS in this analysis. This prospective investigation of MDS implicates both obesity and smoking as modifiable risk factors. (American Journal of Epidemiology 2009 169(12):1492-1499; doi:10.1093/aje/kwp074)

Pesticide Exposure and Respiratory Health of Indigenous Women in Costa Rica

Karin B. Fieten, Hans Kromhout, Dick Heederik and Berna van Wendel de Joode

A cross-sectional study was conducted in 2007 to evaluate the relation between pesticide exposure and respiratory health in a population of indigenous women in Costa Rica. Exposed women (*n* = 69) all worked at plantain plantations.

Unexposed women ($n = 58$) worked at organic banana plantations or other locations without pesticide exposure. Study participants were interviewed using questionnaires to estimate exposure and presence of respiratory symptoms. Spirometry tests were conducted to obtain forced vital capacity and forced expiratory volume in 1 second. Among the exposed, prevalence of wheeze was 20% and of shortness of breath was 36% versus 9% and 26%, respectively, for the unexposed. Prevalence of chronic cough, asthma and atopic symptoms was similar for exposed and unexposed women. Among nonsmokers ($n = 105$), reported exposures to the organophosphate insecticides chlorpyrifos ($n = 25$) and terbufos ($n = 38$) were strongly associated with wheeze (odds ratio = 6.7, 95% confidence interval: 1.6, 28.0; odds ratio = 5.9, 95% confidence interval: 1.4, 25.6, respectively). For both insecticides, a statistically significant exposure-effect association was found. Multiple organophosphate exposure was common; 81% of exposed women were exposed to both chlorpyrifos and terbufos. Consequently, their effects could not be separated. All findings were based on questionnaire data. No relation between pesticide exposure and ventilatory lung function was found. (*American Journal of Epidemiology* 2009 169(12):1500-1506; doi:10.1093/aje/kwp060)

Activity Energy Expenditure and Mobility Limitation in Older Adults: Differential Associations by Sex

Todd M. Manini, James E. Everhart, Kushang V. Patel, Dale A. Schoeller, Steve Cummings, Dawn C. Mackey, Douglas C. Bauer, Eleanor M. Simonsick, Lisa H. Colbert, Marjolein Visser, Frances Tylavsky, Anne B. Newman, Tamara B. Harris and for the Health, Aging and Body Composition Study

In this study, the authors aimed to determine whether higher activity energy expenditure, assessed by using doubly labeled water, was associated with a reduced decline in mobility limitation among 248 older community-dwelling US adults aged 70–82 years enrolled in 1998–1999. Activity energy expenditure was calculated as total energy expenditure (assessed over 2 weeks by using doubly labeled water) minus resting metabolic rate (measured with indirect calorimetry), with adjustment for the thermic effect of food. Across sex-specific tertiles of activity energy expenditure, men in the lowest activity group experienced twice the rate of mobility limitation as men in the highest activity group (41% ($n = 18$) vs. 18% ($n = 8$)). Conversely, women in the lowest and highest activity groups exhibited similarly high rates of mobility limitation (40% ($n = 16$) vs. 38% ($n = 15$)). After adjustment for potential confounders, men with higher activity energy expenditure levels continued to show reduced risk of mobility limitation

(per standard deviation (284 kcal/day): hazard ratio = 0.61, 95% confidence interval: 0.41, 0.92). Women showed no association (per standard deviation (226 kcal/day): hazard ratio = 1.34, 95% confidence interval: 0.98, 1.85). Greater energy expenditure from any and all physical activity was significantly associated with reduced risk of developing mobility limitation among men, but not among women. (*American Journal of Epidemiology* 2009 169(12):1507-1516; doi:10.1093/aje/kwp069)

Optimal Dosing and Dynamic Distribution of Vaccines in an Influenza Pandemic

James Wood, James McCaw, Niels Becker, Terry Nolan and C. Raina MacIntyre

Limited production capacity and delays inherent in vaccine development are major hurdles to the widespread use of vaccines to mitigate the effects of a new influenza pandemic. Antigen-sparing vaccines have the most potential to increase population coverage but may be less efficacious. The authors explored this trade-off by applying simple models of influenza transmission and dose response to recent clinical trial data. In this paper, these data are used to illustrate an approach to comparing vaccines on the basis of antigen supply and inferred efficacy. The effects of delays in matched vaccine availability and seroconversion on epidemic size during pandemic phase 6 were also studied. The authors infer from trial data that population benefits stem from the use of low-antigen vaccines. Delayed availability of a matched vaccine could be partially alleviated by using a 1-dose vaccination program with increased coverage and reduced time to full protection. Although less immunogenic, an overall attack rate of up to 6% lower than a 2-dose program could be achieved. However, if prevalence at vaccination is above 1%, effectiveness is much reduced, emphasizing the need for other control measures. (*American Journal of Epidemiology* 2009 169(12):1517-1524; doi:10.1093/aje/kwp072)

The Effect of Question Order on Self-rated General Health Status in a Multilingual Survey Context

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Current practices recommend placing a self-rated health question before specific health items in survey questionnaires to minimize potential order effects. Because this recommendation is based on data collected in English, its applicability to other

languages is unknown. This study examines whether there is an order effect associated with self-rated health for interviews conducted in English and Spanish languages. An experiment was conducted by using the 2007 California Health Interview Survey, where questions on self-rated health were inserted in 1 of 2 locations: preceding and following question items on specific chronic conditions. Respondents were randomly assigned to 1 of 2 versions of the locations by the split-half method. Although no order effect was present in the English interviews, the authors found a significant and large effect with Spanish interviews: Self-rated health appeared much worse when asked before chronic conditions than when asked after them. This order effect was larger among females than males. Order effects for self-rated health differ by interview language; inferences about the health status of Spanish-speaking populations (and potentially Latinos) depend on question order. If maintaining comparability is important, the authors' finding contradicts current recommendations, as inserting the self-rated health question before specific questions led to larger differences in health status between English and Spanish speakers. (*American Journal of Epidemiology* 2009 169(12):1525-1530; doi:10.1093/aje/kwp070)