Bulletin de veille

« Focus sur 12 pathologies graves »

Avril 2010

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Le Service Documentation de l'EHESP édite **mensuellement** un bulletin de veille. Celui-ci signale les **articles récents**, parus dans des revues scientifiques de renommée internationale, autour de **12 pathologies graves,** ainsi que sur la **pandémie grippale**. Ce bulletin signale également des **rapports officiels et institutionnels** disponibles en texte intégral.

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Etablissement public à caractère scientifique, culturel et professionnel.

Bulletin de veille – Mars 2010
« Focus sur 12 pathologies graves »

Ce bulletin de veille est une **publication mensuelle** qui recueille les publications scientifiques autour des **pathologies** suivantes :

- Bronchite chronique obstructive
- Cancer du poumon
- Dengue
- Dépression
- Diabète
- Grippe A
- Maladie d'Alzheimer
- Maladies cardio-vasculaires
- Maladies liées à l'alcool
- Paludisme
- Pathologies liées à l'obésité
- SIDA
- Tuberculose

La recherche documentaire est effectuée dans la **base de données Medline** et porte sur les **12 titres de revues** suivants :

- American journal of epidemiology
- American journal of public health
- BMC public health
- BMJ (Clinical research ed.) - British medical journal
- International journal of epidemiology
- JAMA : the journal of the American Medical Association
- Lancet
- Nature
- Risk analysis : an official publication of the Society for Risk Analysis
- Science
- Social science & medicine
- The New England journal of medicine

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Articles scientifiques issus de l'interrogation de la base Medline (interrogée le 02/04/2010)

Rapports , dossiers en ligne et articles supplémentaires

Articles scientifiques

Bronchite chronique obstructive

sommaire

(1) KOSHIOL J, ROTUNNO M, CONSONNI D, PESATORI AC, *et al.* **Chronic obstructive pulmonary disease and altered risk of lung cancer in a population-based case-control study**. PLoS One. 2009, vol. 4, n° 10, p.e7380
http://dx.doi.org/10.1371/journal.pone.0007380 **(Accès libre)**

BACKGROUND: Chronic obstructive pulmonary disease (COPD) has been consistently associated with increased risk of lung cancer. However, previous studies have had limited ability to determine whether the association is due to smoking. METHODOLOGY/PRINCIPAL FINDINGS: The Environment And Genetics in Lung cancer Etiology (EAGLE) population-based case-control study recruited 2100 cases and 2120 controls, of whom 1934 cases and 2108 controls reported about diagnosis of chronic bronchitis, emphysema, COPD (chronic bronchitis and/or emphysema), or asthma more than 1 year before enrollment. We estimated odds ratios (OR) and 95% confidence intervals (CI) using logistic regression. After adjustment for smoking, other previous lung diseases, and study design variables, lung cancer risk was elevated among individuals with a history of chronic bronchitis (OR = 2.0, 95% CI = 1.5-2.5), emphysema (OR = 1.9, 95% CI = 1.4-2.8), or COPD (OR = 2.5, 95% CI = 2.0-3.1). Among current smokers, association between chronic bronchitis and lung cancer was strongest among lighter smokers. Asthma was associated with a decreased risk of lung cancer in males (OR = 0.48, 95% CI = 0.30-0.78). CONCLUSIONS/SIGNIFICANCE: These results suggest that the associations of personal history of chronic bronchitis, emphysema, and COPD with increased risk of lung cancer are not entirely due to smoking. Inflammatory processes may both contribute to COPD and be important for lung carcinogenesis.

Cancer du poumon

sommaire

(1) BARTON M, MEYER MR, BOLTON JL, PROSSNITZ ER. **Lung cancer and hormone replacement therapy**. Lancet. 2010 Jan. 9, vol. 375, n° 9709, pp.117-118
http://dx.doi.org/10.1016/S0140-6736(10)60041-4 **(accès réservé EHESP)**

(2) BOLUKBAS S, EBERLEIN M, SCHIRREN J. **Management of lung nodules detected by volume CT scanning**. N Engl J Med. 2010 Feb. 25, vol. 362, n° 8, pp.757-758
http://www.ncbi.nlm.nih.gov/pubmed/20191664 **(accès réservé EHESP)**

(3) CANONICO M, PLU-BUREAU, SCARABIN PY. **Lung cancer and hormone replacement therapy**. Lancet. 2010 Jan. 9, vol. 375, n° 9709, pp.117-119
http://dx.doi.org/10.1016/S0140-6736(10)60039-6 **(accès réservé EHESP)**

(4) CAREL H, JOHNSON S, GAMBLE L. **Living with lymphangioleiomyomatosis**. BMJ. 2010, vol. 340, p.c848
http://www.ncbi.nlm.nih.gov/pubmed/20228149 **(accès réservé EHESP)**

(5) GRANT EC. **Lung cancer and hormone replacement therapy**. Lancet. 2010 Jan. 9, vol. 375, n° 9709, pp.117-119
http://dx.doi.org/10.1016/S0140-6736(10)60040-2 **(accès réservé EHESP)**

(6) NAIR VS. **Management of lung nodules detected by volume CT scanning**. N Engl J Med. 2010 Feb. 25, vol. 362, n° 8, pp.757-759
http://dx.doi.org/10.1056/NEJMc0912888 **(accès réservé EHESP)**

(7) PAULUS JK, ASOMANING K, KRAFT P, JOHNSON BE, *et al.* **Parity and risk of lung cancer in women**. Am J Epidemiol. 2010 Mar. 1, vol. 171, n° 5, pp.557-563
http://dx.doi.org/10.1093/aje/kwp441 **(accès réservé EHESP)**

Patterns of lung cancer incidence suggest that gender-associated factors may influence lung cancer risk. Given the association of parity with risk of some women's cancers, the authors hypothesized that childbearing history may also be associated with lung cancer. Women enrolled in the Lung Cancer Susceptibility Study at Massachusetts General Hospital (Boston, Massachusetts) between 1992 and 2004 (1,004 cases, 848 controls) were available for analysis of the association between parity and lung cancer risk. Multivariate logistic regression was used to estimate adjusted odds ratios and 95% confidence intervals. After results were controlled for age and smoking history, women with at least 1 child had 0.71 times the odds of lung cancer as women without children (odds ratio = 0.71, 95% confidence interval: 0.52, 0.97). A significant linear trend was found: Lung cancer risk decreased with increasing numbers of children (P < 0.001). This inverse association was stronger in never smokers (P = 0.12) and was limited to women over age 50 years at diagnosis (P = 0.17). Age at first birth was not associated with risk. The authors observed a protective association between childbearing and lung cancer, adding to existing evidence that reproductive factors may moderate lung cancer risk in women

(8) SUH JH. **Stereotactic radiosurgery for the management of brain metastases**. N Engl J Med. 2010 Mar. 25, vol. 362, n° 12, pp.1119-1127
http://dx.doi.org/10.1056/NEJMct0806951 **(accès réservé EHESP)**

(9) TIMMERMAN R, PAULUS R, GALVIN J, MICHALSKI J, *et al.* **Stereotactic body radiation therapy for inoperable early stage lung cancer**. JAMA. 2010 Mar. 17, vol. 303, n° 11, pp.1070-1076
http://dx.doi.org/10.1001/jama.2010.261 **(accès réservé EHESP)**

CONTEXT: Patients with early stage but medically inoperable lung cancer have a poor rate of primary tumor control (30%-40%) and a high rate of mortality (3-year survival, 20%-35%) with current management. OBJECTIVE: To evaluate the toxicity and efficacy of stereotactic body radiation therapy in a high-risk population of patients with early stage but medically inoperable lung cancer. DESIGN, SETTING, AND PATIENTS: Phase 2 North American multicenter study of patients aged 18 years or older with biopsy-proven peripheral T1-T2N0M0 non-small cell tumors (measuring <5 cm in diameter) and medical conditions precluding surgical treatment. The prescription dose was 18 Gy per fraction x 3 fractions (54 Gy total) with entire treatment lasting between 1(1/2) and 2 weeks. The study opened May 26, 2004, and closed October 13, 2006; data were analyzed through August 31, 2009. MAIN OUTCOME MEASURES: The primary end point was 2-year actuarial primary tumor control; secondary end points were disease-free survival (ie, primary tumor, involved lobe, regional, and disseminated recurrence), treatment-related toxicity, and overall survival. RESULTS: A total of 59 patients accrued, of which 55 were evaluable (44 patients with T1 tumors and 11 patients with T2 tumors) with a median follow-up of 34.4 months (range, 4.8-49.9 months). Only 1 patient had a primary tumor failure; the estimated 3-year primary tumor control rate was 97.6% (95% confidence interval [CI], 84.3%-99.7%). Three patients had recurrence within the involved lobe; the 3-year primary tumor and involved lobe (local) control rate was 90.6% (95% CI, 76.0%-96.5%). Two patients experienced regional failure; the local-regional control rate was 87.2% (95% CI, 71.0%-94.7%). Eleven patients experienced disseminated recurrence; the 3-year rate of disseminated failure was 22.1% (95% CI, 12.3%-37.8%). The rates for disease-free survival and overall survival at 3 years were 48.3% (95% CI, 34.4%-60.8%) and 55.8% (95% CI, 41.6%-67.9%), respectively. The median overall survival was 48.1 months (95% CI, 29.6 months to not reached). Protocol-specified treatment-related grade 3 adverse events were reported in 7 patients (12.7%; 95% CI, 9.6%-15.8%); grade 4 adverse events were reported

in 2 patients (3.6%; 95% CI, 2.7%-4.5%). No grade 5 adverse events were reported. CONCLUSION: Patients with inoperable non-small cell lung cancer who received stereotactic body radiation therapy had a survival rate of 55.8% at 3 years, high rates of local tumor control, and moderate treatment-related morbidity

Dengue

sommaire

(1)TIPAYAMONGKHOLGUL M, FANG CT, KLINCHAN S, LIU CM, *et al.* **Effects of the El Nino-southern oscillation on dengue epidemics in Thailand, 1996-2005**. BMC Public Health. 2009, vol. 9, p.422
http://dx.doi.org/10.1186/1471-2458-9-422 **(accès libre)**

BACKGROUND: Despite intensive vector control efforts, dengue epidemics continue to occur throughout Southeast Asia in multi-annual cycles. Weather is considered an important factor in these cycles, but the extent to which the El Nino-Southern Oscillation (ENSO) is a driving force behind dengue epidemics remains unclear. METHODS: We examined the temporal relationship between El Nino and the occurrence of dengue epidemics, and constructed Poisson autoregressive models for incidences of dengue cases. Global ENSO records, dengue surveillance data, and local meteorological data in two geographically diverse regions in Thailand (the tropical southern coastal region and the northern inland mountainous region) were analyzed. RESULTS: The strength of El Nino was consistently a predictor for the occurrence of dengue epidemics throughout time lags from 1 to 11 months in the two selected regions of Thailand. Up to 22% (in 8 northern inland mountainous provinces) and 15% (in 5 southern tropical coastal provinces) of the variation in the monthly incidence of dengue cases were attributable to global ENSO cycles. Province-level predictive models were fitted using 1996-2004 data and validated with out-of-fit data from 2005. The multivariate ENSO index was an independent predictor in 10 of the 13 studied provinces. CONCLUSION: El Nino is one of the important driving forces for dengue epidemics across the geographically diverse regions of Thailand; however, spatial heterogeneity in the effect exists. The effects of El Nino should be taken into account in future epidemic forecasting for public health preparedness

Diabète

sommaire

(1)BALKAU B, SIMON D. **Survival in people with type 2 diabetes as a function of HbA(1c)**. Lancet. 2010 Feb. 6, vol. 375, n° 9713, pp.438-440
http://dx.doi.org/10.1016/S0140-6736(09)62192-9 **(accès réservé EHESP)**

(2) CANNON CP. **Balancing the benefits of statins versus a new risk-diabetes**. Lancet. 2010 Feb. 27, vol. 375, n° 9716, pp.700-701
http://dx.doi.org/10.1016/S0140-6736(10)60234-6 **(accès réservé EHESP)**

(3) CORDIDO F. **Insulin regimens in type 2 diabetes**. N Engl J Med. 2010 Mar. 11, vol. 362, n° 10, p.960
http://www.ncbi.nlm.nih.gov/pubmed/20225351 **(accès réservé EHESP)**

(4) CURRIE CJ, PETERS JR, TYNAN A, EVANS M, *et al.* **Survival as a function of HbA(1c) in people with type 2 diabetes: a retrospective cohort study**. Lancet. 2010 Feb. 6, vol. 375, n° 9713, pp.481-489
http://dx.doi.org/10.1016/S0140-6736(09)61969-3 **(accès réservé EHESP)**

BACKGROUND: Results of intervention studies in patients with type 2 diabetes have led to concerns about the safety of aiming for normal blood glucose concentrations. We assessed

survival as a function of HbA(1c) in people with type 2 diabetes. METHODS: Two cohorts of patients aged 50 years and older with type 2 diabetes were generated from the UK General Practice Research Database from November 1986 to November 2008. We identified 27 965 patients whose treatment had been intensified from oral monotherapy to combination therapy with oral blood-glucose lowering agents, and 20 005 who had changed to regimens that included insulin. Those with diabetes secondary to other causes were excluded. All-cause mortality was the primary outcome. Age, sex, smoking status, cholesterol, cardiovascular risk, and general morbidity were identified as important confounding factors, and Cox survival models were adjusted for these factors accordingly. FINDINGS: For combined cohorts, compared with the glycated haemoglobin (HbA(1c)) decile with the lowest hazard (median HbA(1c) 7.5%, IQR 7.5-7.6%), the adjusted hazard ratio (HR) of all-cause mortality in the lowest HbA(1c) decile (6.4%, 6.1-6.6) was 1.52 (95% CI 1.32-1.76), and in the highest HbA(1c) decile (median 10.5%, IQR 10.1-11.2%) was 1.79 (95% CI 1.56-2.06). Results showed a general U-shaped association, with the lowest HR at an HbA(1c) of about 7.5%. HR for all-cause mortality in people given insulin-based regimens (2834 deaths) versus those given combination oral agents (2035) was 1.49 (95% CI 1.39-1.59). INTERPRETATION: Low and high mean HbA(1c) values were associated with increased all-cause mortality and cardiac events. If confirmed, diabetes guidelines might need revision to include a minimum HbA(1c) value. FUNDING: Eli Lilly and Company

(5) DEANGELIS CD, FONTANAROSA PB. **Ensuring integrity in industry-sponsored research: primum non nocere, revisited**. JAMA. 2010 Mar. 24, vol. 303, n° 12, pp.1196-1198
http://dx.doi.org/10.1001/jama.2010.337 **(accès réservé EHESP)**

(6) GALE EA. **Maternal age and diabetes in childhood**. BMJ. 2010, vol. 340, p.c623
http://www.ncbi.nlm.nih.gov/pubmed/20181638 **(accès réservé EHESP)**

(7) HOVORKA R, ALLEN JM, ELLERI D, CHASSIN LJ, *et al.* **Manual closed-loop insulin delivery in children and adolescents with type 1 diabetes: a phase 2 randomised crossover trial**. Lancet. 2010 Feb. 27, vol. 375, n° 9716, pp.743-751
http://dx.doi.org/10.1016/S0140-6736(09)61998-X **(accès réservé EHESP)**

BACKGROUND: Closed-loop systems link continuous glucose measurements to insulin delivery. We aimed to establish whether closed-loop insulin delivery could control overnight blood glucose in young people. METHODS: We undertook three randomised crossover studies in 19 patients aged 5-18 years with type 1 diabetes of duration 6.4 years (SD 4.0). We compared standard continuous subcutaneous insulin infusion and closed-loop delivery (n=13; APCam01); closed-loop delivery after rapidly and slowly absorbed meals (n=7; APCam02); and closed-loop delivery and standard treatment after exercise (n=10; APCam03). Allocation was by computer-generated random code. Participants were masked to plasma and sensor glucose. In APCam01, investigators were masked to plasma glucose. During closed-loop nights, glucose measurements were fed every 15 min into a control algorithm calculating rate of insulin infusion, and a nurse adjusted the insulin pump. During control nights, patients' standard pump settings were applied. Primary outcomes were time for which plasma glucose concentration was 3.91-8.00 mmol/L or 3.90 mmol/L or lower. Analysis was per protocol. This trial is registered, number ISRCTN18155883. FINDINGS: 17 patients were studied for 33 closed-loop and 21 continuous infusion nights. Primary outcomes did not differ significantly between treatment groups in APCam01 (12 analysed; target range, median 52% [IQR 43-83] closed loop vs 39% [15-51] standard treatment, p=0.06; <or=3.90 mmol/L, 1% [0-7] vs 2% [0-41], p=0.13), APCam02 (six analysed; target range, rapidly 53% [48-57] vs slowly absorbed meal 55% [37-64], p=0.97; <or=3.90 mmol/L, 0% [0-4] vs 0% [0-0], p=0.16]), and APCam03 (nine analysed; target range 78% [60-92] closed loop vs 43% [25-65] control, p=0.0245, not significant at corrected level; <or=3.90 mmol/L, 10% [2-15] vs 6% [0-44], p=0.27). A secondary analysis of pooled data documented increased time in the target range (60% [51-88] vs 40% [18-61]; p=0.0022) and reduced time for which glucose concentrations were 3.90 mmol/L or lower (2.1% (0.0-10.0) vs 4.1% (0.0-42.0); p=0.0304). No events with plasma glucose concentration lower than 3.0 mmol/L were recorded during closed-loop delivery, compared with nine events during standard treatment.

INTERPRETATION: Closed-loop systems could reduce risk of nocturnal hypoglycaemia in children and adolescents with type 1 diabetes. FUNDING: Juvenile Diabetes Research Foundation; European Foundation for Study of Diabetes; Medical Research Council Centre for Obesity and Related Metabolic Diseases; National Institute for Health Research Cambridge Biomedical Research Centre

(8) JONES RG, TRIVEDI AN, AYANIAN JZ. **Factors influencing the effectiveness of interventions to reduce racial and ethnic disparities in health care**. Soc Sci Med. 2010 Feb., vol. 70, n° 3, pp.337-341
http://dx.doi.org/10.1016/j.socscimed.2009.10.030 **(accès réservé EHESP)**

Reducing racial and ethnic disparities in health care has become an important policy goal in the United States and other countries, but evidence to inform interventions to address disparities is limited. The objective of this study was to identify important dimensions of interventions to reduce health care disparities. We used qualitative research methods to examine interventions aimed at improving diabetes and/or cardiovascular care for patients from racial and ethnic minority groups within five health care organizations. We interviewed 36 key informants and conducted a thematic analysis to identify important features of these interventions. Key elements of interventions included two contextual factors (external accountability and alignment of incentives to reduce disparities) and four factors related to the organization or intervention itself (organizational commitment, population health focus, use of data to inform solutions, and a comprehensive approach to quality). Consideration of these elements could improve the design, implementation, and evaluation of future interventions to address racial and ethnic disparities in health care

(9) KAPTOGE S, DI AE, LOWE G, PEPYS MB, *et al.* **C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis**. Lancet. 2010 Jan. 9, vol. 375, n° 9709, pp.132-140
http://dx.doi.org/10.1016/S0140-6736(09)61717-7 **(accès réservé EHESP)**

BACKGROUND: Associations of C-reactive protein (CRP) concentration with risk of major diseases can best be assessed by long-term prospective follow-up of large numbers of people. We assessed the associations of CRP concentration with risk of vascular and non-vascular outcomes under different circumstances. METHODS: We meta-analysed individual records of 160 309 people without a history of vascular disease (ie, 1.31 million person-years at risk, 27 769 fatal or non-fatal disease outcomes) from 54 long-term prospective studies. Within-study regression analyses were adjusted for within-person variation in risk factor levels. RESULTS: Log(e) CRP concentration was linearly associated with several conventional risk factors and inflammatory markers, and nearly log-linearly with the risk of ischaemic vascular disease and non-vascular mortality. Risk ratios (RRs) for coronary heart disease per 1-SD higher log(e) CRP concentration (three-fold higher) were 1.63 (95% CI 1.51-1.76) when initially adjusted for age and sex only, and 1.37 (1.27-1.48) when adjusted further for conventional risk factors; 1.44 (1.32-1.57) and 1.27 (1.15-1.40) for ischaemic stroke; 1.71 (1.53-1.91) and 1.55 (1.37-1.76) for vascular mortality; and 1.55 (1.41-1.69) and 1.54 (1.40-1.68) for non-vascular mortality. RRs were largely unchanged after exclusion of smokers or initial follow-up. After further adjustment for fibrinogen, the corresponding RRs were 1.23 (1.07-1.42) for coronary heart disease; 1.32 (1.18-1.49) for ischaemic stroke; 1.34 (1.18-1.52) for vascular mortality; and 1.34 (1.20-1.50) for non-vascular mortality. INTERPRETATION: CRP concentration has continuous associations with the risk of coronary heart disease, ischaemic stroke, vascular mortality, and death from several cancers and lung disease that are each of broadly similar size. The relevance of CRP to such a range of disorders is unclear. Associations with ischaemic vascular disease depend considerably on conventional risk factors and other markers of inflammation. FUNDING: British Heart Foundation, UK Medical Research Council, BUPA Foundation, and GlaxoSmithKline

(10) KRISHNAN S, COZIER YC, ROSENBERG L, PALMER JR. **Socioeconomic status and incidence of type 2 diabetes: results from the Black Women's Health Study**. Am J Epidemiol. 2010 Mar. 1, vol. 171, n° 5, pp.564-570
http://dx.doi.org/10.1093/aje/kwp443 **(accès réservé EHESP)**

The authors examined the relation between individual and neighborhood socioeconomic status (SES) and type 2 diabetes incidence among African-American women in the prospective Black Women's Health Study. Participants have completed mailed biennial follow-up questionnaires since 1995. US Census block group characteristics were used to measure neighborhood SES. Incidence rate ratios were estimated in clustered survival regression models. During 12 years of follow-up of 46,382 participants aged 30-69 years, 3,833 new cases of type 2 diabetes occurred. In models that included both individual and neighborhood SES factors, incidence rate ratios were 1.28 (95% confidence interval: 1.15, 1.43) for < or = 12 years of education relative to > or = 17 years, 1.57 (95% confidence interval: 1.30, 1.90) for household income <$15,000 relative to >$100,000, and 1.65 (95% confidence interval: 1.46, 1.85) for lowest quintile of neighborhood SES relative to highest. The associations were attenuated after adjustment for body mass index, suggesting it is the key intermediate factor in the pathway between SES and diabetes. The association of neighborhood SES with diabetes incidence was present even among women who were more educated and had a higher family income. Efforts to reduce the alarming rate of diabetes in African-American women must focus on both individual lifestyle changes and structural changes in disadvantaged neighborhoods

(11) LEHMAN R, KRUMHOLZ HM. **Glycated haemoglobin below 7%. No to QOF target of less than 7%, again**. BMJ. 2010, vol. 340, p.c985
http://www.ncbi.nlm.nih.gov/pubmed/20179124 **(accès réservé EHESP)**

(12) LEVESQUE LE, HANLEY JA, KEZOUH A, SUISSA S. **Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes**. BMJ. 2010, vol. 340, p.b5087
http://www.ncbi.nlm.nih.gov/pubmed/20228141 **(accès réservé EHESP)**

(13) LOMMERSE K, MWAGOMBA B, VAN DEN AT. **White blood**. Lancet. 2010 Mar. 6, vol. 375, n° 9717, p.801
http://dx.doi.org/10.1016/S0140-6736(10)60336-4 **(accès réservé EHESP)**

(14) LUND SS, VAAG AA. **Insulin regimens in type 2 diabetes**. N Engl J Med. 2010 Mar. 11, vol. 362, n° 10, p.959
http://dx.doi.org/362/10/959 [pii];10.1056/NEJMc0911551 **(accès réservé EHESP)**

(15) MAITRA S. **Can patient self-management explain the health gradient? Goldman and Smith's "Can patient self-management help explain the SES health gradient?" (2002) revisited**. Soc Sci Med. 2010 Mar., vol. 70, n° 6, pp.802-812
http://dx.doi.org/10.1016/j.socscimed.2009.08.043 **(accès réservé EHESP)**

In their much-cited paper, "Can patient self-management help explain the SES health gradient?"Goldman and Smith (2002) use samples of diabetic and HIV+ patients in the United States to conclude that disease self-management is an important explanation for the much-documented positive gradient in education and health outcomes. In this paper, I revisit their analysis and point to some fundamental difficulties in interpreting their results as conclusive evidence in favor of self-management. I also argue that for individuals for whom self-management might be expected to matter -i.e. populations of patients managing complex conditions - economic factors such as resource availability and insurance access might be a more important mechanism behind the gradient than medical compliance. The impact of self-management, though it might matter, is likely to be small

(16) MARGOLIS KL, O'CONNOR PJ, SPERL-HILLEN JM. **Insulin regimens in type 2 diabetes**. N Engl J Med. 2010 Mar. 11, vol. 362, n° 10, pp.959-960
http://www.ncbi.nlm.nih.gov/pubmed/20225350 **(accès réservé EHESP)**

(17) MAYOR S. **Nearly 23,000 people in England aged under 18 have diabetes, survey shows**. BMJ. 2010, vol. 340, p.c980
http://www.ncbi.nlm.nih.gov/pubmed/20164136 **(accès réservé EHESP)**

(18) MITKA M. **Aggressive glycemic control might not be best choice for all diabetic patients**. JAMA. 2010 Mar. 24, vol. 303, n° 12, pp.1137-1138
http://dx.doi.org/10.1001/jama.2010.298 **(accès réservé EHESP)**

(19) NAGAFUCHI S, KATSUTA H, ANZAI K. **Rituximab, B-lymphocyte depletion, and beta-cell function**. N Engl J Med. 2010 Feb. 25, vol. 362, n° 8, p.761
http://dx.doi.org/10.1056/NEJMc0912877 **(accès réservé EHESP)**

(20) NISSEN SE. **Setting the RECORD Straight**. JAMA. 2010 Mar. 24, vol. 303, n° 12, pp.1194-1195
http://dx.doi.org/10.1001/jama.2010.333 **(accès réservé EHESP)**

(21) PARKS M, ROSEBRAUGH C. **Weighing risks and benefits of liraglutide--the FDA's review of a new antidiabetic therapy** . N Engl J Med. 2010 Mar. 4, vol. 362, n° 9, pp.774-777
http://dx.doi.org/10.1056/NEJMp1001578 **(accès réservé EHESP)**

(22) RENARD E. **Closed-loop insulin delivery: is the holy grail near?** Lancet. 2010 Feb. 27, vol. 375, n° 9716, pp.702-703
http://dx.doi.org/10.1016/S0140-6736(09)62165-6 **(accès réservé EHESP)**

(23) SATTAR N, PREISS D, MURRAY HM, WELSH P, *et al.* **Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials**. Lancet. 2010 Feb. 27, vol. 375, n° 9716, pp.735-742
http://dx.doi.org/10.1016/S0140-6736(09)61965-6 **(accès réservé EHESP)**

BACKGROUND: Trials of statin therapy have had conflicting findings on the risk of development of diabetes mellitus in patients given statins. We aimed to establish by a meta-analysis of published and unpublished data whether any relation exists between statin use and development of diabetes. METHODS: We searched Medline, Embase, and the Cochrane Central Register of Controlled Trials from 1994 to 2009, for randomised controlled endpoint trials of statins. We included only trials with more than 1000 patients, with identical follow-up in both groups and duration of more than 1 year. We excluded trials of patients with organ transplants or who needed haemodialysis. We used the I(2) statistic to measure heterogeneity between trials and calculated risk estimates for incident diabetes with random-effect meta-analysis. FINDINGS: We identified 13 statin trials with 91 140 participants, of whom 4278 (2226 assigned statins and 2052 assigned control treatment) developed diabetes during a mean of 4 years. Statin therapy was associated with a 9% increased risk for incident diabetes (odds ratio [OR] 1.09; 95% CI 1.02-1.17), with little heterogeneity (I(2)=11%) between trials. Meta-regression showed that risk of development of diabetes with statins was highest in trials with older participants, but neither baseline body-mass index nor change in LDL-cholesterol concentrations accounted for residual variation in risk. Treatment of 255 (95% CI 150-852) patients with statins for 4 years resulted in one extra case of diabetes. INTERPRETATION: Statin therapy is associated with a slightly increased risk of development of diabetes, but the risk is low both in absolute terms and when compared with the reduction in coronary events. Clinical practice in patients with moderate or high cardiovascular risk or existing cardiovascular disease should not change. FUNDING: None

(24) SELVIN E, STEFFES MW, ZHU H, MATSUSHITA K, *et al.* **Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults**. N Engl J Med. 2010 Mar. 4, vol. 362, n° 9, pp.800-811
http://dx.doi.org/10.1056/NEJMoa0908359 **(accès réservé EHESP)**

BACKGROUND: Fasting glucose is the standard measure used to diagnose diabetes in the United States. Recently, glycated hemoglobin was also recommended for this purpose. METHODS: We compared the prognostic value of glycated hemoglobin and fasting glucose for identifying adults at risk for diabetes or cardiovascular disease. We measured glycated hemoglobin in whole-blood samples from 11,092 black or white adults who did not have a history of diabetes or cardiovascular disease and who attended the second visit (occurring in the 1990-1992 period) of the Atherosclerosis Risk in Communities (ARIC) study. RESULTS: The glycated hemoglobin value at baseline was associated with newly diagnosed diabetes and cardiovascular outcomes. For glycated hemoglobin values of less than 5.0%, 5.0 to less than 5.5%, 5.5 to less than 6.0%, 6.0 to less than 6.5%, and 6.5% or greater, the multivariable-adjusted hazard ratios (with 95% confidence intervals) for diagnosed diabetes were 0.52 (0.40 to 0.69), 1.00 (reference), 1.86 (1.67 to 2.08), 4.48 (3.92 to 5.13), and 16.47 (14.22 to 19.08), respectively. For coronary heart disease, the hazard ratios were 0.96 (0.74 to 1.24), 1.00 (reference), 1.23 (1.07 to 1.41), 1.78 (1.48 to 2.15), and 1.95 (1.53 to 2.48), respectively. The hazard ratios for stroke were similar. In contrast, glycated hemoglobin and death from any cause were found to have a J-shaped association curve. All these associations remained significant after adjustment for the baseline fasting glucose level. The association between the fasting glucose levels and the risk of cardiovascular disease or death from any cause was not significant in models with adjustment for all covariates as well as glycated hemoglobin. For coronary heart disease, measures of risk discrimination showed significant improvement when glycated hemoglobin was added to models including fasting glucose. CONCLUSIONS: In this community-based population of nondiabetic adults, glycated hemoglobin was similarly associated with a risk of diabetes and more strongly associated with risks of cardiovascular disease and death from any cause as compared with fasting glucose. These data add to the evidence supporting the use of glycated hemoglobin as a diagnostic test for diabetes

(25) SMITH SB, QU HQ, TALEB N, KISHIMOTO NY, *et al.* **Rfx6 directs islet formation and insulin production in mice and humans**. Nature. 2010 Feb. 11, vol. 463, n° 7282, pp.775-780
http://dx.doi.org/10.1038/nature08748 **(accès payant)**

Insulin from the beta-cells of the pancreatic islets of Langerhans controls energy homeostasis in vertebrates, and its deficiency causes diabetes mellitus. During embryonic development, the transcription factor neurogenin 3 (Neurog3) initiates the differentiation of the beta-cells and other islet cell types from pancreatic endoderm, but the genetic program that subsequently completes this differentiation remains incompletely understood. Here we show that the transcription factor Rfx6 directs islet cell differentiation downstream of Neurog3. Mice lacking Rfx6 failed to generate any of the normal islet cell types except for pancreatic-polypeptide-producing cells. In human infants with a similar autosomal recessive syndrome of neonatal diabetes, genetic mapping and subsequent sequencing identified mutations in the human RFX6 gene. These studies demonstrate a unique position for Rfx6 in the hierarchy of factors that coordinate pancreatic islet development in both mice and humans. Rfx6 could prove useful in efforts to generate beta-cells for patients with diabetes

(26) SPENCE D. **Bad medicine: type 2 diabetes**. BMJ. 2010, vol. 340, p.c1216
http://www.ncbi.nlm.nih.gov/pubmed/20200060 **(accès réservé EHESP)**

(27) TEELUCKSINGH S, NARAYNSINGH V. **Images in clinical medicine. Neuropathic ulceration**. N Engl J Med. 2010 Mar. 4, vol. 362, n° 9, p.e26
http://dx.doi.org/10.1056/NEJMicm0810905 **(accès réservé EHESP)**

(28) WANG AT, MCCOY CP, MURAD MH, MONTORI VM. **Association between industry affiliation and position on cardiovascular risk with rosiglitazone: cross sectional systematic review**. BMJ. 2010, vol. 340, p.c1344
http://www.ncbi.nlm.nih.gov/pubmed/20299696 **(accès réservé EHESP)**

OBJECTIVE: To explore a possible link between authors' financial conflicts of interest and their position on the association of rosiglitazone with increased risk of myocardial infarction in patients with diabetes. DATA SOURCES: On 10 April 2009, we searched Web of Science and Scopus for articles citing and commenting on either of two index publications that contributed key data to the controversy (a meta-analysis of small trials and a subsequent large trial). Data selection Articles had to comment on rosiglitazone and the risk of myocardial infarction. Guidelines, meta-analyses, reviews, clinical trials, letters, commentaries, and editorials were included. DATA EXTRACTION: For each article, we sought information about the authors' financial conflicts of interest in the report itself and elsewhere (that is, in all publications within two years of the original publication and online). Two reviewers blinded to the authors' financial relationships independently classified each article as presenting a favourable (that is, rosiglitazone does not increase the risk of myocardial infarction), neutral, or unfavourable view on the risk of myocardial infarction with rosiglitazone and on recommendations on the use of the drug. RESULTS: Of the 202 included articles, 108 (53%) had a conflict of interest statement. Ninety authors (45%) had financial conflicts of interest. Authors who had a favourable view of the risk of myocardial infarction with rosiglitazone were more likely to have financial conflicts of interest with manufacturers of antihyperglycaemic agents in general, and with rosiglitazone manufacturers in particular, than authors who had an unfavourable view (rate ratio 3.38, 95% CI 2.26 to 5.06 and 4.29, 2.63 to 7.02, respectively). There was likewise a strong association between favourable recommendations on the use of rosiglitazone and financial conflicts of interest (3.36, 1.94 to 5.83). These links persisted when articles rather than authors were used as the unit of analysis (4.69, 2.84 to 7.72), when the analysis was restricted to opinion articles (6.29, 2.15 to 18.38) or to articles in which the rosiglitazone controversy was the main focus (6.50, 2.56 to 16.53), and both in articles published before and after the Food and Drug Administration issued a safety warning for rosiglitazone (3.43, 0.99 to 11.82 and 4.95, 2.87 to 8.53, respectively). CONCLUSIONS: Disclosure rates for financial conflicts of interest were unexpectedly low, and there was a clear and strong link between the orientation of authors' expressed views on the rosiglitazone controversy and their financial conflicts of interest with pharmaceutical companies. Although these findings do not necessarily indicate a causal link between the position taken on the cardiac risk of rosiglitazone in patients with diabetes and the authors' financial conflicts of interest, they underscore the need for further changes in disclosure procedures in order for the scientific record to be trusted

(29) WARING ME, EATON CB, LASATER TM, LAPANE KL. **Incident diabetes in relation to weight patterns during middle age**. Am J Epidemiol. 2010 Mar. 1, vol. 171, n° 5, pp.550-556
http://dx.doi.org/10.1093/aje/kwp433 **(accès réservé EHESP)**

The authors examined the association between weight patterns during middle age and incident type 2 diabetes mellitus using a subset (n = 1,476) of the Framingham Heart Study original cohort limited-access data set (1948-2003). Participants diagnosed with diabetes before age 50 years were excluded. A functional principal components analysis of body mass index from age 40 years to age 50 years was used to define weight patterns in terms of overall weight status (normal weight, overweight, or obese), weight change (weight loss, stable weight, or weight gain), and weight cycling. Overall overweight and obesity were associated with higher rates of diabetes (for overall overweight, crude hazard ratio (HR) = 3.2, 95% confidence interval (CI): 2.3, 4.6; for overall obesity, crude HR = 8.8, 95% CI: 6.0, 12.8). Weight cycling was also associated with higher rates of diabetes (crude HR = 1.6, 95% CI: 1.2, 2.1). Neither weight loss nor weight gain was associated with incident diabetes. After adjustment for overall weight status, weight cycling was no longer associated with higher rates of diabetes. This study underscores the importance of obesity in diabetes risk and the importance of preventing the development of overweight and obesity earlier in life

(30) WEISS SH. **Niacin compared with ezetimibe**. N Engl J Med. 2010 Mar. 18, vol. 362, n° 11, p.1047
http://www.ncbi.nlm.nih.gov/pubmed/20301797 **(accès réservé EHESP)**

(31) YANG W, LU J, WENG J, JIA W, *et al.* **Prevalence of diabetes among men and women in China**. N Engl J Med. 2010 Mar. 25, vol. 362, n° 12, pp.1090-1101
http://dx.doi.org/10.1056/NEJMoa0908292 **(accès réservé EHESP)**

BACKGROUND: Because of the rapid change in lifestyle in China, there is concern that diabetes may become epidemic. We conducted a national study from June 2007 through May 2008 to estimate the prevalence of diabetes among Chinese adults. METHODS: A nationally representative sample of 46,239 adults, 20 years of age or older, from 14 provinces and municipalities participated in the study. After an overnight fast, participants underwent an oral glucose-tolerance test, and fasting and 2-hour glucose levels were measured to identify undiagnosed diabetes and prediabetes (i.e., impaired fasting glucose or impaired glucose tolerance). Previously diagnosed diabetes was determined on the basis of self-report. RESULTS: The age-standardized prevalences of total diabetes (which included both previously diagnosed diabetes and previously undiagnosed diabetes) and prediabetes were 9.7% (10.6% among men and 8.8% among women) and 15.5% (16.1% among men and 14.9% among women), respectively, accounting for 92.4 million adults with diabetes (50.2 million men and 42.2 million women) and 148.2 million adults with prediabetes (76.1 million men and 72.1 million women). The prevalence of diabetes increased with increasing age (3.2%, 11.5%, and 20.4% among persons who were 20 to 39, 40 to 59, and > or = 60 years of age, respectively) and with increasing weight (4.5%, 7.6%, 12.8%, and 18.5% among persons with a body-mass index [the weight in kilograms divided by the square of the height in meters] of < 18.5, 18.5 to 24.9, 25.0 to 29.9, and > or = 30.0, respectively). The prevalence of diabetes was higher among urban residents than among rural residents (11.4% vs. 8.2%). The prevalence of isolated impaired glucose tolerance was higher than that of isolated impaired fasting glucose (11.0% vs. 3.2% among men and 10.9% vs. 2.2% among women). CONCLUSIONS: These results indicate that diabetes has become a major public health problem in China and that strategies aimed at the prevention and treatment of diabetes are needed

Dépression

sommaire

(1)ANGHELESCU I. **Omega-3 fatty acids for CHD with depression**. JAMA. 2010 Mar. 3, vol. 303, n° 9, p.836
http://dx.doi.org/10.1001/jama.2010.190 **(accès réservé EHESP)**

(2) CHANG MW, BROWN R, NITZKE S. **Participant recruitment and retention in a pilot program to prevent weight gain in low-income overweight and obese mothers**. BMC Public Health. 2009, vol. 9, p.424
http://dx.doi.org/10.1186/1471-2458-9-424 **(accès libre)**

BACKGROUND: Recruitment and retention are key functions for programs promoting nutrition and other lifestyle behavioral changes in low-income populations. This paper describes strategies for recruitment and retention and presents predictors of early (two-month post intervention) and late (eight-month post intervention) dropout (non retention) and overall retention among young, low-income overweight and obese mothers participating in a community-based randomized pilot trial called Mothers In Motion. METHODS: Low-income overweight and obese African American and white mothers ages 18 to 34 were recruited from the Special Supplemental Nutrition Program for Women, Infants, and Children in southern Michigan. Participants (n = 129) were randomly assigned to an intervention (n = 64) or control (n = 65) group according to a stratification procedure to equalize representation in two racial groups (African American and white) and three body mass index categories (25.0-29.9 kg/m(2), 30.0-34.9 kg/m(2), and 35.0-39.9 kg/m(2)). The 10-week theory-based culturally sensitive intervention focused on healthy eating, physical activity, and stress management messages that were delivered via an interactive DVD and reinforced by five peer-support group teleconferences. Forward stepwise multiple logistic regression was performed to examine whether dietary fat, fruit and vegetable intake behaviors, physical activity,

perceived stress, positive and negative affect, depression, and race predicted dropout as data were collected two-month and eight-month after the active intervention phase. RESULTS: Trained personnel were successful in recruiting subjects. Increased level of depression was a predictor of early dropout (odds ratio = 1.04; 95% CI = 1.00, 1.08; p = 0.03). Greater stress predicted late dropout (odds ratio = 0.20; 95% CI = 0.00, 0.37; p = 0.01). Dietary fat, fruit, and vegetable intake behaviors, physical activity, positive and negative affect, and race were not associated with either early or late dropout. Less negative affect was a marginal predictor of participant retention (odds ratio = 0.57; 95% CI = 0.31, 1.03; p = 0.06). CONCLUSION: Dropout rates in this study were higher for participants who reported higher levels of depression and stress. TRIAL REGISTRATION: Current Controlled Trials NCT00944060

(3) GARBARSKI D. **Perceived social position and health: Is there a reciprocal relationship?** Soc Sci Med. 2010 Mar., vol. 70, n° 5, pp.692-699
http://dx.doi.org/10.1016/j.socscimed.2009.11.007 **(accès réservé EHESP)**

Recent work exploring the relationship between socioeconomic status and health has employed a psychosocial concept called perceived social position as a predictor of health. Perceived social position is likely the "cognitive averaging" (Singh-Manoux, Marmot, & Adler, 2005) of socioeconomic characteristics over time and, like other socioeconomic factors, is subject to interplay with health over the life course. Based on the hypothesis that health can also affect perceived social position, in this paper we used structural equation modeling to examine whether perceived social position and three different health outcomes were reciprocally related in the Wisconsin Longitudinal Study, a longitudinal cohort study of older adults in the United States. The relationship between perceived social position and health differed across health outcomes-self-reported health, the Health Utilities Index, and depressive symptoms-as well as across operationalization of perceived social position-compared to the population of the United States, compared to one's community, and a latent variable of which the two items are indicators. We found that perceived social position affected self-reported health when operationalized as latent and US perceived social position, yet there was a reciprocal relationship between self-reported health and community perceived social position. There was a reciprocal relationship between perceived social position and the Health Utilities Index, and depressive symptoms affected perceived social position for all operationalization of perceived social position. The findings suggest that the causal relationship hypothesized in prior studies--that perceived social position affects health--does not necessarily hold in empirical models of reciprocal relationships. Future research should interrogate the relationship between perceived social position and health rather than assume the direction of causality in their relationship

(4) HOLDEN C. **Psychiatry. Experts map the terrain of mood disorders**. Science. 2010 Feb. 26, vol. 327, n° 5969, p.1068
http://dx.doi.org/10.1126/science.327.5969.1068-a **(accès réservé EHESP)**

(5) ILIFFE S, PEALING L. **Subjective memory problems**. BMJ. 2010, vol. 340, p.c1425
http://www.ncbi.nlm.nih.gov/pubmed/20304935 **(accès réservé EHESP)**

(6) JENKINSON ML. **SSRIs and tamoxifen. Why condemn fluoxetine?** BMJ. 2010, vol. 340, p.c1319
http://www.ncbi.nlm.nih.gov/pubmed/20219794 **(accès réservé EHESP)**

(7) JENSEN RA, SHEA S, RANJIT N, EZ-ROUX A, *et al.* **Psychosocial risk factors and retinal microvascular signs: the multi-ethnic study of atherosclerosis**. Am J Epidemiol. 2010 Mar. 1, vol. 171, n° 5, pp.522-531
http://dx.doi.org/10.1093/aje/kwp414 **(accès réservé EHESP)**

The association between psychosocial risk factors and retinal microvascular signs was examined in the Multi-Ethnic Study of Atherosclerosis. Subjects were recruited from Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; New York, New

York; and St. Paul, Minnesota. Levels of depressive symptoms, trait anger, trait anxiety, chronic burdens, emotional support, and cynical distrust were assessed by questionnaire (from July 2000 to July 2002). Digital retinal images (from August 2002 to January 2004) from 6,147 participants were used to evaluate retinopathy and retinal vascular caliber. After controlling for potential confounding factors, the authors found that subjects without access to emotional support (Enriched Social Support Instrument score of <19 vs. > or = 19) had 60% greater odds of retinopathy (odds ratio = 1.6, 95% confidence interval (CI): 1.3, 2.0). Subjects with high Spielberger trait-anxiety scale scores (> or = 22 vs. < or = 14) and subjects with high depressive symptoms (Center for Epidemiology Studies Depression Scale score, > or = 16 vs. <16) were also more likely to have retinopathy (odds ratio = 1.4, 95% CI: 1.1, 1.9 and odds ratio = 1.5, 95% CI: 1.2, 1.9), respectively. In this cross-sectional study, lack of emotional support, increased trait anxiety, and more depressive symptoms were associated with retinopathy signs, independently of other known risk factors

(8) KRAMER T, ILIFFE S, MILLER L, GLEDHILL J, *et al.* **Depression in adolescents. Collaboration to overcome barriers in primary care**. BMJ. 2010, vol. 340, p.c908
http://www.ncbi.nlm.nih.gov/pubmed/20160321 **(accès réservé EHESP)**

Grippe A

sommaire

(1) HANSLIK T, BOELLE PY, FLAHAULT A. **Preliminary estimation of risk factors for admission to intensive care units and for death in patients infected with A(H1N1)2009 influenza virus, France, 2009-2010**. PLoS Curr Influenza. 2010, p.RRN1150
http://www.ncbi.nlm.nih.gov/pubmed/20228857

To estimate the magnitude of the risks associated with age, obesity, pregnancy and diabetes, we compared the prevalence of these conditions reported in hospitalized severe cases to that in the general population, during the 2009-2010 A(H1N1) pandemic flu in France. Pregnancy, obesity, heart failure and diabetes were risk factors for admission into an intensive care unit (OR=5.2 [95%CI 4.0-6.9], 3.8 [3.0-4.9], 3.3 [2.6-4.1] and 2.8 [2.3-3.4], respectively). Only heart failure, obesity, and diabetes were significantly associated with death (OR=6.9 [4.9-9.8], 3.6 [1.9-6.2], and 3.5 [2.5-5.1], respectively). Elderly adults were at lower risk of being admitted into an ICU, but at higher risk of death

(2) **Critical illness due to 2009 A/H1N1 influenza in pregnant and postpartum women: population based cohort study**. BMJ. 2010, vol. 340, p.c1279
http://www.ncbi.nlm.nih.gov/pubmed/20299694 **(accès réservé EHESP)**

OBJECTIVE: To describe the epidemiology of 2009 A/H1N1 influenza in critically ill pregnant women. DESIGN: Population based cohort study. SETTING: All intensive care units in Australia and New Zealand. PARTICIPANTS: All women with 2009 H1N1 influenza who were pregnant or recently post partum and admitted to an intensive care unit in Australia or New Zealand between 1 June and 31 August 2009. MAIN OUTCOME MEASURES: Maternal and neonatal mortality and morbidity. RESULTS: 64 pregnant or postpartum women admitted to an intensive care unit had confirmed 2009 H1N1 influenza. Compared with non-pregnant women of childbearing age, pregnant or postpartum women with 2009 H1N1 influenza were at increased risk of admission to an intensive care unit (relative risk 7.4, 95% confidence interval 5.5 to 10.0). This risk was 13-fold greater (13.2, 9.6 to 18.3) for women at 20 or more weeks' gestation. At the time of admission to an intensive care unit, 22 women (34%) were post partum and two had miscarried. 14 women (22%) gave birth during their stay in intensive care and 26 (41%) were discharged from an intensive care unit with ongoing pregnancy. All subsequently delivered. 44 women (69%) were mechanically ventilated. Of these, nine (14%) were treated with extracorporeal membrane oxygenation. Seven women (11%) died. Of 60 births after 20 weeks' gestation, four were stillbirths and three were infant deaths. 22 (39%) of the liveborn babies were preterm and 32 (57%) were admitted to a neonatal intensive care unit. Of 20 babies tested, two were positive for the 2009

H1N1 virus. CONCLUSIONS: Pregnancy is a risk factor for critical illness related to 2009 H1N1 influenza, which causes maternal and neonatal morbidity and mortality

(3) BROWN LH, AITKEN P, LEGGAT PA, SPEARE R. **Self-reported anticipated compliance with physician advice to stay home during pandemic (H1N1) 2009: results from the 2009 Queensland Social Survey**. BMC Public Health. 2010, vol. 10, p.138
http://dx.doi.org/10.1186/1471-2458-10-138 **(accès libre)**

BACKGROUND: One strategy available to public health officials during a pandemic is physician recommendations for isolation of infected individuals. This study was undertaken during the height of the Australian pandemic (H1N1) 2009 outbreak to measure self-reported willingness to comply with physician recommendations to stay home for seven days, and to compare responses for the current strain of pandemic influenza, avian influenza, seasonal influenza, and the common cold. METHODS: Data were collected as part of the Queensland Social Survey (QSS) 2009, which consisted of a standardized introduction, 37 demographic questions, and research questions incorporated through a cost-sharing arrangement. Four questions related to respondents' anticipated compliance with a physician's advice to stay home if they had a common cold, seasonal influenza, pandemic (H1N1) 2009 influenza or avian influenza were incorporated into QSS 2009, with responses recorded using a balanced Likert scale ranging from "very unlikely" to "very likely." Discordance between responses for different diseases was analysed using McNemar's test. Associations between demographic variables and anticipated compliance were analysed using Pearson's chi-square or chi-square for linear-by-linear association, and confirmed using multivariate logistic regression; $p < 0.05$ was used to establish statistical significance. RESULTS: Self-reported anticipated compliance increased from 59.9% for the common cold to 71.3% for seasonal influenza ($p < .001$), and to 95.0% for pandemic (H1N1) 2009 influenza and 94.7% for avian influenza ($p < 0.001$ for both versus seasonal influenza). Anticipated compliance did not differ for pandemic (H1N1) 2009 and avian influenza ($p = 0.815$). Age and sex were both associated with anticipated compliance in the setting of seasonal influenza and the common cold. Notably, 27.1% of health and community service workers would not comply with physician advice to stay home for seasonal influenza. CONCLUSIONS: Ninety-five percent of people report they would comply with a physicians' advice to stay home for seven days if they are diagnosed with pandemic (H1N1) 2009 or avian influenza, but only 71% can be expected to comply in the setting of seasonal influenza and fewer still can be expected to comply if they are diagnosed with a common cold. Sub-populations that might be worthwhile targets for public health messages aimed at increasing the rate of self-imposed isolation for seasonal influenza include males, younger people, and healthcare workers

(4) CADY SD, SCHMIDT-ROHR K, WANG J, SOTO CS, *et al.* **Structure of the amantadine binding site of influenza M2 proton channels in lipid bilayers**. Nature. 2010 Feb. 4, vol. 463, n° 7281, pp.689-692
http://dx.doi.org/10.1038/nature08722 **(accès payant)**

The M2 protein of influenza A virus is a membrane-spanning tetrameric proton channel targeted by the antiviral drugs amantadine and rimantadine. Resistance to these drugs has compromised their effectiveness against many influenza strains, including pandemic H1N1. A recent crystal structure of M2(22-46) showed electron densities attributed to a single amantadine in the amino-terminal half of the pore, indicating a physical occlusion mechanism for inhibition. However, a solution NMR structure of M2(18-60) showed four rimantadines bound to the carboxy-terminal lipid-facing surface of the helices, suggesting an allosteric mechanism. Here we show by solid-state NMR spectroscopy that two amantadine-binding sites exist in M2 in phospholipid bilayers. The high-affinity site, occupied by a single amantadine, is located in the N-terminal channel lumen, surrounded by residues mutated in amantadine-resistant viruses. Quantification of the protein-amantadine distances resulted in a 0.3 A-resolution structure of the high-affinity binding site. The second, low-affinity, site was observed on the C-terminal protein surface, but only when the drug reaches high concentrations in the bilayer. The orientation and dynamics of the drug are distinct in the two sites, as shown by (2)H NMR. These results indicate that amantadine physically occludes the M2 channel, thus paving the way for developing new antiviral drugs against influenza

viruses. The study demonstrates the ability of solid-state NMR to elucidate small-molecule interactions with membrane proteins and determine high-resolution structures of their complexes

(5) CAPLAN AL. **Unlicensed pandemic influenza A H1N1 vaccines**. Lancet. 2010 Feb. 6, vol. 375, n° 9713, pp.444-445
http://dx.doi.org/10.1016/S0140-6736(09)61675-5 **(accès réservé EHESP)**

(6) COHEN J. **Swine flu pandemic. What's old is new: 1918 virus matches 2009 H1N1 strain**. Science. 2010 Mar. 26, vol. 327, n° 5973, pp.1563-1564
http://dx.doi.org/10.1126/science.327.5973.1563 **(accès réservé EHESP)**

(7) DANIELS N, VALENCIA-MENDOZA A, GELPI A, AVILA MH, *et al.* **The art of public health: pneumococcal vaccine coverage in Mexico**. Lancet. 2010 Jan. 9, vol. 375, n° 9709, pp.114-115
http://dx.doi.org/10.1016/S0140-6736(10)60037-2 **(accès réservé EHESP)**

(8) FINKELSTEIN Y, SCHECHTER T, FREEDMAN SB. **Surgical masks vs N95 respirators for preventing influenza**. JAMA. 2010 Mar. 10, vol. 303, n° 10, pp.938-939
http://dx.doi.org/10.1001/jama.2010.195 **(accès réservé EHESP)**

(9) FREEBAIRN R, MCHUGH G, HICKLING K. **Extracorporeal membrane oxygenation for ARDS due to 2009 influenza A(H1N1)**. JAMA. 2010 Mar. 10, vol. 303, n° 10, pp.941-942
http://dx.doi.org/10.1001/jama.2010.201 **(accès réservé EHESP)**

(10) HALDER N, KELSO JK, MILNE GJ. **Analysis of the effectiveness of interventions used during the 2009 A/H1N1 influenza pandemic**. BMC Public Health. 2010 Mar. 29, vol. 10, n° 1, p.168
http://dx.doi.org/10.1186/1471-2458-10-168 **(accès libre)**

ABSTRACT: BACKGROUND: Following the emergence of the 2009 A/H1N1 influenza pandemic, public health interventions were activated to lessen its potential impact. Computer modelling and simulation can be used to determine the potential effectiveness of the social distancing and antiviral drug therapy interventions that were used at the early stages of the pandemic, providing guidance to public health policy makers as to intervention strategies in future pandemics involving a highly pathogenic influenza strain. METHODS: An individual-based model of a real community with a population of approximately 30,000 was used to determine the impact of alternative interventions strategies, including those used in the initial stages of the 2009 pandemic. Different interventions, namely school closure and antiviral strategies, were simulated in isolation and in combination to form different plausible scenarios. We simulated epidemics with reproduction numbers R0 of 1.5, which aligns with estimates in the range 1.4-1.6 determined from the initial outbreak in Mexico. RESULTS: School closure of 1 week was determined to have minimal effect on reducing overall illness attack rate. Antiviral drug treatment of 50% of symptomatic cases reduced the attack rate by 6.5%, from an unmitigated rate of 32.5% to 26%. Treatment of diagnosed individuals combined with additional household prophylaxis reduced the final attack rate to 19%. Further extension of prophylaxis to close contacts (in schools and workplaces) further reduced the overall attack rate to 13% and reduced the peak daily illness rate from 120 to 22 per 10,000 individuals. We determined the size of antiviral stockpile required; the ratio of the required number of antiviral courses to population was 13% for the treatment-only strategy, 25% for treatment and household prophylaxis and 40% for treatment, household and extended prophylaxis. Additional simulations suggest that coupling school closure with the antiviral strategies further reduces epidemic impact. CONCLUSIONS: These results suggest that the aggressive use of antiviral drugs together with extended school closure may substantially slow the rate of influenza epidemic development. These strategies are more rigorous than those actually

used during the early stages of the relatively mild 2009 pandemic, and are appropriate for future pandemics which have high morbidity and mortality rates

(11) JANJUA NZ, SKOWRONSKI DM, HOTTES TS, DE SG, *et al.* **Seasonal vaccine effectiveness against pandemic A/H1N1**. Lancet. 2010 Mar. 6, vol. 375, n° 9717, pp.801-802
http://dx.doi.org/10.1016/S0140-6736(10)60338-8 **(accès réservé EHESP)**

(12) KAHR V, BARRETT NA, SHANKAR-HARI M, SLACK H, *et al.* **A life-threatening sore throat masquerading as swine flu**. Lancet. 2010 Feb. 6, vol. 375, n° 9713, p.524
http://dx.doi.org/10.1016/S0140-6736(09)61875-4 **(accès réservé EHESP)**

(13) KARLAS A, MACHUY N, SHIN Y, PLEISSNER KP, *et al.* **Genome-wide RNAi screen identifies human host factors crucial for influenza virus replication**. Nature. 2010 Feb. 11, vol. 463, n° 7282, pp.818-822
http://dx.doi.org/10.1038/nature08760 **(accès payant)**

Influenza A virus, being responsible for seasonal epidemics and reoccurring pandemics, represents a worldwide threat to public health. High mutation rates facilitate the generation of viral escape mutants, rendering vaccines and drugs directed against virus-encoded targets potentially ineffective. In contrast, targeting host cell determinants temporarily dispensable for the host but crucial for virus replication could prevent viral escape. Here we report the discovery of 287 human host cell genes influencing influenza A virus replication in a genome-wide RNA interference (RNAi) screen. Using an independent assay we confirmed 168 hits (59%) inhibiting either the endemic H1N1 (119 hits) or the current pandemic swine-origin (121 hits) influenza A virus strains, with an overlap of 60%. Notably, a subset of these common hits was also essential for replication of a highly pathogenic avian H5N1 strain. In-depth analyses of several factors provided insights into their infection stage relevance. Notably, SON DNA binding protein (SON) was found to be important for normal trafficking of influenza virions to late endosomes early in infection. We also show that a small molecule inhibitor of CDC-like kinase 1 (CLK1) reduces influenza virus replication by more than two orders of magnitude, an effect connected with impaired splicing of the viral M2 messenger RNA. Furthermore, influenza-virus-infected p27(-/-) (cyclin-dependent kinase inhibitor 1B; Cdkn1b) mice accumulated significantly lower viral titres in the lung, providing in vivo evidence for the importance of this gene. Thus, our results highlight the potency of genome-wide RNAi screening for the dissection of virus-host interactions and the identification of drug targets for a broad range of influenza viruses

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http://dx.doi.org/10.1038/nature08699 **(accès payant)**

Influenza A virus is an RNA virus that encodes up to 11 proteins and this small coding capacity demands that the virus use the host cellular machinery for many aspects of its life cycle. Knowledge of these host cell requirements not only informs us of the molecular pathways exploited by the virus but also provides further targets that could be pursued for antiviral drug development. Here we use an integrative systems approach, based on genome-wide RNA interference screening, to identify 295 cellular cofactors required for early-stage influenza virus replication. Within this group, those involved in kinase-regulated signalling, ubiquitination and phosphatase activity are the most highly enriched, and 181 factors assemble into a highly significant host-pathogen interaction network. Moreover, 219 of the 295 factors were confirmed to be required for efficient wild-type influenza virus growth, and further analysis of a subset of genes showed 23 factors necessary for viral entry, including members of the vacuolar ATPase (vATPase) and COPI-protein families, fibroblast growth factor receptor (FGFR) proteins, and glycogen synthase kinase 3 (GSK3)-beta. Furthermore, 10 proteins were confirmed to be involved in post-entry steps of influenza virus replication. These include nuclear import components, proteases, and the calcium/calmodulin-dependent protein kinase (CaM kinase) IIbeta (CAMK2B). Notably, growth of swine-origin H1N1 influenza virus is also dependent on the identified host

factors, and we show that small molecule inhibitors of several factors, including vATPase and CAMK2B, antagonize influenza virus replication

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http://www.ncbi.nlm.nih.gov/pubmed/20299693 **(accès réservé EHESP)**

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http://dx.doi.org/10.1001/jama.2010.200 **(accès réservé EHESP)**

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http://dx.doi.org/10.1001/jama.2010.234 **(accès réservé EHESP)**

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http://dx.doi.org/10.1186/1471-2458-10-130 **(accès libre)**

BACKGROUND: In a pandemic young adults are more likely to be infected, increasing the potential for Universities to be explosive disease outbreak centres. Outbreak management is essential to reduce the impact in both the institution and the surrounding community. Through the use of an online survey, we aimed to measure the perceptions and responses of staff and students towards pandemic (H1N1) 2009 at a major university in Sydney, Australia. METHODS: The survey was available online from 29 June to 30 September 2009. The sample included academic staff, general staff and students of the University. RESULTS: A total of 2882 surveys were completed. Nearly all respondents (99.6%, 2870/2882) were aware of the Australian pandemic situation and 64.2% (1851/2882) reported either "no anxiety" or "disinterest." Asian-born respondents were significantly ($p < 0.001$) more likely to believe that the pandemic was serious compared to respondents from other regions. 75.9% (2188/2882) of respondents had not made any lifestyle changes as a result of the pandemic. Most respondents had not adopted any specific behaviour change, and only 20.8% (600/2882) had adopted the simplest health behaviour, i.e. hand hygiene. Adoption of a specific behaviour change was linked to anxiety and Asian origin. Students were more likely to attend the university if unwell compared with staff members. Positive responses from students strongly indicate the potential for expanding online teaching and learning resources for continuing education in disaster settings. Willingness to receive the pandemic vaccine was associated with seasonal influenza vaccination uptake over the previous 3 years. CONCLUSIONS: Responses to a pandemic are subject to change in its pre-, early and mid-outbreak stages. Lessons for these institutions in preparation for a second wave and future disease outbreaks include the need to promote positive public health behaviours amongst young people and students

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The 2009 H1N1 swine flu is the first influenza pandemic in decades. The crystal structure of the hemagglutinin from the A/California/04/2009 H1N1 virus shows that its antigenic structure, particularly within the Sa antigenic site, is extremely similar to human H1N1 viruses circulating early in the 20th century. The co-crystal structure of the 1918 HA with 2D1, an antibody from a survivor of the 1918 Spanish flu that neutralizes both 1918 and 2009 H1N1 viruses, reveals an epitope that is conserved in both pandemic viruses. Thus, antigenic similarity between the 2009 and 1918-like viruses provides an explanation for the age-related immunity to the current influenza pandemic

Maladies d'Alzheimer

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Maladies cardio-vasculaires

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(2) BAZARI F, HIND M, ONG YE. **Horner's syndrome--not to be sneezed at**. Lancet. 2010 Feb. 27, vol. 375, n° 9716, p.776 http://dx.doi.org/10.1016/S0140-6736(09)62025-0 **(accès réservé EHESP)**

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(9) CUMMINGS SR, ENSRUD K, DELMAS PD, LACROIX AZ, *et al.* **Lasofoxifene in postmenopausal women with osteoporosis**. N Engl J Med. 2010 Feb. 25, vol. 362, n° 8, pp.686-696
http://dx.doi.org/10.1056/NEJMoa0808692 **(accès réservé EHESP)**

BACKGROUND: The effects of lasofoxifene on the risk of fractures, breast cancer, and cardiovascular disease are uncertain. METHODS: In this randomized trial, we assigned 8556 women who were between the ages of 59 and 80 years and had a bone mineral density T score of -2.5 or less at the femoral neck or spine to receive once-daily lasofoxifene (at a dose of either 0.25 mg or 0.5 mg) or placebo for 5 years. Primary end points were vertebral fractures, estrogen receptor (ER)-positive breast cancer, and nonvertebral fractures; secondary end points included major coronary heart disease events and stroke. RESULTS: Lasofoxifene at a dose of 0.5 mg per day, as compared with placebo, was associated with reduced risks of vertebral fracture (13.1 cases vs. 22.4 cases per 1000 person-years; hazard ratio, 0.58; 95% confidence interval [CI], 0.47 to 0.70), nonvertebral fracture (18.7 vs. 24.5 cases per 1000 person-years; hazard ratio, 0.76; 95% CI, 0.64 to 0.91), ER-positive breast cancer (0.3 vs. 1.7 cases per 1000 person-years; hazard ratio, 0.19; 95% CI, 0.07 to 0.56), coronary heart disease events (5.1 vs. 7.5 cases per 1000 person-years; hazard ratio, 0.68; 95% CI, 0.50 to 0.93), and stroke (2.5 vs. 3.9 cases per 1000 person-years; hazard ratio, 0.64; 95% CI, 0.41 to 0.99). Lasofoxifene at a dose of 0.25 mg per day, as compared with placebo, was associated with reduced risks of vertebral fracture (16.0 vs. 22.4 cases per 1000 person-years; hazard ratio, 0.69; 95% CI, 0.57 to 0.83) and stroke (2.4 vs. 3.9 cases per 1000 person-years; hazard ratio, 0.61; 95% CI, 0.39 to 0.96) Both the lower and higher doses, as compared with placebo, were associated with an increase in venous thromboembolic events (3.8 and 2.9 cases vs. 1.4 cases per 1000 person-years; hazard ratios, 2.67 [95% CI, 1.55 to 4.58] and 2.06 [95% CI, 1.17 to 3.60], respectively). Endometrial cancer occurred in three women in the placebo group, two women in the lower-dose lasofoxifene group, and two women in the higher-dose lasofoxifene group. Rates of death per 1000 person-years were 5.1 in the placebo group, 7.0 in the lower-dose lasofoxifene group, and 5.7 in the higher-dose lasofoxifene group. CONCLUSIONS: In postmenopausal women with osteoporosis, lasofoxifene at a dose of 0.5 mg per day was associated with reduced risks of nonvertebral and vertebral fractures, ER-positive breast cancer, coronary heart disease, and stroke but an increased risk of venous thromboembolic events. (ClinicalTrials.gov number, NCT00141323.)

(10) DAUWERSE L, ABMA TA, WOLBERS JG. **The war in my head: coping with arteriovenous malformation after a brain haemorrhage**. BMJ. 2010, vol. 340, p.b5400
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(11) DUIVENVOORDEN R, VERGEER M, KASTELEIN JJ. **Niacin compared with ezetimibe**. N Engl J Med. 2010 Mar. 18, vol. 362, n° 11, pp.1046-1047
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(12) FOWKES FG, PRICE JF, STEWART MC, BUTCHER I, *et al.* **Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial**. JAMA. 2010 Mar. 3, vol. 303, n° 9, pp.841-848
http://dx.doi.org/10.1001/jama.2010.221 **(accès réservé EHESP)**

CONTEXT: A low ankle brachial index (ABI) indicates atherosclerosis and an increased risk of cardiovascular and cerebrovascular events. Screening for a low ABI can identify an asymptomatic higher risk group potentially amenable to preventive treatments. OBJECTIVE: To determine the effectiveness of aspirin in preventing events in people with a low ABI identified on screening the general population. DESIGN, SETTING, AND PARTICIPANTS: The Aspirin for Asymptomatic

Atherosclerosis trial was an intention-to-treat double-blind randomized controlled trial conducted from April 1998 to October 2008, involving 28,980 men and women aged 50 to 75 years living in central Scotland, free of clinical cardiovascular disease, recruited from a community health registry, and had an ABI screening test. Of those, 3350 with a low ABI (< or = 0.95) were entered into the trial, which was powered to detect a 25% proportional risk reduction in events. INTERVENTIONS: Once daily 100 mg aspirin (enteric coated) or placebo. MAIN OUTCOME MEASURES: The primary end point was a composite of initial fatal or nonfatal coronary event or stroke or revascularization. Two secondary end points were (1) all initial vascular events defined as a composite of a primary end point event or angina, intermittent claudication, or transient ischemic attack; and (2) all-cause mortality. RESULTS: After a mean (SD) follow-up of 8.2 (1.6) years, 357 participants had a primary end point event (13.5 per 1000 person-years, 95% confidence interval [CI], 12.2-15.0). No statistically significant difference was found between groups (13.7 events per 1000 person-years in the aspirin group vs 13.3 in the placebo group; hazard ratio [HR], 1.03; 95% CI, 0.84-1.27). A vascular event comprising the secondary end point occurred in 578 participants (22.8 per 1000 person-years; 95% CI, 21.0-24.8) and no statistically significant difference between groups (22.8 events per 1000 person-years in the aspirin group vs 22.9 in the placebo group; HR, 1.00; 95% CI, 0.85-1.17). There was no significant difference in all-cause mortality between groups (176 vs 186 deaths, respectively; HR, 0.95; 95% CI, 0.77-1.16). An initial event of major hemorrhage requiring admission to hospital occurred in 34 participants (2.5 per 1000 person-years) in the aspirin group and 20 (1.5 per 1000 person-years) in the placebo group (HR, 1.71; 95% CI, 0.99-2.97). CONCLUSION: Among participants without clinical cardiovascular disease, identified with a low ABI based on screening a general population, the administration of aspirin compared with placebo did not result in a significant reduction in vascular events. TRIAL REGISTRATION: isrctn.org Identifier: ISRCTN66587262

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(14) KAPTOGE S, DI AE, LOWE G, PEPYS MB, *et al.* **C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis**. Lancet. 2010 Jan. 9, vol. 375, n° 9709, pp.132-140
http://dx.doi.org/10.1016/S0140-6736(09)61717-7 **(accès réservé EHESP)**

BACKGROUND: Associations of C-reactive protein (CRP) concentration with risk of major diseases can best be assessed by long-term prospective follow-up of large numbers of people. We assessed the associations of CRP concentration with risk of vascular and non-vascular outcomes under different circumstances. METHODS: We meta-analysed individual records of 160 309 people without a history of vascular disease (ie, 1.31 million person-years at risk, 27 769 fatal or non-fatal disease outcomes) from 54 long-term prospective studies. Within-study regression analyses were adjusted for within-person variation in risk factor levels. RESULTS: Log(e) CRP concentration was linearly associated with several conventional risk factors and inflammatory markers, and nearly log-linearly with the risk of ischaemic vascular disease and non-vascular mortality. Risk ratios (RRs) for coronary heart disease per 1-SD higher log(e) CRP concentration (three-fold higher) were 1.63 (95% CI 1.51-1.76) when initially adjusted for age and sex only, and 1.37 (1.27-1.48) when adjusted further for conventional risk factors; 1.44 (1.32-1.57) and 1.27 (1.15-1.40) for ischaemic stroke; 1.71 (1.53-1.91) and 1.55 (1.37-1.76) for vascular mortality; and 1.55 (1.41-1.69) and 1.54 (1.40-1.68) for non-vascular mortality. RRs were largely unchanged after exclusion of smokers or initial follow-up. After further adjustment for fibrinogen, the corresponding RRs were 1.23 (1.07-1.42) for coronary heart disease; 1.32 (1.18-1.49) for ischaemic stroke; 1.34 (1.18-1.52) for vascular mortality; and 1.34 (1.20-1.50) for non-vascular mortality. INTERPRETATION: CRP concentration has continuous associations with the risk of coronary heart disease, ischaemic stroke, vascular mortality, and death from several cancers and lung disease that are each of broadly similar size. The relevance of CRP to such a range of disorders is unclear. Associations with ischaemic vascular disease depend considerably on conventional risk factors and other markers of inflammation. FUNDING: British Heart Foundation, UK Medical Research Council, BUPA Foundation, and GlaxoSmithKline

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(17) KRAFT HG, KRONENBERG F, UTERMANN G. **Genetic variants in Lp(a) lipoprotein and coronary disease**. N Engl J Med. 2010 Mar. 25, vol. 362, n° 12, pp.1146-1148
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(20) LIPPI G, FRANCHINI M, FAVALORO EJ. **Platelet inhibition with cangrelor**. N Engl J Med. 2010 Mar. 18, vol. 362, n° 11, p.1049
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(21) PATEL MR, PETERSON ED, DAI D, BRENNAN JM, *et al.* **Low diagnostic yield of elective coronary angiography**. N Engl J Med. 2010 Mar. 11, vol. 362, n° 10, pp.886-895
http://dx.doi.org/10.1056/NEJMoa0907272 **(accès réservé EHESP)**

BACKGROUND: Guidelines for triaging patients for cardiac catheterization recommend a risk assessment and noninvasive testing. We determined patterns of noninvasive testing and the diagnostic yield of catheterization among patients with suspected coronary artery disease in a contemporary national sample. METHODS: From January 2004 through April 2008, at 663 hospitals in the American College of Cardiology National Cardiovascular Data Registry, we identified patients without known coronary artery disease who were undergoing elective catheterization. The patients' demographic characteristics, risk factors, and symptoms and the results of noninvasive testing were correlated with the presence of obstructive coronary artery disease, which was defined as stenosis of 50% or more of the diameter of the left main coronary artery or stenosis of 70% or more of the diameter of a major epicardial vessel. RESULTS: A total of 398,978 patients were included in the study. The median age was 61 years; 52.7% of the patients were men, 26.0% had diabetes, and 69.6% had hypertension. Noninvasive testing was performed in 83.9% of the patients. At catheterization, 149,739 patients (37.6%) had obstructive coronary artery disease. No coronary artery disease (defined as <20% stenosis in all vessels) was reported in 39.2% of the patients. Independent predictors of obstructive coronary artery disease included male sex (odds ratio, 2.70; 95% confidence interval [CI], 2.64 to 2.76), older age (odds ratio per 5-year increment, 1.29; 95% CI, 1.28 to 1.30), presence of insulin-dependent diabetes (odds ratio, 2.14; 95% CI, 2.07 to 2.21), and presence of dyslipidemia (odds ratio, 1.62; 95% CI, 1.57 to 1.67). Patients with a positive result on a noninvasive test were moderately more likely to have obstructive coronary artery disease than those who did not undergo any testing (41.0% vs. 35.0%; P<0.001; adjusted odds ratio, 1.28; 95% CI, 1.19 to 1.37). CONCLUSIONS: In this study, slightly more than one third of patients without known disease who underwent elective cardiac catheterization had obstructive coronary artery disease. Better strategies for risk stratification are

needed to inform decisions and to increase the diagnostic yield of cardiac catheterization in routine clinical practice

(22) PFISTERER ME, ZELLWEGER MJ, GERSH BJ. **Management of stable coronary artery disease**. Lancet. 2010 Feb. 27, vol. 375, n° 9716, pp.763-772
http://dx.doi.org/10.1016/S0140-6736(10)60168-7 **(accès réservé EHESP)**

Results of two randomised controlled trials for the management of mild-to-moderate chronic stable coronary artery disease (Clinical Outcomes Utilizing Revascularization and Aggressive drug Evaluation [COURAGE] and Bypass Angioplasty Revascularization Investigation type-2 Diabetes [BARI-2D]) have stimulated a vigorous debate about whether an initial strategy of revascularisation or a conservative approach with drugs is most effective. The conclusions of these two trials were clear: for some patients randomly assigned after angiography to revascularisation or pharmacological therapy, rates of death and myocardial infarction did not differ between the two strategies. What remains unresolved is how to generalise these data to patients without angiography, the role of stress testing, and the preferred approach to patients with relevant ischaemia on stress testing. This Review draws attention to the controversial issues in both management approaches, analyses the strengths and limitations of recent trials, and proposes a treatment algorithm that is applicable to daily clinical practice. Findings suggest that the severity of anginal symptoms and the extent of ischaemia in stress testing could help to identify patients who are at increased risk and who might benefit from an early invasive strategy. On the basis of the data and considerations presented, a strategy of initial optimum pharmacological therapy or direct invasive management can be tailored to an individual's circumstances and preferences

(23) PLESS ML, CHEN YB, COPEN WA, FROSCH MP. **Case records of the Massachusetts General Hospital. Case 9-2010. A 37-year-old woman with paresthesias and ataxia**. N Engl J Med. 2010 Mar. 25, vol. 362, n° 12, pp.1129-1138
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(24) PUSKAS JD, MACK MJ, SMITH CR. **On-pump versus off-pump CABG**. N Engl J Med. 2010 Mar. 4, vol. 362, n° 9, pp.851-854
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(25) RODONDI N, MARQUES-VIDAL P, BUTLER J, SUTTON-TYRRELL K, *et al.* **Markers of atherosclerosis and inflammation for prediction of coronary heart disease in older adults**. Am J Epidemiol. 2010 Mar. 1, vol. 171, n° 5, pp.540-549
http://dx.doi.org/10.1093/aje/kwp428 **(accès réservé EHESP)**

Although both inflammatory and atherosclerosis markers have been associated with coronary heart disease (CHD) risk, data directly comparing their predictive value are limited. The authors compared the value of 2 atherosclerosis markers (ankle-arm index (AAI) and aortic pulse wave velocity (aPWV)) and 3 inflammatory markers (C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-alpha)) in predicting CHD events. Among 2,191 adults aged 70-79 years at baseline (1997-1998) from the Health, Aging, and Body Composition Study cohort, the authors examined adjudicated incident myocardial infarction or CHD death ("hard" events) and "hard" events plus hospitalization for angina or coronary revascularization (total CHD events). During 8 years of follow-up between 1997-1998 and June 2007, 351 participants developed total CHD events (197 "hard" events). IL-6 (highest quartile vs. lowest: hazard ratio = 1.82, 95% confidence interval: 1.33, 2.49; P-trend < 0.001) and AAI (AAI < or = 0.9 vs. AAI 1.01-1.30: hazard ratio = 1.57, 95% confidence interval: 1.14, 2.18) predicted CHD events above traditional risk factors and modestly improved global measures of predictive accuracy. CRP, TNF-alpha, and aPWV had weaker associations. IL-6 and AAI accurately reclassified 6.6% and 3.3% of participants, respectively (P's < or = 0.05). Results were similar for "hard" CHD, with higher reclassification rates for AAI. IL-6 and AAI are associated with future CHD events beyond traditional risk factors and modestly improve risk prediction in older adults

(26) ROMAN MJ. **Niacin compared with ezetimibe**. N Engl J Med. 2010 Mar. 18, vol. 362, n° 11, pp.1047-1048
http://www.ncbi.nlm.nih.gov/pubmed/20301796 **(accès réservé EHESP)**

(27) ROTHWELL PM. **Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension**. Lancet. 2010 Mar. 13, vol. 375, n° 9718, pp.938-948
http://dx.doi.org/10.1016/S0140-6736(10)60309-1 **(accès réservé EHESP)**

Although hypertension is the most prevalent treatable vascular risk factor, how it causes end-organ damage and vascular events is poorly understood. Yet, a widespread belief exists that underlying usual blood pressure can alone account for all blood-pressure-related risk of vascular events and for the benefits of antihypertensive drugs, and this notion has come to underpin all major clinical guidelines on diagnosis and treatment of hypertension. Other potentially informative measures, such as variability in clinic blood pressure or maximum blood pressure reached, have been neglected, and effects of antihypertensive drugs on such measures are largely unknown. Clinical guidelines recommend that episodic hypertension is not treated, and the potential risks of residual variability in blood pressure in treated hypertensive patients have been ignored. This Review discusses shortcomings of the usual blood-pressure hypothesis, provides background to accompanying reports on the importance of blood-pressure variability in prediction of risk of vascular events and in accounting for benefits of antihypertensive drugs, and draws attention to clinical implications and directions for future research

(28) ROTHWELL PM, HOWARD SC, DOLAN E, O'BRIEN E, *et al.* **Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension**. Lancet. 2010 Mar. 13, vol. 375, n° 9718, pp.895-905
http://dx.doi.org/10.1016/S0140-6736(10)60308-X **(accès réservé EHESP)**

BACKGROUND: The mechanisms by which hypertension causes vascular events are unclear. Guidelines for diagnosis and treatment focus only on underlying mean blood pressure. We aimed to reliably establish the prognostic significance of visit-to-visit variability in blood pressure, maximum blood pressure reached, untreated episodic hypertension, and residual variability in treated patients. METHODS: We determined the risk of stroke in relation to visit-to-visit variability in blood pressure (expressed as standard deviation [SD] and parameters independent of mean blood pressure) and maximum blood pressure in patients with previous transient ischaemic attack (TIA; UK-TIA trial and three validation cohorts) and in patients with treated hypertension (Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure Lowering Arm [ASCOT-BPLA]). In ASCOT-BPLA, 24-h ambulatory blood-pressure monitoring (ABPM) was also studied. FINDINGS: In each TIA cohort, visit-to-visit variability in systolic blood pressure (SBP) was a strong predictor of subsequent stroke (eg, top-decile hazard ratio [HR] for SD SBP over seven visits in UK-TIA trial: 6.22, 95% CI 4.16-9.29, p<0.0001), independent of mean SBP, but dependent on precision of measurement (top-decile HR over ten visits: 12.08, 7.40-19.72, p<0.0001). Maximum SBP reached was also a strong predictor of stroke (HR for top-decile over seven visits: 15.01, 6.56-34.38, p<0.0001, after adjustment for mean SBP). In ASCOT-BPLA, residual visit-to-visit variability in SBP on treatment was also a strong predictor of stroke and coronary events (eg, top-decile HR for stroke: 3.25, 2.32-4.54, p<0.0001), independent of mean SBP in clinic or on ABPM. Variability on ABPM was a weaker predictor, but all measures of variability were most predictive in younger patients and at lower (<median) values of mean SBP in every cohort. INTERPRETATION: Visit-to-visit variability in SBP and maximum SBP are strong predictors of stroke, independent of mean SBP. Increased residual variability in SBP in patients with treated hypertension is associated with a high risk of vascular events. FUNDING: None

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http://dx.doi.org/10.1056/NEJMc0912848 **(accès réservé EHESP)**

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(32) TAGGART DP. **On-pump versus off-pump CABG**. N Engl J Med. 2010 Mar. 4, vol. 362, n° 9, pp.852-854
http://www.ncbi.nlm.nih.gov/pubmed/20213877 **(accès réservé EHESP)**

(33) WEBB AJ, FISCHER U, MEHTA Z, ROTHWELL PM. **Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis**. Lancet. 2010 Mar. 13, vol. 375, n° 9718, pp.906-915
http://dx.doi.org/10.1016/S0140-6736(10)60235-8 **(accès réservé EHESP)**

INTRODUCTION: Unexplained differences between classes of antihypertensive drugs in their effectiveness in preventing stroke might be due to class effects on intraindividual variability in blood pressure. We did a systematic review to assess any such effects in randomised controlled trials. METHODS: Baseline and follow-up data for mean (SD) of systolic blood pressure (SBP) were extracted from trial reports. Effect of treatment on interindividual variance (SD2) in blood pressure (a surrogate for within-individual variability), expressed as the ratio of the variances (VR), was related to effects on clinical outcomes. Pooled estimates were derived by use of random-effects meta-analysis. FINDINGS: Mean (SD) SBP at follow-up was reported in 389 (28%) of 1372 eligible trials. There was substantial heterogeneity between trials in VR (p<1 x 10(-40)), 68% of which was attributable to allocated drug class. Compared with other drugs, interindividual variation in SBP was reduced by calcium-channel blockers (VR 0.81, 95% CI 0.76-0.86, p<0.0001) and non-loop diuretic drugs (0.87, 0.79-0.96, p=0.007), and increased by angiotensin-converting enzyme (ACE) inhibitors (1.08, 1.02-1.15, p=0.008), angiotensin-receptor blockers (1.16, 1.07-1.25, p=0.0002), and beta blockers (1.17, 1.07-1.28, p=0.0007). Compared with placebo only, interindividual variation in SBP was reduced the most by calcium-channel blockers (0.76, 0.67-0.85, p<0.0001). Effects were consistent in parallel group and crossover design trials, and in analyses of dose-response. Across all trials, effects of treatment on VR of SBP (r2=0.372, p=0.0006) and on mean SBP (r2=0.328, p=0.0015) accounted for effects on stroke risk (eg, odds ratio 0.79, 0.71-0.87, p<0.0001, for VR< or =0.80), and both remained significant in a combined model. INTERPRETATION: Drug-class effects on interindividual variation in blood pressure can account for differences in effects of antihypertensive drugs on risk of stroke independently of effects on mean SBP. FUNDING: None

(34) WEISS SH. **Niacin compared with ezetimibe**. N Engl J Med. 2010 Mar. 18, vol. 362, n° 11, p.1047
http://www.ncbi.nlm.nih.gov/pubmed/20301797 **(accès réservé EHESP)**

Maladies liées à l'alcool

sommaire

(1) NEWBURY-BIRCH D, BLAND M, CASSIDY P, COULTON S, *et al.* **Screening and brief interventions for hazardous and harmful alcohol use in probation services: a cluster randomised controlled trial protocol**. BMC Public Health. 2009, vol. 9, p.418
http://www.ncbi.nlm.nih.gov/pubmed/19922618 (**accès libre**) ou
http://dx.doi.org/10.1186/1471-2458-9-418 **(accès libre)**

BACKGROUND: A large number of randomised controlled trials in health settings have consistently reported positive effects of brief intervention in terms of reductions in alcohol use. However, although alcohol misuse is common amongst offenders, there is limited evidence of alcohol brief interventions in the criminal justice field. This factorial pragmatic cluster randomised controlled trial with Offender Managers (OMs) as the unit of randomisation will evaluate the effectiveness and cost-effectiveness of different models of screening to identify hazardous and harmful drinkers in probation and different intensities of brief intervention to reduce excessive drinking in probation clients. METHODS AND DESIGN: Ninety-six OMs from 9 probation areas across 3 English regions (the North East Region (n = 4) and London and the South East Regions (n = 5)) will be recruited. OMs will be randomly allocated to one of three intervention conditions: a client information leaflet control condition (n = 32 OMs); 5-minute simple structured advice (n = 32 OMs) and 20-minute brief lifestyle counselling delivered by an Alcohol Health Worker (n = 32 OMs). Randomisation will be stratified by probation area. To test the relative effectiveness of different screening methods all OMs will be randomised to either the Modified Single Item Screening Questionnaire (M-SASQ) or the Fast Alcohol Screening Test (FAST). There will be a minimum of 480 clients recruited into the trial. There will be an intention to treat analysis of study outcomes at 6 and 12 months post intervention. Analysis will include client measures (screening result, weekly alcohol consumption, alcohol-related problems, re-offending, public service use and quality of life) and implementation measures from OMs (the extent of screening and brief intervention beyond the minimum recruitment threshold will provide data on acceptability and feasibility of different models of brief intervention). We will also examine the practitioner and organisational factors associated with successful implementation. DISCUSSION: The trial will evaluate the impact of screening and brief alcohol intervention in routine probation work and therefore its findings will be highly relevant to probation teams and thus the criminal justice system in the UK.Ethical approval was given by Northern & Yorkshire REC. TRIAL REGISTRATION NUMBER: ISRCTN 19160244

Paludisme

sommaire

(1)**The Global Fund: replenishment and redefinition in 2010**. Lancet. 2010 Mar. 13, vol. 375, n° 9718, p.865
http://dx.doi.org/10.1016/S0140-6736(10)60366-2 **(accès réservé EHESP)**

(2) ANSAH EK, NARH-BANA S, EPOKOR M, AKANPIGBIAM S, *et al.* **Rapid testing for malaria in settings where microscopy is available and peripheral clinics where only presumptive treatment is available: a randomised controlled trial in Ghana**. BMJ. 2010, vol. 340, p.c930
http://www.ncbi.nlm.nih.gov/pubmed/20207689 **(accès réservé EHESP)**

OBJECTIVE: To test in West Africa the impact of rapid diagnostic tests on the prescription of antimalarials and antibiotics both where microscopy is used for the diagnosis of malaria and in clinical (peripheral) settings that rely on clinical diagnosis. DESIGN: Randomised, controlled, open label clinical trial. SETTING: Four clinics in the rural Dangme West district of southern Ghana, one in which microscopy is used for diagnosis of malaria ("microscopy setting") and three where microscopy is not available and diagnosis of malaria is made on the basis of clinical symptoms ("clinical setting"). PARTICIPANTS: Patients with suspected malaria. Interventions Patients were randomly assigned to either a rapid diagnostic test or the current diagnostic method at the clinic

(microscopy or clinical diagnosis). A blood sample for a research microscopy slide was taken for all patients. MAIN OUTCOME MEASURES: The primary outcome was the prescription of antimalarials to patients of any age whose double read research slide was negative for malaria. The major secondary outcomes were the correct prescription of antimalarials, the impact of test results on antibiotic prescription, and the correct prescription of antimalarials in children under 5 years. RESULTS: Of the 9236 patients screened, 3452 were randomised in the clinical setting and 3811 in the microscopy setting. Follow-up to 28 days was 97.6% (7088/7263). In the microscopy setting, 722 (51.6%) of the 1400 patients with negative research slides in the rapid diagnostic test arm were treated for malaria compared with 764 (55.0%) of the 1389 patients in the microscopy arm (adjusted odds ratio 0.87, 95% CI 0.71 to 1.1; P=0.16). In the clinical setting, 578 (53.9%) of the 1072 patients in the rapid diagnostic test arm with negative research slides were treated for malaria compared with 982 (90.1%) of the 1090 patients with negative slides in the clinical diagnosis arm (odds ratio 0.12, 95% CI 0.04 to 0.38; P=0.001). The use of rapid diagnostic tests led to better targeting of antimalarials and antibiotics in the clinical but not the microscopy setting, in both children and adults. There were no deaths in children under 5 years at 28 days follow-up in either arm. CONCLUSION: Where microscopy already exists, introducing rapid diagnostic tests had limited impact on prescriber behaviour. In settings where microscopy was not available, however, using rapid diagnostic tests led to a significant reduction in the overprescription of antimalarials, without any evidence of clinical harm, and to better targeting of antibiotics. Trial registration ClinicalTrials.gov NCT00493922

(3) BAIDEN F, OWUSU-AGYEI S, WEBSTER J, CHANDRAMOHAN D. **The need for new antibiotics**. Lancet. 2010 Feb. 20, vol. 375, n° 9715, pp.637-638
http://dx.doi.org/10.1016/S0140-6736(10)60265-6 **(accès réservé EHESP)**

(4) BODDEY JA, HODDER AN, GUNTHER S, GILSON PR, *et al.* **An aspartyl protease directs malaria effector proteins to the host cell**. Nature. 2010 Feb. 4, vol. 463, n° 7281, pp.627-631
http://dx.doi.org/10.1038/nature08728 **(accès payant)**

Plasmodium falciparum causes the virulent form of malaria and disease manifestations are linked to growth inside infected erythrocytes. To survive and evade host responses the parasite remodels the erythrocyte by exporting several hundred effector proteins beyond the surrounding parasitophorous vacuole membrane. A feature of exported proteins is a pentameric motif (RxLxE/Q/D) that is a substrate for an unknown protease. Here we show that the protein responsible for cleavage of this motif is plasmepsin V (PMV), an aspartic acid protease located in the endoplasmic reticulum. PMV cleavage reveals the export signal (xE/Q/D) at the amino terminus of cargo proteins. Expression of an identical mature protein with xQ at the N terminus generated by signal peptidase was not exported, demonstrating that PMV activity is essential and linked with other key export events. Identification of the protease responsible for export into erythrocytes provides a novel target for therapeutic intervention against this devastating disease

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http://dx.doi.org/10.2105/AJPH.2009.177667 **(accès réservé EHESP)**

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http://dx.doi.org/10.1016/S0140-6736(10)60047-5 **(accès réservé EHESP)**

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http://dx.doi.org/10.1016/S0140-6736(10)60049-9 **(accès réservé EHESP)**

(8) KAMAL-YANNI M. **Affordable medicines facility for malaria: reasonable or rash?** Lancet. 2010 Jan. 9, vol. 375, n° 9709, p.121
http://dx.doi.org/10.1016/S0140-6736(10)60048-7 **(accès réservé EHESP)**

(9) LEDFORD H. **Africa yields two full human genomes**. Nature. 2010 Feb. 18, vol. 463, n° 7283, p.857
http://dx.doi.org/10.1038/463857a **(accès payant)**

(10) RUSSO I, BABBITT S, MURALIDHARAN V, BUTLER T, *et al.* **Plasmepsin V licenses Plasmodium proteins for export into the host erythrocyte**. Nature. 2010 Feb. 4, vol. 463, n° 7281, pp.632-636
http://dx.doi.org/10.1038/nature08726 **(accès payant)**

During their intraerythrocytic development, malaria parasites export hundreds of proteins to remodel their host cell. Nutrient acquisition, cytoadherence and antigenic variation are among the key virulence functions effected by this erythrocyte takeover. Proteins destined for export are synthesized in the endoplasmic reticulum (ER) and cleaved at a conserved (PEXEL) motif, which allows translocation into the host cell via an ATP-driven translocon called the PTEX complex. We report that plasmepsin V, an ER aspartic protease with distant homology to the mammalian processing enzyme BACE, recognizes the PEXEL motif and cleaves it at the correct site. This enzyme is essential for parasite viability and ER residence is essential for its function. We propose that plasmepsin V is the PEXEL protease and is an attractive enzyme for antimalarial drug development

(11) WHITTY CJ, LESLIE T, CHANDLER CI, STAEDKE SG. **Management of malaria and other severe infections in rural Africa and Asia**. BMJ. 2010, vol. 340, p.c1527
http://www.ncbi.nlm.nih.gov/pubmed/20237003 **(accès réservé EHESP)**

(12) ZAROCOSTAS J. **Malaria treatment should begin with parasitological diagnosis where possible, says WHO**. BMJ. 2010, vol. 340, p.c1402
http://www.ncbi.nlm.nih.gov/pubmed/20215357 **(accès réservé EHESP**

Pathologies liées à l'obésité

sommaire

(1) **Childhood obesity: affecting choices**. Lancet. 2010 Feb. 20, vol. 375, n° 9715, p.611
http://dx.doi.org/10.1016/S0140-6736(10)60247-4 **(accès réservé EHESP)**

(2) **State of the heart in the USA**. Lancet. 2010 Feb. 27, vol. 375, n° 9716, p.697
http://dx.doi.org/10.1016/S0140-6736(10)60285-1 **(accès réservé EHESP)**

(3) ARNER E, RYDEN M, ARNER P. **Tumor necrosis factor alpha and regulation of adipose tissue**. N Engl J Med. 2010 Mar. 25, vol. 362, n° 12, pp.1151-1153
http://www.ncbi.nlm.nih.gov/pubmed/20335599 **(accès réservé EHESP)** ou
http://dx.doi.org/10.1056/NEJMc0910718 **(accès réservé EHESP)**

(4) BOCHUKOVA EG, HUANG N, KEOGH J, HENNING E, *et al.* **Large, rare chromosomal deletions associated with severe early-onset obesity**. Nature. 2010 Feb. 4, vol. 463, n° 7281, pp.666-670
http://dx.doi.org/10.1038/nature08689 **(accès payant)**

Obesity is a highly heritable and genetically heterogeneous disorder. Here we investigated the contribution of copy number variation to obesity in 300 Caucasian patients with severe early-onset

obesity, 143 of whom also had developmental delay. Large (>500 kilobases), rare (<1%) deletions were significantly enriched in patients compared to 7,366 controls (P < 0.001). We identified several rare copy number variants that were recurrent in patients but absent or at much lower prevalence in controls. We identified five patients with overlapping deletions on chromosome 16p11.2 that were found in 2 out of 7,366 controls (P < 5 x 10(-5)). In three patients the deletion co-segregated with severe obesity. Two patients harboured a larger de novo 16p11.2 deletion, extending through a 593-kilobase region previously associated with autism and mental retardation; both of these patients had mild developmental delay in addition to severe obesity. In an independent sample of 1,062 patients with severe obesity alone, the smaller 16p11.2 deletion was found in an additional two patients. All 16p11.2 deletions encompass several genes but include SH2B1, which is known to be involved in leptin and insulin signalling. Deletion carriers exhibited hyperphagia and severe insulin resistance disproportionate for the degree of obesity. We show that copy number variation contributes significantly to the genetic architecture of human obesity

(5) BYRNE CD, WILD SH. **Body fat and increased risk of cirrhosis**. BMJ. 2010, vol. 340, p.c774
http://www.ncbi.nlm.nih.gov/pubmed/20223874 **(accès réservé EHESP)**

(6) CARTER R, MOODIE M, MARKWICK A, MAGNUS A, *et al.* **Assessing cost-effectiveness in obesity (ACE-obesity): an overview of the ACE approach, economic methods and cost results** . BMC Public Health. 2009, vol. 9, p.419
http://dx.doi.org/10.1186/1471-2458-9-419 **(accès libre)**

BACKGROUND: The aim of the ACE-Obesity study was to determine the economic credentials of interventions which aim to prevent unhealthy weight gain in children and adolescents. We have reported elsewhere on the modelled effectiveness of 13 obesity prevention interventions in children. In this paper, we report on the cost results and associated methods together with the innovative approach to priority setting that underpins the ACE-Obesity study. METHODS: The Assessing Cost Effectiveness (ACE) approach combines technical rigour with 'due process' to facilitate evidence-based policy analysis. Technical rigour was achieved through use of standardised evaluation methods, a research team that assembles best available evidence and extensive uncertainty analysis. Cost estimates were based on pathway analysis, with resource usage estimated for the interventions and their 'current practice' comparator, as well as associated cost offsets. Due process was achieved through involvement of stakeholders, consensus decisions informed by briefing papers and 2nd stage filter analysis that captures broader factors that influence policy judgements in addition to cost-effectiveness results. The 2nd stage filters agreed by stakeholders were 'equity', 'strength of the evidence', 'feasibility of implementation', 'acceptability to stakeholders', 'sustainability' and 'potential for side-effects'. RESULTS: The intervention costs varied considerably, both in absolute terms (from cost saving [6 interventions] to in excess of AUD50m per annum) and when expressed as a 'cost per child' estimate (from <AUD1.0 [reduction of TV advertising of high fat foods/high sugar drinks] to AUD31,553 [laparoscopic adjustable gastric banding for morbidly obese adolescents]). High costs per child reflected cost structure, target population and/or under-utilisation. CONCLUSION: The use of consistent methods enables valid comparison of potential intervention costs and cost-offsets for each of the interventions. ACE-Obesity informs policy-makers about cost-effectiveness, health impact, affordability and 2nd stage filters for important options for preventing unhealthy weight gain in children. In related articles cost-effectiveness results and second stage filter considerations for each intervention assessed will be presented and analysed

(7) CHANG MW, BROWN R, NITZKE S. **Participant recruitment and retention in a pilot program to prevent weight gain in low-income overweight and obese mothers**. BMC Public Health. 2009, vol. 9, p.424
http://dx.doi.org/10.1186/1471-2458-9-424 **(accès libre)**

BACKGROUND: Recruitment and retention are key functions for programs promoting nutrition and other lifestyle behavioral changes in low-income populations. This paper describes strategies for recruitment and retention and presents predictors of early (two-month post intervention) and

late (eight-month post intervention) dropout (non retention) and overall retention among young, low-income overweight and obese mothers participating in a community-based randomized pilot trial called Mothers In Motion. METHODS: Low-income overweight and obese African American and white mothers ages 18 to 34 were recruited from the Special Supplemental Nutrition Program for Women, Infants, and Children in southern Michigan. Participants (n = 129) were randomly assigned to an intervention (n = 64) or control (n = 65) group according to a stratification procedure to equalize representation in two racial groups (African American and white) and three body mass index categories (25.0-29.9 kg/m(2), 30.0-34.9 kg/m(2), and 35.0-39.9 kg/m(2)). The 10-week theory-based culturally sensitive intervention focused on healthy eating, physical activity, and stress management messages that were delivered via an interactive DVD and reinforced by five peer-support group teleconferences. Forward stepwise multiple logistic regression was performed to examine whether dietary fat, fruit and vegetable intake behaviors, physical activity, perceived stress, positive and negative affect, depression, and race predicted dropout as data were collected two-month and eight-month after the active intervention phase. RESULTS: Trained personnel were successful in recruiting subjects. Increased level of depression was a predictor of early dropout (odds ratio = 1.04; 95% CI = 1.00, 1.08; p = 0.03). Greater stress predicted late dropout (odds ratio = 0.20; 95% CI = 0.00, 0.37; p = 0.01). Dietary fat, fruit, and vegetable intake behaviors, physical activity, positive and negative affect, and race were not associated with either early or late dropout. Less negative affect was a marginal predictor of participant retention (odds ratio = 0.57; 95% CI = 0.31, 1.03; p = 0.06). CONCLUSION: Dropout rates in this study were higher for participants who reported higher levels of depression and stress. TRIAL REGISTRATION: Current Controlled Trials NCT00944060

(8) CHEN DR, WEN TH. **Socio-spatial patterns of neighborhood effects on adult obesity in Taiwan: a multi-level model**. Soc Sci Med. 2010 Mar., vol. 70, n° 6, pp.823-833
http://dx.doi.org/10.1016/j.socscimed.2009.11.030 **(accès réservé EHESP)**

Obesity, one of the most significant health problems now facing developed countries, has been increasing steadily in Taiwan. This study addresses how neighborhood factors affect individual obesity by simultaneously examining individual-level socioeconomic status and neighborhood-level characteristics using a multi-level approach combined with a spatial analysis. The data are from Taiwan's 2001 Social Development Survey on Health and Safety; a representative sample of 27,593 adults over 262 townships (i.e. neighborhoods). A spatial autocorrelation model is employed to investigate the spatial clustering of neighborhood affluence. A two-level Generalized Hierarchical Linear Model (GHLM) is used to combine neighborhood-level (level-2) characteristics (i.e., spatial patterns of neighborhood affluence and ethnic composition), and individual-level SES position (level-1) to examine the factors associated with adult obesity risk. Three principal findings were obtained. First, individual obesity risk is significantly higher in spatially clustered neighborhoods of economic affluence. Neighborhood factors associated with obesity are likely to operate over a wide geographical area and are not limited to conditions in the immediate residential neighborhood. Second, aboriginal people living adjacent to the most affluent cluster in northern Taiwan have elevated obesity risk, revealing possible spatial diffusion and ethnic acculturation. Third, adult obesity is, however, associated with socioeconomically disadvantaged groups in different neighborhood contexts. These findings suggest that accounting for spatial interdependencies among neighborhoods enhances the accuracy of estimated neighborhood effects on obesity

(9) FINER N. **Withdrawal of sibutramine. Editorial is judgment in advance of the facts**. BMJ. 2010, vol. 340, p.c1346
http://www.ncbi.nlm.nih.gov/pubmed/20219799 **(accès réservé EHESP)**

(10) GARROW JS. **Withdrawal of sibutramine. Magic bullets now uncontrolled**. BMJ. 2010, vol. 340, p.c1351
http://www.ncbi.nlm.nih.gov/pubmed/20219800 **(accès réservé EHESP)**

(11) HALLBERG P, SCHWAN S, MELHUS H. **Liraglutide for weight loss in obese people**. Lancet. 2010 Feb. 13, vol. 375, n° 9714, pp.551-553
http://dx.doi.org/10.1016/S0140-6736(10)60225-5 **(accès réservé EHESP)**

(12) HART CL, MORRISON DS, BATTY GD, MITCHELL RJ, *et al.* **Effect of body mass index and alcohol consumption on liver disease: analysis of data from two prospective cohort studies**. BMJ. 2010, vol. 340, p.c1240
http://www.ncbi.nlm.nih.gov/pubmed/20223873 **(accès réservé EHESP)**

OBJECTIVE: To investigate whether alcohol consumption and raised body mass index (BMI) act together to increase risk of liver disease. DESIGN: Analysis of data from prospective cohort studies. SETTING: Scotland. PARTICIPANTS: Data were from two of the Midspan prospective cohort studies (9559 men): "Main" study 1965-8, participants from workplaces across central belt of Scotland, population of island of Tiree, and mainland relatives, and "Collaborative" study, 1970-3, participants from 27 workplaces in Glasgow, Clydebank, and Grangemouth. Follow-up was to 31 December 2007 (median 29 years, range 0.13-42). We divided participants into nine groups based on measures of body mass index (BMI) (underweight/normal weight <25, overweight 25 to <30, and obese >or=30) and alcohol consumption (none, 1-14, and >or=15 units per week). MAIN OUTCOME MEASURES: Liver disease morbidity and mortality. RESULTS: 80 (0.8%) men died with liver disease as the main cause and 146 (1.5%) with liver disease as any cause. In the Collaborative study, 196 men (3.3%) had liver disease defined by a death, admission, or cancer registration. BMI and alcohol consumption were strongly associated with liver disease mortality in analyses adjusted for other confounders (P=0.001 and P<0.0001 respectively). Drinkers of 15 or more units per week in any BMI category and obese drinkers had raised relative rates for all definitions of liver disease, compared with underweight/normal weight non-drinkers. Drinkers of 15 or more units per week had adjusted relative rates for liver disease mortality of 3.16 (95% confidence interval 1.28 to 7.8) for underweight/normal weight men, 7.01 (3.02 to 16.3) for overweight, and 18.9 (6.84 to 52.4) for obese men. The relative rate for obese men who consumed 1-14 units per week was 5.3 (1.36 to 20.7). The relative excess risk due to interaction between BMI and alcohol consumption was 5.58 (1.09 to 10.1); synergy index=2.89 (1.29 to 6.47). CONCLUSIONS: Raised BMI and alcohol consumption are both related to liver disease, with evidence of a supra-additive interaction between the two. The occurrence of both factors in the same populations should inform health promotion and public health policies

(13) KAVIKONDALA S, JIANG CQ, ZHANG WS, CHENG KK, *et al.* **Intergenerational 'mismatch' and adiposity in a developing population: the Guangzhou biobank cohort study**. Soc Sci Med. 2010 Mar., vol. 70, n° 6, pp.834-843
http://dx.doi.org/10.1016/j.socscimed.2009.11.009 **(accès réservé EHESP)**

Intergenerational 'mismatch' between maternal and adult environments, common in developing economies, has been hypothesized as contributing to obesity. In a rapidly developing population, we examined whether maternal conditions, proxied by maternal literacy, were associated with adult adiposity, proxied by body mass index (BMI) and waist-hip ratio (WHR) and whether these associations were modified by later life conditions, proxied by socio-economic position (SEP) at three life stages. We also examined if maternal conditions had sex-specific associations with adult adiposity. In a cross-sectional study of 19,957 adults (> or =50 years) from the Guangzhou Biobank Cohort Study (phases 2 and 3 in 2005-2008), we used multivariable linear regression to assess the association of maternal literacy with BMI and WHR, and whether the associations varied with sex, age or SEP. The adjusted association of maternal literacy with WHR varied with sex. In women, but not men, maternal illiteracy was associated with higher WHR and BMI, adjusted for age; these associations remained, although attenuated, after adjusting for lifestyle, life course SEP and paternal literacy. There was little evidence that associations varied with SEP at any stage, although continuity of poor conditions into early life may have exacerbated the association of maternal illiteracy with higher WHR in women. Poor maternal conditions in developing populations may increase vulnerability to adiposity in women. Whether such sex-specific intergenerational effects are driven by epigenetics, maternal sex hormones or other mechanisms, remains to be determined. However, mismatched maternal and later life conditions

do not appear to be associated with adiposity. Our findings, although preliminary, imply that a transient epidemic of obesity may occur in the first generation of women who experience economic development

(14) KRIEMLER S, ZAHNER L, SCHINDLER C, MEYER U, *et al.* **Effect of school based physical activity programme (KISS) on fitness and adiposity in primary schoolchildren: cluster randomised controlled trial**. BMJ. 2010, vol. 340, p.c785
http://www.ncbi.nlm.nih.gov/pubmed/20179126 **(accès réservé EHESP)**

OBJECTIVE: To assess the effectiveness of a school based physical activity programme during one school year on physical and psychological health in young schoolchildren. DESIGN: Cluster randomised controlled trial. SETTING: 28 classes from 15 elementary schools in Switzerland randomly selected and assigned in a 4:3 ratio to an intervention (n=16) or control arm (n=12) after stratification for grade (first and fifth grade), from August 2005 to June 2006. PARTICIPANTS: 540 children, of whom 502 consented and presented at baseline. INTERVENTION: Children in the intervention arm (n=297) received a multi-component physical activity programme that included structuring the three existing physical education lessons each week and adding two additional lessons a week, daily short activity breaks, and physical activity homework. Children (n=205) and parents in the control group were not informed of an intervention group. For most outcome measures, the assessors were blinded. MAIN OUTCOME MEASURES: Primary outcome measures included body fat (sum of four skinfolds), aerobic fitness (shuttle run test), physical activity (accelerometry), and quality of life (questionnaires). Secondary outcome measures included body mass index and cardiovascular risk score (average z score of waist circumference, mean blood pressure, blood glucose, inverted high density lipoprotein cholesterol, and triglycerides). RESULTS: 498 children completed the baseline and follow-up assessments (mean age 6.9 (SD 0.3) years for first grade, 11.1 (0.5) years for fifth grade). After adjustment for grade, sex, baseline values, and clustering within classes, children in the intervention arm compared with controls showed more negative changes in the z score of the sum of four skinfolds (-0.12, 95 % confidence interval -0.21 to -0.03; P=0.009). Likewise, their z scores for aerobic fitness increased more favourably (0.17, 0.01 to 0.32; P=0.04), as did those for moderate-vigorous physical activity in school (1.19, 0.78 to 1.60; P<0.001), all day moderate-vigorous physical activity (0.44, 0.05 to 0.82; P=0.03), and total physical activity in school (0.92, 0.35 to 1.50; P=0.003). Z scores for overall daily physical activity (0.21, -0.21 to 0.63) and physical quality of life (0.42, -1.23 to 2.06) as well as psychological quality of life (0.59, -0.85 to 2.03) did not change significantly. CONCLUSIONS: A school based multi-component physical activity intervention including compulsory elements improved physical activity and fitness and reduced adiposity in children. Trial registration Current Controlled Trials ISRCTN15360785

(15) LIU B, BALKWILL A, REEVES G, BERAL V. **Body mass index and risk of liver cirrhosis in middle aged UK women: prospective study**. BMJ. 2010, vol. 340, p.c912
http://www.ncbi.nlm.nih.gov/pubmed/20223875 **(accès réservé EHESP)**

OBJECTIVE: To determine the relation between body mass index (BMI) and liver cirrhosis and the contribution that BMI and alcohol consumption make to the incidence of liver cirrhosis in middle aged women in the UK. DESIGN: Prospective cohort study (Million Women Study). SETTING: Women recruited from 1996 to 2001 in NHS breast screening centres and followed by record linkage to routinely collected information on hospital admissions and deaths. PARTICIPANTS: 1 230 662 women (mean age 56 years at recruitment) followed for an average of 6.2 years. MAIN OUTCOME MEASURES: Relative risk and absolute risk of first hospital admission with or death from liver cirrhosis adjusted for age, recruitment region, alcohol consumption, smoking, socioeconomic status, and physical activity. RESULTS: 1811 women had a first hospital admission with or died from liver cirrhosis during follow-up. Among women with a BMI of 22.5 or above, increasing BMI was associated with an increased incidence of liver cirrhosis: the adjusted relative risk of cirrhosis increased by 28% (relative risk 1.28, 95% confidence interval 1.19 to 1.38; P<0.001) for every 5 unit increase in BMI. Although the relative increase in the risk of liver cirrhosis per 5 unit increase in BMI did not differ significantly according to the amount of alcohol consumed, the absolute risk did. Among women who reported drinking less than 70 g alcohol per week, the absolute risk of liver cirrhosis per 1000 women over five

years was 0.8 (0.7 to 0.9) for those with a BMI between 22.5 and 25 and 1.0 (0.9 to 1.2) for those with a BMI of 30 or more. Among women who reported drinking 150 g alcohol or more per week, the corresponding figures were 2.7 (2.1 to 3.4) and 5.0 (3.8 to 6.6). CONCLUSIONS: Excess body weight increases the incidence of liver cirrhosis. In middle aged women in the UK, an estimated 17% of incident or fatal liver cirrhosis is attributable to excess body weight. This compares with an estimated 42% attributable to alcohol

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http://www.ncbi.nlm.nih.gov/pubmed/20181637 **(accès réservé EHESP)**

(17) PEARSON WS, BHAT-SCHELBERT K, FORD ES, MOKDAD AH. **The impact of obesity on time spent with the provider and number of medications managed during office-based physician visits using a cross-sectional, national health survey**. BMC Public Health. 2009, vol. 9, p.436
http://dx.doi.org/10.1186/1471-2458-9-436 **(accès libre)**

BACKGROUND: Obesity is associated with morbidity, mortality, and increased health care costs. Few studies have examined the impact of obesity on outpatient office visits. The purpose of this study was to determine if outpatient visits by obese persons required more time with the provider and more prescription medication management compared to visits made by non-obese persons. METHODS: Obesity status was determined for 9,280 patient visits made by persons aged 18 years or older in the 2006 National Ambulatory Medical Care Survey. Multivariate analyses compared obese and non-obese visits, stratified by sex, for duration of the visit and the number of medications mentioned at the visit. RESULTS: Average duration of visit was higher among visits with patients determined to be obese. However, these differences were not considered significant after statistical testing. Visits made by obese female patients were significantly more likely to involve more than two prescription medications (OR 1.26, 95% CI 1.05 - 1.51) and visits made by obese male patients were significantly more likely to involve more than two prescription medications (OR 1.46, 95% CI 1.16 - 1.83) as compared to visits made by non-obese patients. CONCLUSION: Time spent with the provider was found to be greater among visits with obese patients, but not significantly different from visits with non-obese patients. The number of medications for each visit was found to be significantly greater for visits where the patient was considered to be obese. Increased time for the visit and increased numbers of medication for each visit translate into increased costs. These findings document the impact of obesity on our health care system and have great implications on medical care cost and planning

(18) PETO R, WHITLOCK G, JHA P. **Effects of obesity and smoking on U.S. life expectancy**. N Engl J Med. 2010 Mar. 4, vol. 362, n° 9, pp.855-856
http://dx.doi.org/10.1056/NEJMc1000079 **(accès réservé EHESP)**

(19) STOMMEL M, SCHOENBORN CA. **Accuracy and usefulness of BMI measures based on self-reported weight and height: findings from the NHANES & NHIS 2001-2006**. BMC Public Health. 2009, vol. 9, p.421
http://dx.doi.org/10.1186/1471-2458-9-421 **(accès libre)**

BACKGROUND: The Body Mass Index (BMI) based on self-reported height and weight ("self-reported BMI") in epidemiologic studies is subject to measurement error. However, because of the ease and efficiency in gathering height and weight information through interviews, it remains important to assess the extent of error present in self-reported BMI measures and to explore possible adjustment factors as well as valid uses of such self-reported measures. METHODS: Using the combined 2001-2006 data from the continuous National Health and Nutrition Examination Survey, discrepancies between BMI measures based on self-reported and physical height and weight measures are estimated and socio-demographic predictors of such discrepancies are identified. Employing adjustments derived from the socio-demographic predictors, the self-reported measures of height and weight in the 2001-2006 National Health

Interview Survey are used for population estimates of overweight & obesity as well as the prediction of health risks associated with large BMI values. The analysis relies on two-way frequency tables as well as linear and logistic regression models. All point and variance estimates take into account the complex survey design of the studies involved. RESULTS: Self-reported BMI values tend to overestimate measured BMI values at the low end of the BMI scale (< 22) and underestimate BMI values at the high end, particularly at values > 28. The discrepancies also vary systematically with age (younger and older respondents underestimate their BMI more than respondents aged 42-55), gender and the ethnic/racial background of the respondents. BMI scores, adjusted for socio-demographic characteristics of the respondents, tend to narrow, but do not eliminate misclassification of obese people as merely overweight, but health risk estimates associated with variations in BMI values are virtually the same, whether based on self-report or measured BMI values. CONCLUSION: BMI values based on self-reported height and weight, if corrected for biases associated with socio-demographic characteristics of the survey respondents, can be used to estimate health risks associated with variations in BMI, particularly when using parametric prediction models

(20) THUM T, ANKER SD. **Liraglutide for weight loss in obese people**. Lancet. 2010 Feb. 13, vol. 375, n° 9714, pp.551-552
http://dx.doi.org/10.1016/S0140-6736(10)60226-7 **(accès réservé EHESP)**

(21) VAN SLUIJS EM, MCMINN A. **Preventing obesity in primary schoolchildren**. BMJ. 2010, vol. 340, p.c819
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(22) VEIGA OL, GOMEZ-MARTINEZ S, MARTINEZ-GOMEZ D, VILLAGRA A, *et al.* **Physical activity as a preventive measure against overweight, obesity, infections, allergies and cardiovascular disease risk factors in adolescents: AFINOS Study protocol**. BMC Public Health. 2009, vol. 9, p.475
http://dx.doi.org/10.1186/1471-2458-9-475 **(accès libre)**

BACKGROUND: Prior studies addressing the impacts of regular physical activity or sedentary habits on the immune system have been conducted in adults and laboratory settings. Thus, it is practically unknown how a healthy active lifestyle could affect low-grade inflammation processes, infections or allergies in young persons. The AFINOS Study was designed to determine the relationship between the regular physical activity levels of adolescents and overweight, infection, and allergies along with the presence of metabolic and immunological biomarkers of a deteriorated health status. A further objective of the AFINOS Study is to assess the health status and lifestyle habits of an adolescent population in an effort to identify any protective factors that could be used as preventive measures, since many chronic diseases and their associated co-morbidities often persist from adolescence into adulthood. METHODS/DESIGN: This study was conducted as three separate sub-studies in three different populations as follows: (a) Study 1 was performed on a population sample of adolescents; (b) Study 2 on the adolescents' parents; and (c) Study 3 on a subset of the adolescents from Study 1. Study 1 assessed health and lifestyle indicators through a questionnaire administered to a representative sample of adolescents from the Madrid Region (n = 2400) aged 13 to 16 years. In Study 2, the parents of the teenagers participating in Study 1 were required to fill out a questionnaire. Finally in Study 3, body composition, physical activity, health-related physical fitness, and blood measurements were determined in a subset (n = 200) of the individuals included in Study 1. DISCUSSION: This paper describes the rationale, design, and methodologies used in the AFINOS Study. This multidisciplinary, multicenter study seeks to evaluate several aspects of existing relationships between routine physical activity/sedentary behaviour and several health status markers, specifically those related to the immune system. The results of this cross-sectional study will serve for comparisons with the available data obtained in laboratory settings and in adults. In addition, knowledge regarding the health status and lifestyle habits of Spanish adolescents and their parents will be useful for designing preventive measures

(23) WALTERS RG, JACQUEMONT S, VALSESIA A, DE SMITH AJ, *et al.* **A new highly penetrant form of obesity due to deletions on chromosome 16p11.2**. Nature. 2010 Feb. 4, vol. 463, n° 7281, pp.671-675
http://dx.doi.org/10.1038/nature08727 **(accès payant)**

Obesity has become a major worldwide challenge to public health, owing to an interaction between the Western 'obesogenic' environment and a strong genetic contribution. Recent extensive genome-wide association studies (GWASs) have identified numerous single nucleotide polymorphisms associated with obesity, but these loci together account for only a small fraction of the known heritable component. Thus, the 'common disease, common variant' hypothesis is increasingly coming under challenge. Here we report a highly penetrant form of obesity, initially observed in 31 subjects who were heterozygous for deletions of at least 593 kilobases at 16p11.2 and whose ascertainment included cognitive deficits. Nineteen similar deletions were identified from GWAS data in 16,053 individuals from eight European cohorts. These deletions were absent from healthy non-obese controls and accounted for 0.7% of our morbid obesity cases (body mass index (BMI) >or= 40 kg m(-2) or BMI standard deviation score >or= 4; P = 6.4 x 10(-8), odds ratio 43.0), demonstrating the potential importance in common disease of rare variants with strong effects. This highlights a promising strategy for identifying missing heritability in obesity and other complex traits: cohorts with extreme phenotypes are likely to be enriched for rare variants, thereby improving power for their discovery. Subsequent analysis of the loci so identified may well reveal additional rare variants that further contribute to the missing heritability, as recently reported for SIM1 (ref. 3). The most productive approach may therefore be to combine the 'power of the extreme' in small, well-phenotyped cohorts, with targeted follow-up in case-control and population cohorts

(24) WARING ME, EATON CB, LASATER TM, LAPANE KL. **Incident diabetes in relation to weight patterns during middle age**. Am J Epidemiol. 2010 Mar. 1, vol. 171, n° 5, pp.550-556
http://dx.doi.org/10.1093/aje/kwp433 **(accès réservé EHESP)**

The authors examined the association between weight patterns during middle age and incident type 2 diabetes mellitus using a subset (n = 1,476) of the Framingham Heart Study original cohort limited-access data set (1948-2003). Participants diagnosed with diabetes before age 50 years were excluded. A functional principal components analysis of body mass index from age 40 years to age 50 years was used to define weight patterns in terms of overall weight status (normal weight, overweight, or obese), weight change (weight loss, stable weight, or weight gain), and weight cycling. Overall overweight and obesity were associated with higher rates of diabetes (for overall overweight, crude hazard ratio (HR) = 3.2, 95% confidence interval (CI): 2.3, 4.6; for overall obesity, crude HR = 8.8, 95% CI: 6.0, 12.8). Weight cycling was also associated with higher rates of diabetes (crude HR = 1.6, 95% CI: 1.2, 2.1). Neither weight loss nor weight gain was associated with incident diabetes. After adjustment for overall weight status, weight cycling was no longer associated with higher rates of diabetes. This study underscores the importance of obesity in diabetes risk and the importance of preventing the development of overweight and obesity earlier in life

SIDA

sommaire

(1) **HIV: consensus indicators are needed for concurrency**. Lancet. 2010 Feb. 20, vol. 375, n° 9715, pp.621-622
http://dx.doi.org/10.1016/S0140-6736(09)62040-7 **(accès réservé EHESP)**

(2) **The Global Fund: replenishment and redefinition in 2010**. Lancet. 2010 Mar. 13, vol. 375, n° 9718, p.865
http://dx.doi.org/10.1016/S0140-6736(10)60366-2 **(accès réservé EHESP)**

(3) BDOOL KARIM SS, NAIDOO K, GROBLER A, PADAYATCHI N, *et al.* **Timing of initiation of antiretroviral drugs during tuberculosis therapy**. N Engl J Med. 2010 Feb. 25, vol. 362, n° 8, pp.697-706
http://dx.doi.org/10.1056/NEJMoa0905848 **(accès réservé EHESP)**

BACKGROUND: The rates of death are high among patients with coinfection with tuberculosis and the human immunodeficiency virus (HIV). The optimal timing for the initiation of antiretroviral therapy in relation to tuberculosis therapy remains controversial. METHODS: In an open-label, randomized, controlled trial in Durban, South Africa, we assigned 642 patients with both tuberculosis and HIV infection to start antiretroviral therapy either during tuberculosis therapy (in two integrated-therapy groups) or after the completion of such treatment (in one sequential-therapy group). The diagnosis of tuberculosis was based on a positive sputum smear for acid-fast bacilli. Only patients with HIV infection and a CD4+ cell count of less than 500 per cubic millimeter were included. All patients received standard tuberculosis therapy, prophylaxis with trimethoprim-sulfamethoxazole, and a once-daily antiretroviral regimen of didanosine, lamivudine, and efavirenz. The primary end point was death from any cause. RESULTS: This analysis compares data from the sequential-therapy group and the combined integrated-therapy groups up to September 1, 2008, when the data and safety monitoring committee recommended that all patients receive integrated antiretroviral therapy. There was a reduction in the rate of death among the 429 patients in the combined integrated-therapy groups (5.4 deaths per 100 person-years, or 25 deaths), as compared with the 213 patients in the sequential-therapy group (12.1 per 100 person-years, or 27 deaths); a relative reduction of 56% (hazard ratio in the combined integrated-therapy groups, 0.44; 95% confidence interval, 0.25 to 0.79; P=0.003). Mortality was lower in the combined integrated-therapy groups in all CD4+ count strata. Rates of adverse events during follow-up were similar in the two study groups. CONCLUSIONS: The initiation of antiretroviral therapy during tuberculosis therapy significantly improved survival and provides further impetus for the integration of tuberculosis and HIV services. (ClinicalTrials.gov number, NCT00398996.)

(4) BUVE A, LYNEN L. **Treating HIV infection with drugs for HSV-2 infection?** Lancet. 2010 Mar. 6, vol. 375, n° 9717, pp.782-784
http://dx.doi.org/10.1016/S0140-6736(10)60097-9 **(accès réservé EHESP)**

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http://dx.doi.org/10.1126/science.327.5970.1196-b **(accès réservé EHESP)**

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(8) ENSERINK M. **Scientific publishing. Elsevier to editor: change controversial journal or resign**. Science. 2010 Mar. 12, vol. 327, n° 5971, p.1316
http://dx.doi.org/10.1126/science.327.5971.1316 **(accès réservé EHESP)**

(9) HAASE AT. **Targeting early infection to prevent HIV-1 mucosal transmission**. Nature. 2010 Mar. 11, vol. 464, n° 7286, pp.217-223
http://dx.doi.org/10.1038/nature08757 **(accès payant)**

Measures to prevent sexual mucosal transmission of human immunodeficiency virus (HIV)-1 are urgently needed to curb the growth of the acquired immunodeficiency syndrome (AIDS) pandemic and ultimately bring it to an end. Studies in animal models and acute HIV-1 infection reviewed here reveal potential viral vulnerabilities at the mucosal portal of entry in the earliest stages of infection that might be most effectively targeted by vaccines and microbicides, thereby preventing acquisition and averting systemic infection, CD4 T-cell depletion and pathologies that otherwise rapidly ensue

(10) HARE S, GUPTA SS, VALKOV E, ENGELMAN A, *et al.* **Retroviral intasome assembly and inhibition of DNA strand transfer**. Nature. 2010 Mar. 11, vol. 464, n° 7286, pp.232-236
http://dx.doi.org/10.1038/nature08784 **(accès payant)**

Integrase is an essential retroviral enzyme that binds both termini of linear viral DNA and inserts them into a host cell chromosome. The structure of full-length retroviral integrase, either separately or in complex with DNA, has been lacking. Furthermore, although clinically useful inhibitors of HIV integrase have been developed, their mechanism of action remains speculative. Here we present a crystal structure of full-length integrase from the prototype foamy virus in complex with its cognate DNA. The structure shows the organization of the retroviral intasome comprising an integrase tetramer tightly associated with a pair of viral DNA ends. All three canonical integrase structural domains are involved in extensive protein-DNA and protein-protein interactions. The binding of strand-transfer inhibitors displaces the reactive viral DNA end from the active site, disarming the viral nucleoprotein complex. Our findings define the structural basis of retroviral DNA integration, and will allow modelling of the HIV-1 intasome to aid in the development of antiretroviral drugs

(11) HORTON R. **Offline: AIDS is not zero sum**. Lancet. 2010 Feb. 20, vol. 375, n° 9715, p.624
http://dx.doi.org/10.1016/S0140-6736(10)60244-9 **(accès réservé EHESP)**

(12) KOFF WC. **Accelerating HIV vaccine development**. Nature. 2010 Mar. 11, vol. 464, n° 7286, pp.161-162
http://dx.doi.org/10.1038/464161a **(accès payant)**

(13) LEINER S. **A controlled trial of initial antiviral regimens for HIV-1 infection**. N Engl J Med. 2010 Mar. 4, vol. 362, n° 9, pp.854-855
http://www.ncbi.nlm.nih.gov/pubmed/20213882 **(accès réservé EHESP)**

(14) LINGAPPA JR, BAETEN JM, WALD A, HUGHES JP, *et al.* **Daily aciclovir for HIV-1 disease progression in people dually infected with HIV-1 and herpes simplex virus type 2: a randomised placebo-controlled trial**. Lancet. 2010 Mar. 6, vol. 375, n° 9717, pp.824-833
http://dx.doi.org/10.1016/S0140-6736(09)62038-9 **(accès réservé EHESP)**

BACKGROUND: Most people infected with HIV-1 are dually infected with herpes simplex virus type 2. Daily suppression of this herpes virus reduces plasma HIV-1 concentrations, but whether it delays HIV-1 disease progression is unknown. We investigated the effect of aciclovir on HIV-1 progression. METHODS: In a trial with 14 sites in southern Africa and east Africa, 3381 heterosexual people who were dually infected with herpes simplex virus type 2 and HIV-1 were randomly assigned in a 1:1 ratio to aciclovir 400 mg orally twice daily or placebo, and were followed up for up to 24 months. Eligible participants had CD4 cell counts of 250 cells per microL or higher and were not taking antiretroviral therapy. We used block randomisation, and patients and investigators were masked to treatment allocation. Effect of aciclovir on HIV-1 disease progression was defined by a primary composite endpoint of first occurrence of CD4 cell counts of fewer than 200 cells per microL, antiretroviral therapy initiation, or non-trauma related death. As an exploratory analysis, we assessed the endpoint of CD4 falling to <350 cells per microL. Analysis was by intention to treat. The trial is registered with ClinicalTrials.gov, number NCT00194519. FINDINGS: At enrolment, the median CD4 cell count was 462 cells per microL

and median HIV-1 plasma RNA was 4.1 log(10) copies per microL. Aciclovir reduced risk of HIV-1 disease progression by 16%; 284 participants assigned aciclovir versus 324 assigned placebo reached the primary endpoint (hazard ratio [HR] 0.84, 95% CI 0.71-0.98, p=0.03). In those with CD4 counts >or=350 cells per microL, aciclovir delayed risk of CD4 cell counts falling to <350 cells per microL by 19% (0.81, 0.71-0.93, p=0.002) INTERPRETATION: The role of suppression of herpes simplex virus type 2 in reduction of HIV-1 disease progression before initiation of antiretroviral therapy warrants consideration. FUNDING: Bill & Melinda Gates Foundation

(15) MUGYENYI P, WALKER AS, HAKIM J, MUNDERI P, *et al.* **Routine versus clinically driven laboratory monitoring of HIV antiretroviral therapy in Africa (DART): a randomised non-inferiority trial**. Lancet. 2010 Jan. 9, vol. 375, n° 9709, pp.123-131
http://dx.doi.org/10.1016/S0140-6736(09)62067-5 **(accès réservé EHESP)**

BACKGROUND: HIV antiretroviral therapy (ART) is often managed without routine laboratory monitoring in Africa; however, the effect of this approach is unknown. This trial investigated whether routine toxicity and efficacy monitoring of HIV-infected patients receiving ART had an important long-term effect on clinical outcomes in Africa. METHODS: In this open, non-inferiority trial in three centres in Uganda and one in Zimbabwe, 3321 symptomatic, ART-naive, HIV-infected adults with CD4 counts less than 200 cells per microL starting ART were randomly assigned to laboratory and clinical monitoring (LCM; n=1659) or clinically driven monitoring (CDM; n=1662) by a computer-generated list. Haematology, biochemistry, and CD4-cell counts were done every 12 weeks. In the LCM group, results were available to clinicians; in the CDM group, results (apart from CD4-cell count) could be requested if clinically indicated and grade 4 toxicities were available. Participants switched to second-line ART after new or recurrent WHO stage 4 events in both groups, or CD4 count less than 100 cells per microL (LCM only). Co-primary endpoints were new WHO stage 4 HIV events or death, and serious adverse events. Non-inferiority was defined as the upper 95% confidence limit for the hazard ratio (HR) for new WHO stage 4 events or death being no greater than 1.18. Analyses were by intention to treat. This study is registered, number ISRCTN13968779. FINDINGS: Two participants assigned to CDM and three to LCM were excluded from analyses. 5-year survival was 87% (95% CI 85-88) in the CDM group and 90% (88-91) in the LCM group, and 122 (7%) and 112 (7%) participants, respectively, were lost to follow-up over median 4.9 years' follow-up. 459 (28%) participants receiving CDM versus 356 (21%) LCM had a new WHO stage 4 event or died (6.94 [95% CI 6.33-7.60] vs 5.24 [4.72-5.81] per 100 person-years; absolute difference 1.70 per 100 person-years [0.87-2.54]; HR 1.31 [1.14-1.51]; p=0.0001). Differences in disease progression occurred from the third year on ART, whereas higher rates of switch to second-line treatment occurred in LCM from the second year. 283 (17%) participants receiving CDM versus 260 (16%) LCM had a new serious adverse event (HR 1.12 [0.94-1.32]; p=0.19), with anaemia the most common (76 vs 61 cases). INTERPRETATION: ART can be delivered safely without routine laboratory monitoring for toxic effects, but differences in disease progression suggest a role for monitoring of CD4-cell count from the second year of ART to guide the switch to second-line treatment. FUNDING: UK Medical Research Council, the UK Department for International Development, the Rockefeller Foundation, GlaxoSmithKline, Gilead Sciences, Boehringer-Ingelheim, and Abbott Laboratories

(16) PARIENTI JJ. **A controlled trial of initial antiviral regimens for HIV-1 infection**. N Engl J Med. 2010 Mar. 4, vol. 362, n° 9, p.854
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(17) SAREWITZ D. **Better all the time**. Nature. 2010 Feb. 4, vol. 463, n° 7281, p.607
http://dx.doi.org/10.1038/463607a **(accès payant)**

(18) SIDIBE M, BUSE K. **Fomenting a prevention revolution for HIV**. Lancet. 2010 Feb. 13, vol. 375, n° 9714, pp.533-535
http://dx.doi.org/10.1016/S0140-6736(10)60138-9 **(accès réservé EHESP)**

(19) SINGH JA. **Organ transplantation between HIV-infected patients**. Lancet. 2010 Feb. 6, vol. 375, n° 9713, pp.442-443
http://dx.doi.org/10.1016/S0140-6736(09)60338-X **(accès réservé EHESP)**

(20) VIRGIN HW, WALKER BD. **Immunology and the elusive AIDS vaccine**. Nature. 2010 Mar. 11, vol. 464, n° 7286, pp.224-231
http://dx.doi.org/10.1038/nature08898 **(accès payant)**

Developing a human immunodeficiency virus (HIV) vaccine is critical to end the global acquired immunodeficiency syndrome (AIDS) epidemic, but many question whether this goal is achievable. Natural immunity is not protective, and despite immunogenicity of HIV vaccine candidates, human trials have exclusively yielded disappointing results. Nevertheless, there is an indication that success may be possible, but this will be dependent on understanding the antiviral immune response in unprecedented depth to identify and engineer the types of immunity required. Here we outline fundamental immunological questions that need to be answered to develop a protective HIV vaccine, and the immediate need to harness a much broader scientific community to achieve this goal

Tuberculose

sommaire

(1) **The Global Fund: replenishment and redefinition in 2010**. Lancet. 2010 Mar. 13, vol. 375, n° 9718, p.865
http://dx.doi.org/10.1016/S0140-6736(10)60366-2 **(accès réservé EHESP)**

(2) BDOOL KARIM SS, NAIDOO K, GROBLER A, PADAYATCHI N, *et al.* **Timing of initiation of antiretroviral drugs during tuberculosis therapy**. N Engl J Med. 2010 Feb. 25, vol. 362, n° 8, pp.697-706
http://dx.doi.org/10.1056/NEJMoa0905848 **(accès réservé EHESP)**

BACKGROUND: The rates of death are high among patients with coinfection with tuberculosis and the human immunodeficiency virus (HIV). The optimal timing for the initiation of antiretroviral therapy in relation to tuberculosis therapy remains controversial. METHODS: In an open-label, randomized, controlled trial in Durban, South Africa, we assigned 642 patients with both tuberculosis and HIV infection to start antiretroviral therapy either during tuberculosis therapy (in two integrated-therapy groups) or after the completion of such treatment (in one sequential-therapy group). The diagnosis of tuberculosis was based on a positive sputum smear for acid-fast bacilli. Only patients with HIV infection and a CD4+ cell count of less than 500 per cubic millimeter were included. All patients received standard tuberculosis therapy, prophylaxis with trimethoprim-sulfamethoxazole, and a once-daily antiretroviral regimen of didanosine, lamivudine, and efavirenz. The primary end point was death from any cause. RESULTS: This analysis compares data from the sequential-therapy group and the combined integrated-therapy groups up to September 1, 2008, when the data and safety monitoring committee recommended that all patients receive integrated antiretroviral therapy. There was a reduction in the rate of death among the 429 patients in the combined integrated-therapy groups (5.4 deaths per 100 person-years, or 25 deaths), as compared with the 213 patients in the sequential-therapy group (12.1 per 100 person-years, or 27 deaths); a relative reduction of 56% (hazard ratio in the combined integrated-therapy groups, 0.44; 95% confidence interval, 0.25 to 0.79; P=0.003). Mortality was lower in the combined integrated-therapy groups in all CD4+ count strata. Rates of adverse events during follow-up were similar in the two study groups. CONCLUSIONS: The initiation of antiretroviral therapy during tuberculosis therapy significantly improved survival and provides further impetus for the integration of tuberculosis and HIV services. (ClinicalTrials.gov number, NCT00398996.)

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BACKGROUND: Tuberculosis screening is recommended for people with human immunodeficiency virus (HIV) infection to facilitate early diagnosis and safe initiation of antiretroviral therapy and isoniazid preventive therapy. No internationally accepted, evidence-based guideline addresses the optimal means of conducting such screening, although screening for chronic cough is common. METHODS: We consecutively enrolled people with HIV infection from eight outpatient clinics in Cambodia, Thailand, and Vietnam. For each patient, three samples of sputum and one each of urine, stool, blood, and lymph-node aspirate (for patients with lymphadenopathy) were obtained for mycobacterial culture. We compared the characteristics of patients who received a diagnosis of tuberculosis (on the basis of having one or more specimens that were culture-positive) with those of patients who did not have tuberculosis to derive an algorithm for screening and diagnosis. RESULTS: Tuberculosis was diagnosed in 267 (15%) of 1748 patients (median CD4+ T-lymphocyte count, 242 per cubic millimeter; interquartile range, 82 to 396). The presence of a cough for 2 or 3 weeks or more during the preceding 4 weeks had a sensitivity of 22 to 33% for detecting tuberculosis. The presence of cough of any duration, fever of any duration, or night sweats lasting 3 or more weeks in the preceding 4 weeks was 93% sensitive and 36% specific for tuberculosis. In the 1199 patients with any of these symptoms, a combination of two negative sputum smears, a normal chest radiograph, and a CD4+ cell count of 350 or more per cubic millimeter helped to rule out a diagnosis of tuberculosis, whereas a positive diagnosis could be made only for the 113 patients (9%) with one or more positive sputum smears; mycobacterial culture was required for most other patients. CONCLUSIONS: In persons with HIV infection, screening for tuberculosis should include asking questions about a combination of symptoms rather than only about chronic cough. It is likely that antiretroviral therapy and isoniazid preventive therapy can be started safely in people whose screening for all three symptoms is negative, whereas diagnosis in most others will require mycobacterial culture

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BACKGROUND: Tuberculosis (TB) is a global health concern. Inadequate case finding and case holding has been cited as major barrier to the control of TB. The TB literature is written almost entirely from a biomedical perspective, while recent studies show that it is imperative to understand lay perception to determine why people seek treatment and may stop taking treatment. The Eastern Cape is known as a province with high TB incidence, prevalence and with one of the worst cure rates of South Africa. Its inhabitants can be considered lay experts when it comes to TB. Therefore, we investigated knowledge, perceptions of (access to) TB treatment and adherence to treatment among an Eastern Cape population. METHODS: An area-stratified sampling design was applied. A total of 1020 households were selected randomly in proportion to the total number of households in each neighbourhood. RESULTS: TB knowledge can be considered fairly good among this community. Respondents' perceptions suggest that stigma may influence TB patients' decision in health seeking behavior and adherence to TB treatment. A full

95% of those interviewed believe people with TB tend to hide their TB status out of fear of what others may say. Regression analyses revealed that in this population young and old, men and women and the lower and higher educated share the same attitudes and perceptions. Our findings are therefore likely to reflect the actual situation of TB patients in this population. CONCLUSIONS: The lay experts' perceptions suggests that stigma appears to effect case holding and case finding. Future interventions should be directed at improving attitudes and perceptions to potentially reduce stigma. This requires a patient-centered approach to empower TB patients and active involvement in the development and implementation of stigma reduction programs

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OBJECTIVE: To determine whether BCG revaccination at 19 months of age reduces overall child mortality. DESIGN: Randomised trial, with follow-up to age 5. SETTING: A health project in Bissau, Guinea-Bissau, which maintains a health and demographic surveillance system in an urban area with 90 000 inhabitants. PARTICIPANTS: 2871 children aged 19 months to 5 years with low or no reactivity to tuberculin and who were not severely sick on the day of enrollment. INTERVENTION: BCG vaccination or no vaccination (control). MAIN OUTCOME MEASURE: Hazard ratios for mortality. RESULTS: 77 children died during follow-up. Compared with controls, the BCG revaccinated children had a hazard ratio of 1.20 (95% confidence interval 0.77 to 1.89). Two hundred and fifty children were admitted to hospital for the first time between enrollment and the end of the study, with an incidence rate ratio for BCG revaccinated children versus controls of 1.04 (0.81 to 1.33). The trial was stopped prematurely because of a cluster of deaths in the BCG arm of the study. This increase in mortality occurred at a time when many children had received missing vaccinations or vitamin A or iron supplementation; the hazard ratio for BCG revaccinated children compared with controls was 2.69 (1.05 to 6.88) in the period after these campaigns. Throughout the trial, the effect of BCG revaccination on mortality was significantly different (P=0.006) in children who had received diphtheria-tetanus-pertussis (DTP) booster vaccination before enrollment (hazard ratio 0.36, 0.13 to 0.99) and children who had not received the booster before enrollment (1.78, 1.04 to 3.04). CONCLUSIONS: There was no overall beneficial effect of being revaccinated with BCG. The effect of BCG revaccination on mortality might depend on other health interventions. Trial registration Clinical Trials ICA4-CT-2002-10053-REVAC

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