Association of funding and conclusions in randomized drug trials: A reflection of treatment effect or adverse events?

CONTEXT: Previous studies indicate that industry-sponsored trials tend to draw pro-industry conclusions.
OBJECTIVE: To explore whether the association between funding and conclusions in randomized drug trials reflects treatment effects or adverse events.
DESIGN: Observational study of 370 randomized drug trials included in meta-analyses from Cochrane reviews selected from the Cochrane Library, May 2001. From a random sample of 167 Cochrane reviews, 25 contained eligible meta-analyses (assessed a binary outcome; pooled at least 5 full-paper trials of which at least 1 reported adequate and 1 reported inadequate allocation concealment). The primary binary outcome from each meta-analysis was considered the primary outcome for all trials included in each meta-analysis. The association between funding and conclusions was analyzed by logistic regression with adjustment for treatment effect, adverse events, and additional confounding factors (methodological quality, control intervention, sample size, publication year, and place of publication).
MAIN OUTCOME MEASURE: Conclusions in trials, classified into whether the experimental drug was recommended as the treatment of choice or not.
RESULTS: The experimental drug was recommended as treatment of choice in 16% of trials funded by nonprofit organizations, 30% of trials not reporting funding, 35% of trials funded by both nonprofit and for-profit organizations, and 51% of trials funded by for-profit organizations ($P < .001$; χ^2 test). Logistic regression analyses indicated that funding, treatment effect, and double blinding were the only significant predictors of conclusions. Adjusted analyses showed that trials funded by for-profit organizations were significantly more likely to recommend the experimental drug as treatment of choice (odds ratio, 5.3; 95% confidence interval, 2.0–14.4) compared with trials funded by nonprofit organizations. This association did not appear to reflect treatment effect or adverse events.
CONCLUSIONS: Conclusions in trials funded by for-profit organizations may be more positive due to biased interpretation of trial results. Readers should carefully evaluate whether conclusions in randomized trials are supported by data.

Als-Nielsen B, Chen W, Gluud C, Kjaergard LL. JAMA 2003; 290:921–8.
(http://jama.ama-assn.org)

Association between BRCA1 mutations and ratio of female to male births in offspring of families with breast cancer, ovarian cancer, or both

CONTEXT: Defects in X-chromosome inactivation distort sex ratio in mice. The BRCA1 gene is also involved in X-chromosome inactivation, suggesting the possibility that some sex-ratio distortion may be associated with BRCA1-related human cancer syndromes.
OBJECTIVE: To determine whether BRCA1 mutations are associated with distortion of the sex ratio of births in families with breast cancer, ovarian cancer, or both.
DESIGN AND SETTING: Analysis of germline mutations in participants from Spain who had been screened for BRCA between 1998 and 2002.
PARTICIPANTS: Sixty-eight families with at least 3 breast cancer cases or ovarian cancer cases, or both types of cancer in 2 generations (germline mutations: BRCA1, $n = 17$; BRCA2, $n = 15$; and BRCA unrelated, $n = 36$). An average of 4 relatives per family were tested for the corresponding BRCA mutation.
MAIN OUTCOME MEASURE: Male and female births registered in breast and/or ovarian pedigrees tested for the presence of BRCA1 and BRCA2 germline mutations.
RESULTS: Of BRCA1-related breast and/or ovarian cancer pedigrees, there was a 2-fold excess of female births (218 female vs 109 male births). Of BRCA2-related or BRCA-unrelated breast and/or ovarian cancer pedigrees, there was not an excess of female births (175 female/150 male and 344 female/315 male, respectively). Of 327 BRCA1 births, 218 (67%) were female births compared with 54% among BRCA2 pedigrees (175/327; $P < .001$) and 52% among BRCA-unrelated pedigrees (344/659; $P < .001$). Female births increased in the offspring of BRCA1 carriers compared with BRCA2 carriers (67% vs 52%; $P = .004$).
CONCLUSION: In these families with breast and/or ovarian cancer, mutations in BRCA1 but not BRCA2 were associated with a sex ratio skewed against male births.

de la Hoya M, Fernandez JM, Tosar A, Godino J, Sanchez de Abajo A, Vidart JA, et al. JAMA 2003;290:929–31.
(http://jama.ama-assn.org)

Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism*

BACKGROUND: Warfarin is very effective in the prevention of recurrent venous thromboembolism. However, it is also associated with a substantial risk of bleeding. It is possible that a lower dose of warfarin after the initial three months might result in fewer serious side effects.
METHODS: This randomized, double-blind trial studied a total of 738 patients who had completed three or more months of warfarin usage prior to enrollment for the prevention of recurrent thromboembolism. The patients were assigned either to warfarin therapy with a target international normalized ratio

** Modified abstract.*

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(INR) of 2.0 to 3.0 (conventional therapy) or a target INR of 1.5 to 1.9 (low intensity). The patients were followed for an average of 2.4 years.

RESULTS: Sixteen of the 369 patients who were assigned to the low-intensity therapy had recurrent venous thromboembolism (1.9 per 100 person-years), compared to six of 369 who were assigned to the conventional therapy (0.7 per 100 person-years; hazard ratio, 2.8; 95%CI, 1.1 to 7.0). A major bleeding episode occurred in nine patients assigned to low-dose therapy and eight patients assigned to conventional therapy (hazard ratio, 1.2; 95%CI 0.4 to 3.0). There was no significant difference in the frequency of overall bleeding between the two study groups.

CONCLUSIONS: Conventional warfarin therapy is more effective than low-intensity (as defined above) therapy for the prevention of recurrent venous thromboembolism. In addition, the low-intensity therapy does not reduce the risk of clinically significant bleeding.

Kearon C, Ginsberg JS, Kovacs MJ, Anderson DR, Wells P, Julian JA, et al, Forth; Extended Low-Intensity Anticoagulation for Thrombo-Embolism Investigators. N Engl J Med 2003;349: 631–9.
(http://www.nejm.org)

Potential health and economic impact of adding a human papillomavirus vaccine to screening programs

CONTEXT: Recently published results suggest that effective vaccines against cervical cancer-associated human papillomavirus (HPV) may become available within the next decade.

OBJECTIVE: To examine the potential health and economic effects of an HPV vaccine in a setting of existing screening.

DESIGN, SETTING, AND POPULATION: A Markov model was used to estimate the lifetime (age 12–85 years) costs and life expectancy of a hypothetical cohort of women screened for cervical cancer in the United States. Three strategies were compared: (1) vaccination only; (2) conventional cytological screening only; and (3) vaccination followed by screening. Two of the strategies incorporated a vaccine targeted against a defined proportion of high-risk (oncogenic) HPV types. Screening intervals of 1, 2, 3, and 5 years and starting ages for screening of 18, 22, 24, 26, and 30 years were chosen for 2 of the strategies (conventional cytological screening only and vaccination followed by screening).

MAIN OUTCOME MEASURES: Incremental cost per life-year gained.

RESULTS: Vaccination only or adding vaccination to screening conducted every 3 and 5 years was not cost-effective. However, at more frequent screening intervals, strategies combining vaccination and screening were preferred. Vaccination plus biennial screening delayed until age 24 years had the most attractive cost-effectiveness ratio (44 889 dollars) compared with screening only beginning at age 18 years and conducted every 3 years. However, the strategy of vaccination with annual screening beginning at age 18 years had the largest overall reduction in cancer incidence and mortality at a cost of 236 250 dollars per life-year gained compared with vaccination and annual screening beginning at age 22 years. The cost-effectiveness of vaccination plus delayed screening was highly sensitive to age of vaccination, duration of vaccine efficacy, and cost of vaccination.

CONCLUSIONS: Vaccination for HPV in combination with screening can be a cost-effective health intervention, but it depends on maintaining effectiveness during the ages of peak oncogenic HPV incidence. Identifying the optimal age for vaccination should be a top research priority.

Kulasingam SL, Myers ER. JAMA 2003;13;290:781–9.
(http://jama.ama-assn.org)

Exposure to non-steroidal anti-inflammatory drugs during pregnancy and risk of miscarriage: Population based cohort study

OBJECTIVE: To evaluate whether prenatal use of non-steroidal anti-inflammatory drugs (NSAIDs) is associated with increased risk of miscarriage.

DESIGN: Population based cohort study. Prenatal use of NSAIDs, aspirin, and paracetamol (acetaminophen) ascertained by in-person interview.

SETTING: Kaiser Permanente Medical Care Program, a healthcare delivery system, in the San Francisco area of the United States.

PARTICIPANTS: 1055 pregnant women recruited and interviewed immediately after their positive pregnancy test. Median gestational age at entry to the study was 40 days.

MAIN OUTCOME MEASURES: Pregnancy outcomes up to 20 weeks of gestation.

RESULTS: 53 women (5%) reported prenatal NSAID use around conception or during pregnancy. After adjustment for potential confounders, prenatal NSAID use was associated with an 80% increased risk of miscarriage (adjusted hazard ratio 1.8 [95% confidence interval 1.0 to 3.2]). The association was stronger if the initial NSAID use was around the time of conception or if NSAID use lasted more than a week. Prenatal aspirin use was similarly associated with an increased risk of miscarriage. However, prenatal use of paracetamol, pharmacologically different from NSAIDs and aspirin, was not associated with increased risk of miscarriage regardless of timing and duration of use.

CONCLUSION: Prenatal use of NSAIDs and aspirin increased the risk of miscarriage. These findings need confirmation in studies designed specifically to examine the apparent association.

Li DK, Liu L, Odouli R. BMJ 2003;327:368.
(http://bmj.com/)

Ultralow-dose micronized 17beta-estradiol and bone density and bone metabolism in older women: A randomized controlled trial

CONTEXT: Estrogen therapy is known to prevent osteoporosis, but studies have shown that conventional doses increase adverse events. Whether lower doses, one quarter of standard treatment, prevent bone loss is not known.
OBJECTIVE: To examine the effect of 3 years of treatment with 0.25 mg/d of micronized 17 beta-estradiol on bone mineral density (BMD) and bone turnover in healthy older postmenopausal women.
DESIGN, SETTING, AND PARTICIPANTS: Randomized, double-blind, placebo-controlled trial conducted from July 24, 1998, through June 14, 2002, at a university general clinical research center in the United States. Healthy, community-dwelling women (N = 167) who were older than 65 years at enrollment.
INTERVENTION: Dosage of 0.25 mg/d of micronized 17 beta-estradiol ($n = 83$) or placebo ($n = 84$); all women who had not had a hysterectomy received 100 mg/d of oral micronized progesterone for 2-week periods every 6 months.
MAIN OUTCOME MEASURES: The BMD of the hip, spine, wrist, and total body measured annually for 3 years. Serum and urine biochemical markers of bone resorption and formation and sex hormones were measured at baseline, 3 months, and during years 1 and 3 of treatment.
RESULTS: Mean BMD increased at all sites for participants taking low-dose estrogen (17 beta-estradiol) compared with placebo ($P < .001$). Compared with participants receiving placebo, participants taking low-dose estrogen had BMD increases of 2.6% for the femoral neck; 3.6%, total hip; 2.8%, spine; and 1.2%, total body. Markers of bone turnover, N-telopeptides of type 1 collagen, and bone alkaline phosphatase decreased significantly ($P < .001$) in participants taking low-dose estrogen compared with placebo. Estradiol, estrone, and sex hormone-binding globulin levels increased in the estrogen-treated group compared with placebo. The adverse effect profile was similar; specifically, there were no statistically significant differences in breast tenderness, changes in endometrial thickness or pathological effects, or annual mammographic results between the 2 groups. The number of abnormal mammograms over 3 years was 15 for the low-dose estrogen group and 10 for the placebo group (8 occurred at baseline) ($P = .26$). There were no reports of breast cancer during the study.
CONCLUSIONS: In older women, a dosage of 0.25 mg/d of 17 beta-estradiol increased bone density of the hip, spine, and total body, and reduced bone turnover, with minimal adverse effects. Future studies evaluating the effect of low-dose estrogen on fractures are indicated.

Prestwood KM, Kenny AM, Kleppinger A, Kulldorff M. JAMA 2003;290:1042–8.
(http://jama.ama-assn.org)

Oxygen-saturation targets and outcomes in extremely preterm infants*

BACKGROUND: Studies have shown that chronic hypoxemia may occur in preterm infants who require supplemental oxygen for extended periods of time. This may contribute to poor growth and development. A few uncontrolled studies have suggested that maintenance of a higher oxygen-saturation may promote better growth and development.
METHODS: A total of 358 infants born at less than 30 weeks of gestation who remained dependent on supplemental oxygen at a time when they would have been 32 weeks' gestational age, were entered into a randomized, double-blind, multicenter trial. They were randomly assigned to a target functional oxygen-saturation of either 91 to 94 percent (standard group) or 95 to 98 percent (high saturation group). They remained at the assigned saturation range for the duration of their supplemental-oxygen therapy. The primary outcomes were the growth and the neurodevelopmental measures at 12 months (plus the number of weeks of prematurity) of age.
RESULTS: There were no significant differences between the two groups in weight, length, or head circumference at a corrected age of 12 months. Likewise, there were no significant major developmental abnormalities in the two groups. There were six deaths due to pulmonary causes in the high-saturation group and one death in the standard group ($P = .12$). The high-saturation group required oxygen for a longer period of time after randomization (median, 40 vs. 18 days; $P = .001$). The high-saturation group also had a higher rate of dependence on supplemental oxygen at 36 weeks of postmenstrual age and more often required home-based oxygen therapy.
CONCLUSIONS: There was no significant improvement in either growth or development in preterm infants who were give high-saturation oxygen therapy.

Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM. N Engl J Med 2003;349:959–67.
(http://www.nejm.org)

Screening in brief intervention trials targeting excessive drinkers in general practice: Systematic review and meta-analysis

OBJECTIVE: To determine the effectiveness of programmes of screening in general practice for excessive alcohol use and providing brief interventions.
DESIGN: Systematic review and meta-analysis of randomised controlled trials that used screening as a precursor to brief intervention.
SETTING: General practice.
MAIN OUTCOME MEASURES: Number needed to treat, proportion of patients positive on screening, proportion given brief interventions, and effect of screening.

** Modified abstract.*

RESULTS: The eight studies included for meta-analysis all used health questionnaires for screening, and the brief interventions included feedback, information, and advice. The studies contained several sources of bias that might lead to overestimates of the effects of intervention. External validity was compromised because typically three out of four people identified by screening as excessive users of alcohol did not qualify for the intervention after a secondary assessment. Overall, in 1000 screened patients, 90 screened positive and required further assessment, after which 25 qualified for brief intervention; after one year 2.6 (95% confidence interval 1.7 to 3.4) reported they drank less than the maximum recommended level.

CONCLUSIONS: Although even brief advice can reduce excessive drinking, screening in general practice does not seem to be an effective precursor to brief interventions targeting excessive alcohol use. This meta-analysis raises questions about the feasibility of screening in general practice for excessive use of alcohol.

Beich A, Thorsen T, Rollnick S. BMJ 2003;327:536–42. (http://bmj.com/)