

for health benefits in the same cohort.<sup>1</sup> We did not observe a dose-response relationship between moderate-intensity and vigorous-intensity physical activity and all-cause mortality risk in “insufficiently active weekend warriors” who reported 1 or 2 sessions per week but did not meet physical activity guidelines of at least 150 minutes per week of moderate-intensity aerobic activity or at least 75 minutes per week of vigorous-intensity aerobic activity. We did observe a linear trend when investigating total physical activity of any intensity. We concluded that some of the health benefits might be explained by nonexercise activity, such as light-intensity walking. More than 40% of the weekend warriors were in desk-bound occupations, and we would suggest that participation in sport and exercise at the weekend is enough to increase cardiorespiratory fitness and to reduce the mortality risk associated with the sedentary lifestyle of Western societies.

We thank Lam and colleagues for their letter too. They suggested that air pollution was subject to geographical variation and that air pollution was a relevant confounding variable. We did not adjust for air pollution; however, the available evidence suggests that air pollution is only related to lung cancer mortality.<sup>2</sup> Lam and colleagues also suggested that treatment availability was subject to geographical variation and that treatment availability was also a pertinent confounding variable. There is some evidence of a North-South divide in health care in the United Kingdom; however, socioeconomic factors may explain differences in physical activity<sup>3</sup> and other exposures and outcomes.<sup>4,5</sup> Compared with the inactive participants in our study, the hazard ratio for cancer mortality was 0.79 (95% CI, 0.66-0.94) in the regularly active and 0.82 (95% CI, 0.63-1.06) in the weekend warriors after adjustment for age, sex, smoking habit, longstanding illness, and socioeconomic status (the regularly active reported  $\geq 150$  minutes/wk in moderate-intensity aerobic activity or  $\geq 75$  minutes/wk in vigorous-intensity aerobic activity from  $\geq 3$  sessions; the weekend warriors reported the same amounts of activity per week from 1 or 2 sessions). Lam and colleagues mentioned a clustering effect in our subsample. The core sample is weighted so that it might be representative of the population living in private households.<sup>6</sup> When we have weighted the subsample, it has had little bearing on the association between physical activity and mortality.

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- Hamer M, O'Donovan G, Lee IM, Stamatakis E. The “weekend warrior” physical activity pattern: how little is enough? *Br J Sports Med*. 2017;pii: bjsports-2017-097538. doi:10.1136/bjsports-2017-097538
- Cohen AJ, Brauer M, Burnett R, et al. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. *Lancet*. 2017;389(10082): 1907-1918. doi:10.1016/S0140-6736(17)30505-6
- Roth M. Self-reported physical activity in adults. In: Craig R, Mindell J, Hirani V, eds. *Health Survey for England 2008, Volume 1: Physical activity and fitness*. London: National Centre for Social Research; 2008:21-58.
- Beard E, Brown J, West R, Angus C, Kaner E, Michie S. Healthier central England or North-South divide? Analysis of national survey data on smoking and high-risk drinking. *BMJ Open*. 2017;7(3):e014210.
- GBD 2015 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388(10053): 1659-1724.
- Craig R, Mindell J, Hirani V. Weighting the data. In: Craig R, Mindell J, Hirani V, eds. *Health Survey for England 2008, Volume 2: Methods and Documentation*. London: National Centre for Social Research; 2010:24-29.

## Discrepant Expectations About Benefits and Harms

**To the Editor** The systematic review by Hoffmann and Del Mar<sup>1</sup> in a recent issue of *JAMA Internal Medicine* showed robust but sad evidence that most health care professionals divergently misconceive benefits and harms of their interventions (treatments, screenings, tests) and deserves comment.

First, the various explanations have overlooked (1) an enduring but obvious innumeracy<sup>2</sup> and (2) illiteracy that is not openly acknowledged. In their review, Hoffmann and Del Mar rightly used the terms “benefits” and “harms,” but PubMed search results reach 2818 for “benefit-risk” and 1159 for “benefit/risk” vs 8 for “potential benefit” and “risk of harm” combined, 123 for “benefit-harm,” and 33 for “benefit/harm.” When health care professionals intervene, benefits are guaranteed while harms are only a “potential risk”.

Second, solutions for shared decision making with patients should have been mentioned. For example, evidence-based tools with simple pictographs showing absolute numbers and consistent denominators (ie, per 1000 persons), time frames, and visuals using the same scale for information on benefits and harms of the options would have been helpful,<sup>3</sup> as would resources like the Patient-Centered Outcomes Research Trust Fund (<http://www.pcori.org/research-results/2013/development-and-user-testing-decision-aid-ventricular-assist-device-placement>) and the Harding Center for Risk Literacy (<https://www.mpib-berlin.mpg.de/en/research/harding-center>) which provide patient independence through risk assessment, a critical issue.<sup>4</sup> SHARE-IT (<http://magicproject.org/research-projects/share-it/>) is a project still in development and wrongly uses the benefit and/or risk semantics.

Last, underestimation of harms and overestimation of benefits is a much wider problem. Regulatory agencies grant market approvals for drugs faster and faster on surrogate end points without clinical relevance while market withdrawal is often unreasonably delayed, even in the case of drug-related deaths.<sup>5</sup>

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- Hoffmann TC, Del Mar C. Clinicians' expectations of the benefits and harms of treatments, screening, and tests: a systematic review [published online January 9, 2017]. *JAMA Intern Med*. doi:10.1001/jamainternmed.2016.8254
- Peters E, Hibbard J, Slovic P, Dieckmann N. Numeracy skill and the communication, comprehension, and use of risk-benefit information. *Health Aff (Millwood)*. 2007;26(3):741-748.
- Braillon A, Bewley S. Shared decision-making for cancer screening: visual tools and a 4-step method. *JAMA Intern Med*. 2015;175(11):1862.
- Barry MJ. The prostate cancer treatment bazaar: comment on "physician visits prior to treatment for clinically localized prostate cancer". *Arch Intern Med*. 2010;170(5):450-452.
- Braillon A, Menkes DB. Balancing accelerated approval for drugs with accelerated withdrawal. *JAMA Intern Med*. 2016;176(4):566-567.

**To the Editor** We appreciate the systematic review by Hoffmann and Del Mar<sup>1</sup> in a recent issue of *JAMA Internal Medicine* estimating the accuracy of physicians' expectations of benefits and harms and worry with them that inaccuracies may lead to suboptimal medical care. Nonetheless, we are concerned that their approach might obscure rather than illuminate the measurement of physicians' predictive accuracy and its implications.

Surveys and questionnaires based on clinical vignettes or "typical patients" provide us with a measure of agreement between clinician estimates and those published in the literature for standard target populations. This information is important because it tells us about clinicians' awareness—and perhaps acceptance—of relevant research data. However, there are 2 main reasons why these kinds of studies ought to be interpreted as rough indicators and do not necessarily answer the question of whether clinicians truly tend to underestimate harms and overestimate benefits as the authors conclude.

First, there is increasing recognition that the degree of transportability of research estimates to different populations and settings, as well as their stability over time, cannot be taken for granted.<sup>2,3</sup> While in some cases this concern might be addressed by accepting a credible range surrounding the point estimate, in other cases it might be safer not to assume transportability and further investigate variance in local base rates before inferring inaccuracy from the presence of high variance in clinicians' predictions.<sup>4</sup>

Second, because expectations of benefit and harm are in practice relative to actual patients with various idiosyncrasies and real settings, physicians' predictive accuracy ought to be estimated in the field.<sup>5</sup> While the accuracy of physicians as a group can be measured cross-sectionally with respect to a theoretical reference standard, for purposes of service improvement it might be far more informative to investigate individual physicians' calibration longitudinally by generating a track record of correct or incorrect predictions for samples of patients with particular conditions.

Of course, we accept that the study of physicians' risk estimates in the real world is more complicated and expensive than relying on theoretical cases. However, if our aim is to im-

prove medical care, our actions ought to be informed by relevant and methodologically sound evidence, which is, after all, the central premise behind the systematic review by Hoffmann and Del Mar.<sup>1</sup>

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- Hoffmann TC, Del Mar C. Clinicians' expectations of the benefits and harms of treatments, screening, and tests: a systematic review. *JAMA Intern Med*. 2017; 177(3):407-419. doi:10.1001/jamainternmed.2016.8254
- Bareinboim E, Pearl J. Causal inference and the data-fusion problem. *Proc Natl Acad Sci U S A*. 2016;113(27):7345-7352. doi:10.1073/pnas.1510507113
- Siontis GC, Tzoulaki I, Castaldi PJ, Ioannidis JP. External validation of new risk prediction models is infrequent and reveals worse prognostic discrimination. *J Clin Epidemiol*. 2015;68(1):25-34. doi:10.1016/j.jclinepi.2014.09.007
- Humphreys K, Blodgett JC, Roberts LW. The exclusion of people with psychiatric disorders from medical research. *J Psychiatr Res*. 2015;70:28-32. doi:10.1016/j.jpsychires.2015.08.005
- Stein J, Louie J, Flanders S, et al. Performance characteristics of clinical diagnosis, a clinical decision rule, and a rapid influenza test in the detection of influenza infection in a community sample of adults. *Ann Emerg Med*. 2005;46(5):412-419.

**In Reply** We thank Dr Braillon for his comments. First, we agree that innumeracy and naiveté about clinical epidemiology concepts are some of the underlying contributions to the misperceptions that we report in our systematic review.<sup>1</sup> Clinician illiteracy in health statistics has been articulated previously.<sup>2,3</sup> However, we disagree that the benefits of interventions are certain while the harms are only a potential risk. Few interventions have certain benefits: there is both the chance of benefit and the chance of harm from most interventions.

Second, we agree, as we mention in our article,<sup>1</sup> that shared decision making is part of the solution. While there are various risk communication strategies, tools, and resources that can be used to facilitate this, word limits precluded us from elaborating on these. Finally, we also agree that the issue of accurate knowledge about intervention benefit and harm extends beyond clinicians' knowledge and is influenced by what occurs (or does not occur) in other contexts, such as regulatory agencies, and the phases before the research knowledge filters to clinicians. Efficient access to accurate and up-to-date knowledge about intervention benefits and harms is desperately needed because current knowledge generation and dissemination systems are flawed and a patchwork of reactive and ad hoc solutions.

We also thank Drs Sepulveda and Fuller for their comments and concerns about the use of clinical vignettes in some of the primary studies included in our review.<sup>1</sup> We agree that such responses provide information about clinician awareness, and possibly acceptance, of research data about benefits

and harms, but that “real world” use of such data are tricky, and some caution is needed when considering extrapolating from research estimates to other settings and populations. We acknowledge that the ideal method for assessing the accuracy of people’s risk perception estimates have not been identified and that across the studies included in our review,<sup>1</sup> and our review of patient expectations,<sup>4</sup> a variety of methods to measure this were used, most of which are unvalidated and suggest that more research evaluating various methods is needed.

The second comment by Drs Sepulveda and Fuller—that collecting data from real settings, presumably from recording what clinicians predict about the likely benefits and harms of clinical management options under consideration with actual patients—is an interesting idea to explore with research. Our search found no studies that used an approach like this. The article they cite as an exemplar<sup>5</sup> (which studied the diagnostic ability of clinicians in an emergency department or urgent care clinic to distinguish influenza from influenzalike illness, and compared the performance of clinical judgement, a rapid diagnostic test and a clinical prediction rule, against a laboratory gold standard) does not measure quantification of the benefits or harms of clinical management; hence this study does not meet the criteria for inclusion in our systematic review.<sup>1</sup>

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- Hoffmann TC, Del Mar C. Clinicians’ expectations of the benefits and harms of treatments, screening, and tests: a systematic review [published online January 9, 2017]. *JAMA Intern Med*. doi:10.1001/jamainternmed.2016.8254
- Gigerenzer G, Gaissmaier W, Kurz-Milcke E, Schwartz LM, Woloshin S. Helping doctors and patients make sense of health statistics. *Psychol Sci Public Interest*. 2007;8(2):53-96.
- Wegwarth O, Schwartz LM, Woloshin S, Gaissmaier W, Gigerenzer G. Do physicians understand cancer screening statistics? a national survey of primary care physicians in the United States. *Ann Intern Med*. 2012;156(5):340-349.
- Hoffmann TC, Del Mar C. Patients’ expectations of the benefits and harms of treatments, screening, and tests: a systematic review. *JAMA Intern Med*. 2015; 175(2):274-286.
- Stein J, Louie J, Flanders S, et al. Performance characteristics of clinical diagnosis, a clinical decision rule, and a rapid influenza test in the detection of influenza infection in a community sample of adults. *Ann Emerg Med*. 2005;46(5):412-419.

## Facts Concerning Duexis Prescribing Habits Related to Combination Therapies

**To the Editor** In their Viewpoint about high prices for drugs with generic alternatives specifically citing Duexis (Horizon Pharma) published in a recent issue of *JAMA Internal Medicine*, Hakim and Ross<sup>1</sup> omitted important facts about Duexis and physician prescribing habits related to combination therapies.

Although Hakim and Ross correctly noted that Duexis is approved for the relief of signs and symptoms of rheumatoid arthritis and osteoarthritis and to decrease the risk of devel-

oping upper gastrointestinal ulcers in patients who are taking ibuprofen for those indications, their Viewpoint<sup>1</sup> created the misperception that the medication is a simple combination of 2 readily available medicines. In fact, Duexis is specially formulated to contain prescription strength ibuprofen and a protective core of famotidine at a higher dose because standard doses fail to provide gastric protection.<sup>2</sup> The US Food and Drug Administration approved Duexis based on 2 randomized phase 3 clinical studies that enrolled more than 1500 patients.<sup>3</sup>

Moreover, the authors did not mention that the approval of Duexis marked a new indication for famotidine.<sup>3</sup> Previously, famotidine was not approved to decrease the risk of developing upper gastrointestinal ulcers in patients taking ibuprofen or any other nonsteroidal anti-inflammatory (NSAID). Indeed, famotidine is still not approved as a standalone therapy or in combination with another active ingredient for this use (except in Duexis). There is no approved generic, over-the-counter, or clinically equivalent medicine except Duexis, which has been shown to provide gastroprotection.

By providing the benefits of an NSAID and a gastroprotective medicine to reduce NSAID-induced upper gastrointestinal ulcers in a single pill, the risk of patient nonadherence for gastrointestinal protection is reduced. Data show that less than 25% of physicians coprescribe an NSAID and a medicine to reduce the frequency of the ulcers they may cause.<sup>4</sup>

The article also misstates Horizon Pharma’s means of distributing its medicines. Horizon Pharma has never owned, does not currently own, and has no option to purchase any pharmacies. In the first half of 2016, our primary care medicines, including Duexis, were dispensed by approximately 20 000 regional, local, and retail pharmacies.

As the health care system becomes increasingly complex, Horizon Pharma considers it our responsibility to ensure that patients receive the medicine their physicians prescribe and eliminate barriers to access. We hope that important topics such as patient access, clinical relevance, and unmet medical need again become the primary focus of the dialogue to enable physicians to make appropriate clinical decisions.

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- Hakim A, Ross JS. High prices for drugs with generic alternatives: the curious case of Duexis. *JAMA Intern Med*. 2017;177(3):305-306.
- Taha AS, Hudson N, Hawkey CJ, et al. Famotidine for the prevention of gastric and duodenal ulcers caused by nonsteroidal antiinflammatory drugs. *N Engl J Med*. 1996;334(22):1435-1439.
- Laine L, Kivitz AJ, Bello AE, Grahn AY, Schiff MH, Taha AS. Double-blind randomized trials of single-tablet ibuprofen/high-dose famotidine vs. ibuprofen alone for reduction of gastric and duodenal ulcers. *Am J Gastroenterol*. 2012; 107(3):379-386.
- Moore RA, Derry S, Phillips CJ, McQuay HJ. Nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 selective inhibitors (coxibs) and gastrointestinal harm: review of clinical trials and clinical practice. *BMC Musculoskelet Disord*. 2006;7:79.