measuring changes in health-related quality of life, symptoms, or function “...have suffered from methodological issues and poor data quality, limiting their use in regulatory decisions.” They indicate that those methodological weaknesses justify keeping drugs on the market when there is no clear evidence of clinical benefit. However, there are numerous reliable, validated quality-of-life measures that are used in research; they have been and should be used to determine whether oncology drugs have a significant impact, or they should be revised to be more appropriate to measure such impact. Blumenthal and colleagues give several examples where cancer-related symptoms were measured to determine quality of life; these examples support our conclusions rather than challenging them.

While we agree with Blumenthal and colleagues that the cost of a cancer drug “...is not within the purview of the FDA,” FDA approval of oncology drugs that have no proven clinical benefit in terms of patient health or quality of life is well within the purview of the FDA. New cancer drugs are unaffordable for many patients and their families. It is appropriate for physicians and patients to expect that the FDA would require proven clinical benefits before drugs are approved, or at least rescind approval if postmarket studies do not prove that those drugs provide measurable benefits to patients, and not just to biomarkers or nonclinical end points. The statement by Blumenthal and colleagues that requiring such proof would not be practical could have a chilling effect on physicians as they make treatment decisions on behalf of their patients.

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Additional Information: The following 4 US Food and Drug Administration programs are intended to facilitate and expedite development and review of new drugs to address unmet medical need in the treatment of a serious or life-threatening condition: fast track designation, breakthrough therapy designation, accelerated approval, and priority review designation.


In Reply We thank Blumenthal and colleagues for their thoughtful comments regarding our Editor’s Note.3 They have correctly identified that the 18 cancer drugs examined in the research letter by Rupp et al were not all approved via the accelerated pathway as stated; in fact, many of these cancer drugs were regular approvals. We thank them for pointing out this error and appreciate this opportunity to respond to their other comments.

We applaud the US Food and Drug Administration (FDA) efforts to integrate patient-reported quality-of-life (QOL) measures into regulatory decisions and to identify clinically relevant changes in QOL measures. These efforts should be expedited because of their importance to patients. In the meantime, cancer drugs without survival or QOL benefit must undergo rapid withdrawal as outlined in the Federal Food, Drug, and Cosmetic Act4 and the Code of Federal Regulations,5 although this process unfortunately remains rare and slow to occur.

We find the claim of Blumenthal and colleagues that it is not practical to require drug companies to conduct phase III trials capable of detecting changes in overall survival among patients with chronic myeloid leukemia or multiple myeloma to be contradicted by their following statements that “…therapeutic gains have led to substantial improvements in survival,” and that these malignancies have been “…converted to chronic diseases with impressive 10-year survival rates.” Perhaps most importantly, it is disconcerting that surrogate end points, such as progression-free survival and major molecular response, continue to be accepted by the FDA for regular approvals. Less than 1 in 7 cancer drugs approved based on a surrogate end point will go on to have overall survival benefit. If there is an appropriate use of surrogate end points in the FDA approval process, it is in the setting of accelerated approvals where there is both a need to expedite access to potentially life-saving drugs and a framework for required confirmatory trials to prove clinical benefit.

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Is Weekend-Only Physical Activity Enough to Compensate for a Sedentary Lifestyle?

To the Editor In their Original Investigation in a recent issue of JAMA Internal Medicine, O’Donovan et al1 have shown that all-cause mortality, as well as cardiovascular disease and cancer mortality, were all significantly lower in individuals who met international physical activity (PA) guidelines issued by the US Department of Health2 and the World Health Organization3 (ie,
performing PA ≥3 days/week to accumulate 150 min/wk of moderate-intensity PA, corresponding to 3.0-5.9 metabolic equivalents [METs], where 1 MET is the resting metabolic rate or ≥75 min/wk of vigorous-intensity PA [≥6 METs], or a combination of the above) compared with inactive individuals reporting no moderate or vigorous-intensity PA over a normal week (hazard ratio [HR] for all-cause mortality, 0.65; 95% CI, 0.58-0.73). Importantly, compared with inactive individuals, HR was also lower not only in those not meeting international recommendations of total weekly PA time despite doing PA on 3 or more days per week (ie, insufficiently active; HR, 0.69; 95% CI, 0.65-0.74) but also in those reporting doing PA only on 1 to 2 days per week (ie, weekend warriors; HR, 0.70; 95% CI, 0.60-0.82). These results are important because they indicate the tremendous potential of PA, even at small doses, to decrease mortality risk and emphasize the concept that even a little PA is probably much better than none.

The findings of O'Donovan et al1 persisted after adjustment for other lifestyle confounders such as age, sex, smoking, occupation or prevalent long-standing illness at baseline. However, other components of our daily lifestyle that can also impact health outcomes such as low-intensity PA (<3 METs), total activity time (ie, including all PA intensities) and especially total sedentary (ie, sitting) time were not entered in the analyses. Sedentary time is a strong potential confounder that might at least partly attenuate the mortality benefits of the PA accumulated during the rest of the day. A recent meta-analysis showed that an adult sitting for 10 hr/d has significantly increased all-cause mortality risk (HR, 1.52; 95% CI, 1.46-1.58), even after adjustment for PA (HR, 1.34; 95% CI, 1.28-1.40) compared with their less sedentary peers.4

It would have been interesting if O’Donovan et al1 had determined what the minimum amount of PA is that compensates for the sedentary lifestyle of western societies. Is weekend-only PA really enough?

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In Reply We thank Santos-Lozano and colleagues for their Letter to the Editor. They recognized that our study was important because it demonstrated the “tremendous potential” of leisure time physical activity to reduce mortality risk. Santos-Lozano and colleagues said that it would have been interesting if we were to have adjusted for “the sedentary lifestyle of western societies,” and they raised the important question, “Is weekend physical activity enough?” Sitting and other sedentary behaviors were investigated in the 2008 Health Survey for England but not in other iterations of the Health Survey for England or the Scottish Health Survey. We have investigated the minimal physical activity dose

To the Editor In their Original Investigation published in a recent issue of JAMA Internal Medicine, O’Donovan et al1 claim that “weekend warrior” and other leisure time physical activity patterns characterized by 1 or 2 sessions per week may be sufficient to reduce all-cause, cardiovascular disease, and cancer mortality risks. We notice that the authors may have overlooked a major confounder in this study: the geographical variations within the sample. Since the analyzed data covered various geographical areas in England and Scotland, we expect the geographical variations within the sample would be an important factor affecting mortality rate, independent of the physical activity level of the participants. Such a claim can be justified by the fact that the mortality rate for respiratory cancers were higher in northern Italy than southern Italy2 due to different levels of exposure to air pollution. The survival rate for cancers was also different across countries, due to different availability of effective treatments.3 In this connection, geographical areas should be an important confounder that needs to be adjusted in the analyses.

Similarly, because the sampling involved stratification based on geographical areas, we expect there is clustering effect within the sample.4 Ignoring the clustering effect in the analyses may lead to an elevated type I error. However, adjustment for clustering effect was not addressed in this study.

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for health benefits in the same cohort.\textsuperscript{1} 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.\textsuperscript{2} 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\textsuperscript{3} and other exposures and outcomes.\textsuperscript{4,5} 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 ≥150 minutes/wk in moderate-intensity aerobic activity or ≥75 minutes/wk in vigorous-intensity aerobic activity from ≥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.\textsuperscript{6} When we have weighted the subsample, it has had little bearing on the association between physical activity and mortality.

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Discrepant Expectations About Benefits and Harms

To the Editor The systematic review by Hoffmann and Del Mar\textsuperscript{1} 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\textsuperscript{2} 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/harm” 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,\textsuperscript{3} 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.\textsuperscript{4} 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.\textsuperscript{5}

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