pattern was seen, as shown in the Figure (B).

To our knowledge, this is the first report to show that registry-based survival data in the most common hematologic malignancies do follow NBL. As mentioned previously, in numerical sets that abide by NBL, deviations indicate nonrandom data modifications. These modifications can be fraudulent or could be resulting from human error in data maintenance or effects of an external agent not related to the data itself (perhaps the effects of a certain therapy on survival). Nevertheless, NBL is an easy and simple way to evaluate quality of survival data. Our results warrant validation in other data sets, especially those with different therapeutic interventions.

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Association Between Weekly Exercise Time and Mortality

To the Editor: We read with great interest the work of Schnohr et al1 about the association between weekly exercise time and cardiovascular disease (CVD) mortality. During ±25 years of follow-up, 4779 deaths (54.9% of study population) were recorded, of which 2054 (23.6%) were CVD related. The authors reported a U-shaped association between weekly exercise time and CVD mortality and all-cause mortality, with the lowest risk for individuals exercising 2.6 to 4.5 h/wk. These findings remained consistent after correction for competing risks, stratified analyses, and analyses to account for reverse causation. The outcomes of this study are contradictory to the current dogma that exercise is a potent medicine at any dose.2 We are intrigued by these findings and want to share some thoughts with the authors.

The categorization of individuals into 5 distinct groups is an important methodologic consideration as the middle (third) group is used as the reference group to explore the presence of a U shape. The authors describe that participants were allocated to an exercise group of 0 h/wk, 0.1 to 2.5 h/wk, 2.6 to 4.5 h/wk, 4.6 to 10 h/wk, or more than 10 h/wk on the basis of the frequency distribution of the data. It appeared, however, that the reference group had a substantially smaller sample size (n=494, 6% of total cohort) compared with the other groups (n=1602 to n=2679, 18% to 31% of total cohort). It is unclear why this approach was chosen, whether the exercise time data had a Gaussian distribution (or not), and whether different group distributions (eg, quintiles) would have led to different outcomes. To improve our understanding of the dose-response association between exercise volumes and mortality, it would also be interesting to use nonlinear models (eg, restricted cubic spline analysis) with weekly exercise time as continuous variable.

Another concern is the assessment of the exposure variable. Exercise habits are known to be highly variable across the human life span,3,4 and a single measurement of weekly exercise time could induce a nondifferential measurement error, especially after a long follow-up time, such as in this study. This error could subsequently result in an underestimation of the true effect of exercise on health. Indeed, a recent study reported a U-shaped association between exercise volumes and CVD mortality and all-cause mortality when a single measure of physical activity was used.5 Adding repeated measures of physical activity to the analysis changed the outcome dramatically as the U-shape association was replaced by a curvilinear association, indicating that the largest exercise volumes yielded the greatest health benefits. Outcomes of this study should therefore be interpreted with care. We also encourage the authors to analyze their data in a similar fashion as repeated measurements appear to be available in the Copenhagen City Heart Study.

This work adds novel data to the ongoing debate about the dose-response association of exercise and
health outcomes and whether such a thing as too much exercise exists. Although it is tempting to speculate about an upper limit of exercise recommendations, in our opinion this is a step too far based on data that are presented to this point.

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In Reply—Association Between Weekly Exercise Time and Mortality

To the Editor: We would like to thank the esteemed Drs Aengevaeren, Eijsvogels, and Bakker for their insightful comments regarding our recently published manuscript.1 We chose the cohort doing 2.6 to 4.5 h/wk of exercise as the reference group because this approximates the 30 minutes daily of leisure-time physical activity recommended by national guidelines in Denmark.

In response to the request that we analyze this data set by a nonlinear model evaluating weekly exercise time as a continuous variable, we performed a Cox regression analysis for all-cause mortality using restricted cubic splines for exercise volume with adjustment for age, sex, education, smoking, alcohol, body mass index, and diabetes. In this analysis, the optimal exercise volume was around 3.5 h/wk; both lower and higher volumes were associated with increased all-cause mortality risk (Figure). Compared with the reference group (moderate exercise dose), the magnitude of the increased mortality risk was strikingly high (≈40%) for those doing little or no physical activity but only modestly increased (≈10%) for those doing very high exercise volumes.

![Figure: Hazard ratio for mortality as a function of cumulative weekly duration of leisure-time physical activities (sports).](https://doi.org/10.1016/j.mayocp.2021.12.010)