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No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: The observation that greater HLA mismatch is associated with better disease-free survival after cord-blood transplantation is clearly provocative and merits additional evaluation. The question posed by Nusbaum regarding further delineation of the mechanism or mechanisms involved in this association — specifically, separating out the effect of matching between two units versus donor–recipient matching — is important but unfortunately was beyond the scope of our study. The complexity of double-unit cord-blood transplantation, in which we need to consider the effect of HLA matching in six directions rather than two in addition to understanding the effect of the HLA match of the predominating unit responsible for hematopoiesis in the long term, demands substantially larger sample sizes within each subgroup for a meaningful analysis.

In response to the comments by Sanz and colleagues: we too are particularly interested in segregating out the effect of the engrafting from the nonengrafting unit in recipients of a double-unit cord-blood transplant. However, this is also a complex analysis that was beyond the scope of our study. It is possible that the immunologic graft-versus-graft response that is known to occur between the first and second cord-blood units might be responsible for some of the outcomes that we reported. For example, the higher incidence of acute GVHD after double-unit cord-blood transplantation might be related to an "in vivo mixed lymphocyte response" between the two units, which in turn could have deleterious effects such as delayed platelet recovery[1] but also beneficial effects such as a lower relapse rate.[2] Alternatively, it is possible that the "tolerability" of greater HLA mismatch in patients receiving a cord-blood transplant unveils a greater graft-versus-leukemia effect without the expected concomitant increase in transplantation-related mortality. In fact, the beneficial effect of HLA mismatch on relapse and survival after cord-blood transplantation has already been reported.[3] Although these possibilities are intriguing, they are only hypotheses at this time. If these observations hold in future studies, perhaps researchers who analyze databases with larger sample sizes can begin to explore the driving factors responsible for this apparent beneficial effect of HLA mismatch after double-unit cord-blood transplantation.

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Cardiovascular Risk and Events and Country Income Stratum

TO THE EDITOR: Yusuf et al. (Aug. 28 issue)[1] found that although the INTERHEART Risk Score classifies residents of high-income countries as being at greater cardiovascular risk than residents of low- and middle-income countries, the rates of major cardiovascular events and

death are substantially higher in low-income countries. This discrepancy may be explained by the omission of socioeconomic factors from the INTERHEART Risk Score. If these factors had been considered, a greater risk would probably have been predicted among the residents of less wealthy countries than was determined by the investigators, and consequently the inconsistency between the predicted and observed health outcomes would have been less than was observed.

The Moli-sani study has shown that healthful behaviors, such as adherence to a Mediterranean diet, are strongly linked to material resources, even in a high-income country such as Italy.[2] Even small income differences produce a shaped gradient in modifiable risk factors, with more disadvantaged persons having not only more risk factors but also fewer protective factors than those with higher incomes.[3] The work by Yusuf et al. is a further confirmation of the need to include socioeconomic factors in any approach aimed at predicting health risk, especially at a time of economic crisis when health has definite economic determinants.[3]

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TO THE EDITOR: Yusuf et al. conclude that the higher rates of cardiovascular disease observed in low- and middle-income countries, as compared with high-income countries, are unexplained by the prevalence of traditional cardiovascular risk factors, such as hypertension and diabetes. Unfortunately, the study did not consider two nontraditional factors that are important in poorer countries: household and ambient air pollution. Household air pollution from the use of solid fuels (biomass or coal) for cooking is ubiquitous among the world's poorest 3 billion people,[1] and ambient air pollution is most severe in middle-income countries such as India and China.[2] The Global Burden of Disease study showed that in India approximately 35% of all cases of ischemic heart disease were due to household air pollution and nearly 30% were due to ambient air pollution, as compared, for example, with 29% of cases that were due to tobacco smoking.[3] Evidence for the relationship between household air pollution and cardiovascular disease, unlike that for other risk factors, including ambient air pollution, does not currently derive from studies of disease but from studies of intermediate effect[4] and directly linking evidence across four major types of combustion air pollution: smoking, household air pollution, secondhand tobacco smoke, and ambient air pollution.[5]

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TO THE EDITOR: Yusuf et al. found a striking inverse relationship in low-income countries between the lowest INTERHEART Risk Score (a composite score of traditional risk factors without the use of laboratory testing) and the highest rates of death from cardiovascular causes and major cardiovascular events. Their findings

suggest a considerable, unattributed risk of cardiovascular disease in these resource-limited settings.

Atherosclerosis is a chronic inflammatory process that begins in early life,[1] and several stimuli initiate and maintain the inflammatory state. Infectious diseases have long been implicated as potential contributors to the development of atherosclerosis and to plaque instability and rupture.[2] Infections occur earlier in life and with greater frequency and severity in resource-limited settings than they do in industrialized countries.[3,4] The greater burden of infectious disease may contribute to the higher mortality from cardiovascular disease and more severe cardiovascular disease in income-poor settings than in asset-rich settings, despite the lower prevalence of traditional cardiovascular risk factors. Comparisons of country-specific rates of infection-related mortality and hospitalization, especially in childhood, should be feasible and may be informative regarding potentially modifiable but underappreciated risk factors for cardiovascular disease later in life.

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THE AUTHOR REPLIES: The investigators in our study agree that socioeconomic factors are important. We are validating approaches that can be used across countries at differing economic levels, and we intend to apply them to the study population. In future analyses, we will be relating levels of outdoor and indoor air pollution to cardiovascular disease and also infections in adulthood (but not in childhood, because these data were not collected) to incident cardiovascular diseases.

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FOLFOXIRI and Bevacizumab for Metastatic Colorectal Cancer

TO THE EDITOR: In their article on the Triplet plus Bevacizumab (TRIBE) study, Loupakis et al. (Oct. 23 issue)[1] conclude that chemotherapy with fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) plus bevacizumab improved the outcome of patients with metastatic colorectal cancer, as compared with a control group receiving fluorouracil, leucovorin, and irinotecan (FOLFIRI) plus bevacizumab. However, I question the basis for this conclusion.

First, although the median duration of progression-free survival was 12.1 months in the FOLFOXIRI group, as compared with 9.7 months in the control group, there was no significant improvement in overall survival with FOLFOXIRI. Second, FOLFOXIRI caused significantly more grade 3 or 4 events of neurotoxicity, diarrhea, neutropenia, and stomatitis, which are serious side effects. Third, even though tumors with nonmutated *KRAS* occurred in 37.3% of patients in the FOLFOXIRI group and 38.7% of those in the control group, subsequent treatment with an anti–epidermal growth factor receptor antibody (anti-EGFR) was performed in only 33% of patients in the FOLFOXIRI group and 29% of those in the control group, and the *KRAS* mutation status is not indicated for any of these patients. In addition, anti-EGFR was administered as second-line treatment in 31% of the patients in the FOLFOXIRI group, as compared with only 15% of the patients in the control group.

This study commenced around the same time