

depressant late in pregnancy, indicating no increased risk for PPHN if the antidepressant was not an SSRI. These data argue against confounding by indication as an alternative explanation if exposure to antidepressants in general in late pregnancy represents more severe underlying disease.

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## Mortality after the Hospitalization of a Spouse

**TO THE EDITOR:** The study by Christakis and Allison (Feb. 16 issue)<sup>1</sup> has broad implications for our health care system but leaves important questions unanswered. The mortality rates in this study among the elderly persons (referred to as partners) whose husband or wife had been hospitalized were determined according to the first hospital admission of the spouse; multiple admissions of the spouse were not considered in the analysis. These additional admissions may have a substantial impact. Furthermore, the causes of death of the partners are not reported. These deaths may have been preventable. As an example, it is conceivable that partners could share the same high-risk cardiovascular environment that led to the admission of the spouse and the death of the partner from cardiovascular causes. Understanding these factors could influence the future care of partners of hospitalized patients.

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1. Christakis NA, Allison PD. Mortality after the hospitalization of a spouse. *N Engl J Med* 2006;354:719-30.

**TO THE EDITOR:** The study by Christakis and Allison underscores the complex connection between marriage and health. However, their use of hospitalization as a marker of caregiver stress among partners residing within the ZIP Codes of the hospitalized spouse involves an immense conceptual leap. Without information regarding spousal cohabitation, care provisions, and the experience of stress, the authors attribute the observed mortality effect largely to mechanisms of caregiver stress. Although we have previously reported on an association between caregiving and mortality,<sup>1</sup> caution is advised in reaching this conclusion on the basis of the data reported in this study.

The finding that husbands fare worse than wives in the face of spousal illness is particularly troubling for an interpretation regarding the stress of caregiving. Caregiving is typically provided by wives, daughters, and daughters-in-law, with husbands infrequently serving as the primary caregiver. Moreover, men who do provide care consistently have lower levels of stress than do women.<sup>2</sup> Taken together, these factors would predict greater mortality for wives than husbands.

Despite these concerns, we applaud the authors' call for interventions to support the partners of inpatients and suggest that chronically ill spouses may be ideal targets of these services.

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**THE AUTHORS REPLY:** Our work used the admission of a spouse to a hospital as a marker for the onset of serious spousal disease, and it followed spouses and their partners for long after the hospitalization. No doubt, additional admissions with the same or other diseases could be markers for still worse illness in a spouse that might contribute to additional health problems in partners. However, this fact does not undercut our findings; indeed, our approach can be seen as a kind of intention-to-treat analysis in which we observe the implications of spousal hospitalization regardless of what happens subsequently.

Patel et al. are right to suggest that some deaths among caregiving partners may be preventable. However, the specific causes of death or of any excess mortality were not the focus of our study.

Patel et al. are also concerned about possible joint risks shared by spouses and partners that might explain both the onset of illness in a spouse and the death of a partner. We quite agree, and it is for this reason that we were reassured that the couple-level fixed-effects analyses we reported in our article and in the online Supplementary Appendix, which account for any stable shared exposures or for any history of cardiovascular risk factors, yielded the same results as those in the Cox models.

Lingler et al. raise questions about the possible mechanism of the association between spousal hospitalization and the death of a partner. Our study was not designed to examine the precise mechanisms, though our findings are consistent with long-standing work on the role of stress and social support in interpersonal health effects. We were clear to state that a demographic study such as ours, which involved more than a

million people, could not also contain information about what happens at the level of individual couples. We did not claim that husbands fare worse than wives as a result of having a sick spouse, and, indeed, the differences between men and women were generally not statistically significant. Quite the contrary, our work suggests that interpersonal health effects may be a basic biosocial phenomenon affecting men and women alike.<sup>1,2</sup>

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## Drug-Related Hepatotoxicity

**TO THE EDITOR:** In the excellent review of drug-related hepatotoxicity by Navarro and Senior (Feb. 16 issue),<sup>1</sup> antithyroid agents were not included in the authors' list of medications that cause injury to the liver. Both classes of antithyroid agents, propylthiouracil and methimazole, are known rarely to cause liver dysfunction, which is among the small number of their idiosyncratic toxic effects. The antithyroid drugs have distinct patterns of injury: propylthiouracil has hepatocellular toxic effects and methimazole induces cholestasis.<sup>2</sup> The severity of these toxic effects ranges from elevated levels of enzymes without permanent injury to fulminant hepatic failure leading to liver transplantation.<sup>3</sup> Although the mechanism of the cholestatic picture seen with methimazole is unclear, propylthiouracil may induce vasculitides related to antineutrophil cytoplasmic antibodies, suggesting an immunologic mechanism underlying hepatocellular injury due to propylthiouracil.

As the authors suggest with regard to other drugs, we do not routinely monitor liver enzymes in patients receiving antithyroid medications, since mild elevations of aminotransferase levels are common when 300 mg or more of propylthiouracil is prescribed daily, independent of baseline levels of liver enzymes in patients with thyrotoxicosis.<sup>4</sup>

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**TO THE EDITOR:** Navarro and Senior mention that the most common cause of acute liver failure in the United States is acetaminophen overdose and describe prevention strategies for hepatotoxicity but not the effect of controlling the public supply of this medication. In the United Kingdom, changes in legislation in 1998 limited the number of tablets in a packet of acetaminophen sold by pharmacies to 32 (16 g) and by other outlets to 16 (8 g). This limitation has resulted in a significant change in the incidence of acetaminophen overdoses.<sup>1</sup> The rates of admission to liver units have dropped by 30 percent since this legislation came into force,