CORRESPONDENCE

Work Hours and Depression in U.S. First-Year Physicians

TO THE EDITOR: The proportion of physicians who have a positive screening for depression increases by a factor of five to six times with the start of residency.[1] The long work hours that are typical of residency are a potential driver of worsening depressive symptoms.[2] We used an emulated trial design, a method that is suited to simulate a randomized trial when a trial is not feasible, to estimate the association between work-hour levels and change in depressive symptoms during the first year of residency.

We analyzed data from repeated cohorts of U.S. physicians who were recruited annually from April through June during the years 2009 to 2020 to participate in the Intern Health Study (17,082 participants), a national sample of interns (physicians in their first postgraduate year). We assessed depressive symptoms by means of the Patient Health Questionnaire 9-item version (PHQ-9[3]) at baseline (1 to 2 months before the start of the internship) and then quarterly throughout the internship year. On the PHQ-9, depression is categorized as minimal by a score of 0 to 4, mild by a score of 5 to 9, moderate by a score of 10 to 14, moderately severe by a score of 15 to 19, and severe by a score of 20 to 27.[3] At baseline, we also assessed participants' demographic characteristics (i.e., age, sex, marital status, and parental status), surgical or nonsurgical specialty, early family environment, personality trait of neuroticism, and history of depression. We gathered data on participant-reported work hours over the preceding week, stressful life events, and medical errors quarterly during the internship.

We emulated a target trial of the effect of weekly work hours on depression, categorizing weekly work hours into increasing levels, starting from 0 to 20 hours per week and going up to more than 90 hours per week (Table S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). We used standardization to estimate the mean change in PHQ-9 scores from baseline associated with each work-hour level, with adjustment for covariates and modeling with post-stratification and attrition weights (see the Supplementary Methods section).

At baseline, the interns' median PHQ-9 total score was 2.0 points and the mean (±SD) score was 2.7±3.1 points. The mean work hours, as assessed quarterly, were 63±19 per week (median, 67 hours per week; interquartile range, 50 to 76). At higher work-hour levels, interns' PHQ-9 total scores more often fell within higher cate-

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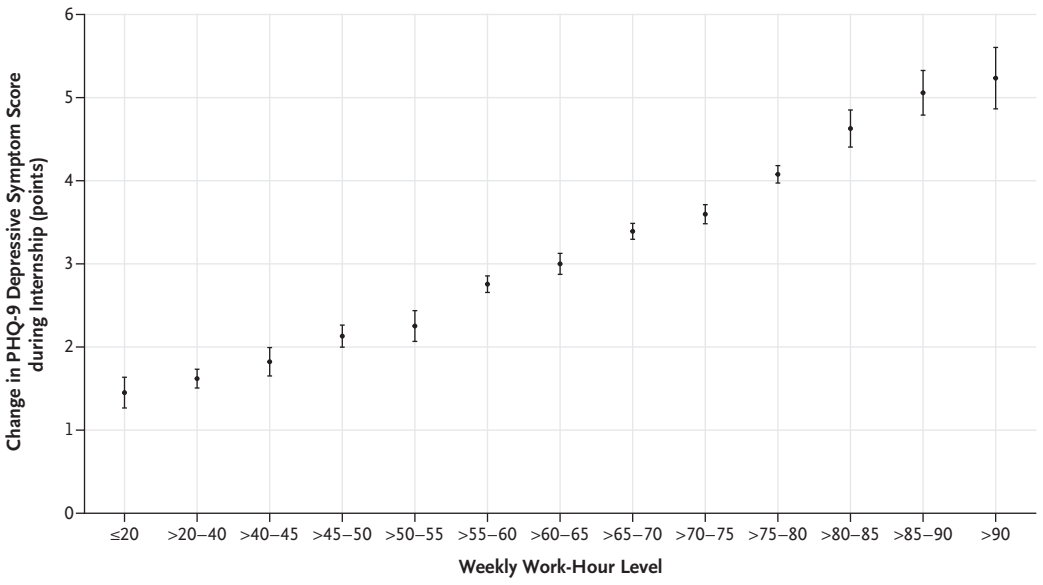

Figure 1. Estimated Mean Change in the PHQ-9 Score for Depressive Symptoms during Physician Internship, According to Weekly Work-Hour Levels, among 17,082 Participants in the Intern Health Study, 2009–2020.

Scores on the Patient Health Questionnaire 9-item version (PHQ-9) were assessed at baseline (1 to 2 months before the start of the internship) and then quarterly throughout the internship year. On the PHQ-9, depression is categorized as minimal by a score of 0 to 4, mild by a score of 5 to 9, moderate by a score of 10 to 14, moderately severe by a score of 15 to 19, and severe by a score of 20 to 27. The widths of the 95% confidence intervals (I bars) have not been adjusted for multiplicity and may not be used in place of hypothesis testing. The analysis was adjusted for the baseline factors of sex, surgical or nonsurgical specialty, personality trait of neuroticism, history of depression before the internship, early family environment, age, cohort calendar year, marital status, parental status, and time-varying factors of stressful life events and medical errors (see the Supplementary Appendix for details of measures).

gories of severity of depression, with 33.4% of the interns meeting PHQ-9 criteria for depression at a level of more than 90 work hours per week (Fig. S2). After standardization, the estimated change from baseline in the PHQ-9 score increased (indicating worsening depressive symptoms) with increasing work-hour levels, a pattern consistent with a dose–response relationship (Fig. 1). For the work-hour category of more than 40 and up to 45 hours per week, the estimated increase from baseline in the PHQ-9 score was 1.8 points (95% confidence interval [CI], 1.7 to 2.0). In contrast, in the work-hour category of more than 90 hours per week, the increase was 5.2 points (95% CI, 4.9 to 5.6). Sensitivity analyses, which included an analysis for clustering according to institution, provided results that were similar to those of the primary analysis.

In this large, national cohort study involving U.S. medical interns, higher work hours were associated with progressively greater increases in depressive symptoms from baseline. Specifically, the increase in symptom scores was almost 3 times as high in the highest work-hour category (>90 hours per week) as in the work-hour category of more than 40 and up to 45 hours per week, which is the category closest to the hours typical of most nonmedical professions. Given that this was an observational study, it is possible that the results could be explained by residual confounding, even though the design and analytic approaches we used emulated those of a clinical trial.

Reduction in work hours has received only limited mention in the recent recommendations and policy statements addressing clinician well-being.[4,5] Our findings suggest that limiting the number of hours worked per week by residents has the potential to reduce rates of depression among early-career trainees.

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IL-1RA Antibodies in Myocarditis after SARS-CoV-2 Vaccination

TO THE EDITOR: Myocarditis associated with messenger RNA (mRNA) vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) predominantly affects male adolescents and young male adults (14 to <30 years of age) and typically occurs after receipt of the second vaccine dose.[1,2] In adults with critical coronavirus disease 2019 (Covid-19) and in cases of mul-

Figure 1 (facing page). Autoantibodies Targeting IL-1RA in Myocarditis after SARS-CoV-2 Vaccination.

Blood plasma samples were obtained from 69 patients with suspected myocarditis after receipt of vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In 61 patients, endomyocardial biopsy (EMB) was performed, and myocarditis was confirmed on EMB in 40 patients (**Panel A**). Plasma samples that were obtained from 8 patients with no confirmatory investigation on EMB, from 21 patients in whom the diagnosis of myocarditis was ruled out, and from 40 patients in whom myocarditis was confirmed on EMB were analyzed for antibodies against endogenous interleukin-1 receptor antagonist (IL-1RA) and progranulin by enzyme-linked immunosorbent assay (ELISA). Data are shown sorted according to the age of the study participants (**Panel B**). OD_{490} denotes optical density as measured at a wavelength of 490 nm. The frequency of anti–IL-1RA antibodies in plasma samples from patients with vaccine-associated myocarditis was confirmed or ruled out on EMB and was sorted according to age. Control participants were 214 healthy adults who had samples obtained 1 week after receipt of the second dose of SARS-CoV-2 vaccine and 127 patients with myocarditis whose samples were obtained before 2020 (**Panel C**).

Western blots of native gradient polyacrylamide gel electrophoresis (PAGE) revealed immune-complexed IL-1RA and weakened bands resembling free IL-1RA (16 kDa) in plasma samples seropositive for anti–IL-1RA. In identical samples, isoelectric focusing of IL-1RA revealed a differentially charged IL-1RA isoform (**Panel D**). Multiple Spearman's correlation analyses were conducted of IL-1RA plasma levels in anti–IL-1RA–positive patients (left graph) and autoantibody-negative patients (right graph) with the use of troponin T (Trop T; in units per milliliter), creatine kinase (CK and CK-MB; in picograms per milliliter), pro–B-type natriuretic peptide (pro-BNP; in units per milliliter), and CD3+ cells (normal value, <7 per square millimeter) and CD68+ cells (per square millimeter) infiltrating the tissue of the right or left ventricle, respectively, as well as C-reactive protein (CRP; in milligrams per deciliter). Numbers indicate the respective Spearman's r (*P<0.05, and **P<0.01) (**Panel E**). IL-1RA plasma levels were determined by ELISA in patients with vaccination-associated myocarditis. Data are shown as violin plots; in each plot, dots indicate individual samples, the solid horizontal line the median, dotted horizontal lines the upper and lower quartiles, and the shaded area the probability density. Data were analyzed by Brown-Forsythe and Welch analysis of variance and Dunnett's T3 multiple comparisons test (**Panel F**). Human embryonic kidney IL-1 reporter cells (releasing secreted embryonic alkaline phosphatase on IL-1β signaling) were incubated with tumor necrosis factor α (TNF-α), IL-1β , and IL-1β with anakinra or recombinant human IL-1RA (rec hIL-1RA). Plasma from adult patients with critical coronavirus disease 2019, without and with IL-1RA antibodies, and from patients with myocarditis after SARS-CoV-2 vaccination, without or with IL-1RA antibodies, were added (all plasma in 1:20 dilution). Recombinant anti–IL-1RA antibody and recombinant anti–stomatin-like protein 2 antibody were used as positive and negative controls, respectively (**Panel G**). I bars indicate the standard deviation of the mean. OD_{650} denotes optical density as measured at a wavelength of 650 nm, and VAM vaccination-associated myocarditis.