Assessments of human effects on ecological conditions should account for natural variability among ecosystems because many naturally varying watershed and site-level conditions affect both what we expect natural structure and function of the ecosystem to be and the sensitivity of ecosystems to human disturbance. Curiously, we do not find great improvements in relationships of diatom-assessed conditions and human disturbance by accounting for natural variability with advanced modeling methods. One plausible reason for this problem is covariation among natural and human factors across landscapes. We tested this hypothesis with structural equation modeling (SEM) and the diatom results of the USEPA’s 2008-2009 National Rivers and Streams Assessment. First, we developed machine learning models to predict expected metric values for all assessed sites in the US if they matched reference condition. Then we assessed sites as the deviation in metric values from sample counts and from modeled expected reference condition. We constructed SEMs for each ecoregion that determined: 1) how much variation in diatom multimetric indices were explained by in-stream physical-chemical conditions (pChem) and 2) how much variation in pChem could be explained by independent and covarying effects of natural factors (geology, climate, hydrology, soils) and anthropogenic factors (agricultural and urban land use). We found that direct influences on diatom MMIs by in-stream environments were greater than natural and human factors at the national scale and in all but one ecoregion. The explained variance of in-stream environments by natural and human factors ranged from 0.30 to 0.75, for which natural factors independently accounted for the largest proportion of explained variance at the national scale and in seven ecoregions. Covariation between natural and human factors accounted for a higher proportion of explained variance of in-stream environments than unique effects of human factors in most ecoregions. Ecoregions with relatively weak effects from human factors had high levels of covariance among natural and human factors and relatively high levels of human disturbance at reference sites when compared to highly disturbed sites. We conclude that accounting for effects of natural factors and their covariation with human factors in surrounding watersheds is important for accurate ecological assessments.