LETTER

Highly correlated hedonic and eudaimonic well-being thwart genomic analysis

In PNAS, Frederickson and colleagues (1) claim "hedonic and eudaimonic well-being engage distinct gene regulatory programs despite their similar effects on total well-being and depressive symptoms." Complex analyses depend entirely on distinguishing hedonic vs. eudaimonic well-being with a self-report measure. Any interpretation needs to accommodate the high likelihood of confounding and reverse causality with genetic influences on both gene expression and well-being.

Unfortunately, the two relevant subscales are interchangeable, correlating as much as their respective internal consistencies allow ($r = 0.79$; $P < 0.0001$). They can serve as proxies for depressive symptoms, correlating $r = -0.67$, $P < 0.0001$ and $r = -0.66$, $P < 0.0001$, respectively. The authors' claim about distinctive gene regulatory programs despite similar associations with self-report measures is misleading. Identifying distinct programs depends on statistical controls being applied, whereas comments about self-report measures depend on simple bivariate relations.

Little can be done to salvage assessment of what should be independent constructs from such highly correlated measures. The authors' use of each as the statistical control for the other produces an artifactual opposition. Resulting residuals have little resemblance to the variables as originally conceptualized and measured. Classical test theory indicates that when one variable is introduced as a statistical control for another with which it is highly correlated, most of the true variance in the latter variable is eliminated. This occurs with both eudaimonic introduced as a control for hedonic well-being and vice versa.

The situation is aggravated by adjustments for "age, sex, race/ethnicity, body mass index (BMI), smoking, alcohol consumption, recent minor illness symptoms, and leukocyte subset prevalence" (1). It is not clear how these control variables were selected, whether other control variables were considered, or what theory or diagnostics determined whether criteria for confounding were met (2). Observational epidemiology is replete with warnings that indiscriminate adjustment for numerous covariates leads to "peculiar and erroneous conclusions" (3) and "generate apparently robust, independent, yet spurious associations." (4). Alternately, "statistical adjustment by an excessive number of variables or parameters, uninformed by substantive knowledge (e.g., lacking coherence with biologic, clinical, epidemiological, or social knowledge) can obscure a true effect or create an apparent effect when none exists" (5).

The effort to answer an age-old question about whether one should strive for meaningfulness or happiness with genomics may be noble. However, the very grandiosity of claiming that it has been settled in such a modest study invites critical scrutiny of means and methods that this work cannot sustain.

An adequate effort would require prior validation of the independence of hedonic vs. eudaimonic well-being and their discriminant validity with respect to affective measures. Statistical control procedures are not of much assistance here. If these psychometric conditions could be met, then a study of genomic expression could be undertaken, informed by past demonstrations of the need for hundreds of subjects if robust, replicable results are to be obtained. The present article does not provide a basis for anticipating what results would be obtained or whether the effort would even be justified.

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