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Uncovering the Pathways Linking Depression and Physical Health

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The contributions of Wickrama and colleagues [1], and Dockray and colleagues [2], to this issue of *Journal of Adolescent Health* are both independently important, and perfectly complimentary. Each makes a unique contribution to our understanding of the associations between depression and physical health in populations of adolescence and young adults, and each has differing methodological strengths. The Wickrama et al. study uses three waves of existing data from a large representative, longitudinal sample (Add Health) to examine prospective associations between depression and multiple self-reported health outcomes measured 6 years later. Without data on biological mediators, however, the authors can only speculate on the mechanisms by which associations between depression and health might occur. The Dockray et al. study, on the other hand, is a primary data collection effort on a smaller, community-based sample, designed to examine the role of a specific biological pathway (HPA axis hyper-reactivity) linking depression to a specific health outcome, obesity. The Dockray et al. data, however, are cross-sectional, and hence the causal direction of associations between depression, HPA axis activity and obesity remain ambiguous.

In this first generation of studies on adolescent depression and health, no one study can do it all. Combined, these two studies provide compelling evidence of the importance of adolescent depressive symptoms for adolescent and young adult health outcomes. Here, I highlight a few strengths and limitations of each of these innovative studies, point out some notable convergences and divergences in their results, and briefly envision some characteristics of a “next generation” of research on adolescent depression and physical health that combines the considerable methodological strengths of the Wickrama et al., and Dockray et al. studies.

Beyond the use of a large, prospective longitudinal dataset, another strength of the Wickrama et al. study is its employment of a person-centered approach to examine the impact of varying *trajectories of depressive symptoms* across 3 waves of data on *changes* in physical health problems from adolescence through young adulthood. Perhaps not surprisingly, they find that adolescents with consistently high depressive symptoms show the largest increase in health problems, including increases in sexually transmitted diseases, asthma, diabetes, physical limitations and perceived general health. Even more compelling, from a causal standpoint, is their final analysis, in which SES variables, and also initial and concurrent (Wave III) levels of depressive symptoms are covaried in an SEM model, suggesting that results are not due to SES confounds, nor to the influence of current depression on reporting of health outcomes. A lingering question regarding the Wickrama et al. study (beyond the question of mechanism) is whether their theoretically constructed person-centered pathways (of high-high, high-low, low-high and low-low depression over time) would emerge if an empirical strategy to identifying

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trajectories of depressive symptoms had been employed, or whether additional trajectories not expected by the authors may in fact be present in the data.

A major strength of the Dockray et al., study is that it started from a specific hypothesis regarding mechanism -- the authors designed a nuanced study and protocol intended to examine the possibility that HPA axis reactivity may be an important mediator of the associations between depression and body mass index (BMI) or obesity. The authors use a well-validated stress reactivity protocol, and their measurement and reporting of salivary cortisol reactivity is exemplary. They are also careful to account for potential confounds such as time of day, age, pubertal stage, SES, and physical activity levels. The authors find their expected associations between depression and cortisol reactivity for both boys and girls, but only find associations between cortisol reactivity and BMI for girls, and hence, cortisol reactivity is found to be a significant partial mediator for the associations between depression and BMI for girls only. As noted earlier, and acknowledged by the authors, the cross-sectional nature of the data does not allow for the conclusion that the heightened cortisol reactivity preceded and/or contributed to the development of obesity, nor can the causal order of associations between depression and cortisol reactivity be determined. Nonetheless, the study clearly identifies cortisol reactivity as a potential mediator to be examined in future longitudinal research, at least for girls. One also wonders how the heightened cortisol reactivity in this study relates to basal cortisol patterns across the day. Particularly given known findings of basal cortisol dysregulation in the context of major depression [3], the addition of a basal protocol to the next stage of this research would further enhance its considerable contributions.

One point of contrast between the two papers is that associations between depression and obesity, the central focus in the Dockray et al. study, were not significant in the Wickrama et al. study. Although Wickrama et al., covaried gender, they did not test for the possibility that gender might serve to *moderate* associations between depression and obesity. Given the important gender differences known in the literature, and found in the Dockray et al. study, future studies will need to address the possibility that associations between depression and health outcomes, and the pathways by which they occur, may vary according to gender. One point of similarity is that both studies used continuous measures of depressive symptomatology. Future studies should compare the predictive power of depressive symptoms with clinical diagnoses of major depressive disorder. Prior meta-analytic evidence in adults has shown that although variations in depressive symptoms do matter, clinical depression is much more profoundly associated with dysregulations in another health-relevant biological pathway, inflammation [4].

In summary, these studies suggest that the association between adolescent depression and physical health merits further attention from the adolescent (and adult) health research communities. The next generation of research should combine the relative strengths of each of these two papers: studies should be *longitudinal in nature*, and need to *measure and test the biological and behavioral* mechanisms proposed to mediate associations between depression and later health outcomes. Even short term longitudinal data (over a period of weeks or months) incorporating repeated measures of emotional health, physical health, and mediating biological and behavioral pathways could make an important contribution. As suggested by Dockray et al., such research should take into account the possibility that pathways linking depression and health may vary in strength and mechanism according to gender. As implied by Wikrama et al., the timing and chronicity of exposure to depression may play an important role in understanding later impacts on physical health. Future research should also consider the possibility that the mechanisms that link depression to various physical health outcomes may either be overlapping, distinct, or a combination thereof. For example, alterations in HPA axis activity may play more prominent roles in the development of obesity and diabetes [5], whereas inflammatory changes may play a more prominent role in the downstream development of

asthma and cardiovascular disorder [4], and poor health behaviors such as decreases in physical activity or poor adherence to medication regimens may play a role in both types of health outcomes [6]. By taking the important lessons learned from the Dockray et al., and Wickrama et al., papers, the next generation of research should bring us closer to understanding the biological and behavioral mechanisms by which depression and physical health are related, and underscore the importance of adolescent emotional experience in setting up long term pathways of physical health.

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