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A Narrow Heritability Evaluation of Gestational Age at Birth

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TO THE EDITORS

Wu *et. al*.(Wu et al. 2015) estimated the heritability of gestational age at birth (GA) in a sample of approximately 2 million singleton births from the Utah Population Database (UPDB). Aside from the large sample size, their approach obscures the genetic and environmental influences they aimed to elucidate. Existing studies provide more clarity on the nature of these effects primarily by taking advantage of multiple relationship types that are routinely available in population datasets (including the UPDB) and the application of methods rooted in biometrical genetic theory and current practice. Readers may not be aware that the authors (or reviewers) are apparently unfamiliar with this work since it is not cited nor do they compare their own estimates with those obtained from numerous prior studies using long-established statistical genetic models and methods for estimation and hypothesis-testing,

The authors add to the extant literature another assessment of the influence of both fetal and maternal genes on GA. What they refer to is the established 2-character model of Haley and Jinks (Haley et al. 1981) where genetic influences on a quantitative trait stem from two possible sources: the direct effect of the fetal genotype on the GA of the fetus and the indirect environmental effect of the maternal genotype on their offspring GA. Nowhere does the current paper allude to this long-established notion, to the possible genetic covariance between fetal and maternal effects (see (Eaves et al. 2014)), nor do they refer to the possibility of their resolution by inclusion of parental GA in addition to those of a limited set of collateral relatives. The authors dismiss the twin method as incapable of providing the necessary statistical contrasts to estimate these effects when twin mothers are used as the index case. The problem with this interpretation is that it is questionable whether the mother really is the index case since it is not her GA that is being measured in these studies. The method used is better viewed as extended twin design since it is the GA of the children of twins (COT) that is being measured. Following the work of Nance and Corey (Nance and

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Corey 1976) the biometrical genetic COT model has already been implemented sufficiently to estimate the separate influence of the fetal and maternal genetic contributions to GA (York et al. 2009). Lynch and Walsh (Lynch and Walsh 1998) describe several advantages of the COT method over the classical twin design.

Despite criticism of the twin method, Wu *et. al*. do not provide their own solution for estimating the separate effects of the genetic and environmental components. Although the multigenerational UPDB has an array of both ancestral and collateral relationships, they restrict their estimation of variance components to only full and half-sibships. Under this design they recognize their maternal genetic effect is confounded with that of the familial environment. Lunde *et. al*. (Lunde et al. 2007) has previously described a similar method to separate these effects using parent-offspring, full siblings and maternal half sibling correlations. Although the authors omit parent offspring relationships from their analysis to avoid inter-generational effects, they miss an opportunity to make a valuable methodological contribution to account for cohort effects and provide clarity to the covariance of maternal and fetal effects (passive genotype-environment covariance).

Now understanding that the solution to using twin samples to estimate the 2-factor GA model has previously been provided (York et al. 2009) and implemented (York et al. 2013a; York et al. 2010), we can consider the authors' next assertion that twin studies can result in biased estimates of heritability. There is no question that the classical twin method might be subject to bias in the same way any other method would be at fault that was in violation of its assumptions. Yet, it is not clear from this manuscript which assumption of the twin (and family) design the authors' perceive to be violated in studies of GA. Our own published data (York et al. 2013a; York et al. 2009, 2010) integrating GA measures from large samples of pregnancies of male and female MZ and DZ twins, full siblings and maternal and paternal half siblings not only resolve the effects of fetal and maternal genotype but also provide a test of the assumptions of the model including the consistency of parameter estimates across multiple different sets of relationships. This is typically regarded as a *sine qua non* for any attempt to estimate genetic and environmental parameters from kinship covariances (see e.g. (Jinks and Fulker 1970)). Nevertheless, Falconer and MacKay (Falconer and Mackay 1996) indicate that potential difficulties with twin data can be overcome by the design of studies that estimate the covariance patterns in several different relationship types in addition to those joined by twins and has been shown to increase statistical power (Posthuma and Boomsma 2000). In contrast to the authors' assertions, the inclusion of twin data has been shown to overcome bias incurred by the common environment component of the full-sib correlations (Falconer and Mackay 1996).

Thus, it is an empirical question whether relationships with identical variance component expectations differ in their covariance patterns. If they did then it may imply, for instance, that different relationships are explained by different genetic and environmental influences or that twin samples are not representative of the population. A cursory review of GA studies in this area would indicate that this is likely not the case. It has already been shown that children of twin correlations are near identical to children of siblings correlations that are equivalent for variance component expectations (York et al. 2013a). For example, the children of sister-sister sibships and dizygotic sisters would both be related as cousins (1/8

fetal genetic and 1/2 maternal genetic influences). The estimated correlation and 95% confidence interval for the former relationship is 0.115 (0.102, 0.129) and the latter is 0.116 (0.068, 0.167). Similar correspondence is seen for brother-brother sibships with dizygotic male pairs and brother-sister sibships with opposite sex dizygotic pairs. Such concordance in results across relationships would not be present if there were significant violations incurred by the use of twin data.

Wu *et. al*. do not hold their own study up to the same standard by providing tests of their model assumptions. For instance, they assume equality of the common environmental variance component between maternal half-siblings and full-siblings. Neither do they consider an equivalent term for paternal half-siblings which theoretically could be present. The authors indicate environmental influences that are invariant across pregnancies of the same mother would be accounted for by the maternal component, but make no accommodation for covariates that change across pregnancies such as the strong influence of maternal age on preterm birth risk. Accounting for the presence of either environmental source would serve to further clarify genetic influences.

In the context of studies that provide unique solutions to variance components (reviewed in (York et al. 2013b)) the results of Wu *et. al*. are consistent with a moderate influence of fetal and maternal effects on GA. Their estimate of the fetal genetic contribution of 13.3% is in line with previous estimates of that range between 5-35%. Their estimated non-familial environmental effect of 60.3% is also similar to these previously reported studies that report estimates between 45-61%. Their maternal effect, confounded by maternal genes and the familial environment, makes it difficult to compare with these studies. These heritability estimates do not imply whether the effect of individual genes will be small or large (Visscher et al. 2008) and does not support the authors' assertion that multiplex pedigrees are better positioned than samples of unrelated individuals to identify genetic associations.

Fundamental to the identification of allelic variation that contributes to GA (and preterm birth) is initial assessments of genetic architecture using twin and family methods to guide the field in the right direction. Genetic studies of GA (and preterm birth) have recently passed through a period of confusion that rests, partly, on the application of methods that have confounded genetic and environmental effects which resulted downstream to the exclusion of fetal genetic influences (reviewed in (York et al. 2013b)) or have made claims that overreach their interpretation regarding genetic factors that influence the marked racial disparity in PTB risk (Kaufman et al. 2007; Kistka et al. 2007; Spriggs 2007).

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