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Unpacking the heritability of body mass index and other ratios

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Abstract

Objectives: Ratios of weight to height, especially body mass index (BMI = kg/m^2), are often used in epidemiological and genetic studies of health, but the limitations of quantitative genetic analysis of ratios are not widely known. The heritability of these ratios can be closely approximated from a bivariate quantitative genetic model of weight and height which clarifies how BMI heritabilities change.

Methods: I explored this bivariate approximation and alternative measures through simulated datasets fit with linear mixed models. Simulated data were based on published heritabilities and other statistics for BMI and related anthropometric dimensions from four human samples.

Results: Inspection of the bivariate approximation and analysis of simulated data show the heritability of weight/height crucially depends on the phenotypic (r_P) and genetic correlations (r_A) between weight and height. Changes in these correlations can have dramatic effects on the heritability of BMI. For example, when $r_P \ll r_A$ heritability of BMI is reduced to 35-50% of its value when the correlations are equal.

Discussion: Increasing adiposity likely decreases the phenotypic correlations more than the genetic correlation resulting in reduced heritability of the ratio. This contrasts with the commonly reported stability or increase of BMI heritability and implies it may result from increased genetic variance in weight in obesogenic environments. The bivariate model offers other advantages over ratios, including estimating the *conditional* genetic variance or heritability of weight that is unassociated with height, which may prove useful in quantitative and molecular genetic studies.

1 | INTRODUCTION

Ratios of weight to height, or mass to stature, are widely used in epidemiological and genetic studies of human health. This is particularly true of the body mass index (BMI = kg/m^2), though many other possible ratios have been proposed and used to a lesser degree (eg, kg/m, kg/m^3, and m/kg$^{1/3}$). BMI is often advocated as a measure of weight or adiposity uncorrelated with height (Heymsfield, Gallagher, Mayer, Beetsch, & Pietrobelli, 2007). Elsewhere, animal ecologists have used similar ratios as an index of body condition attempting to capture muscle deposition and fat stores on a standardized skeletal frame (Stevenson & Woods, 2006). Ratios are also commonly used to describe morphological shape such as limb proportions or cranial indices (Bass, 1995; Fleagle, 2013). All of these ratios are likely to be polygenic, complex traits having many loci scattered throughout the genome that contribute to their phenotypic variability (Lynch & Walsh, 1998). Enough twin and family studies of BMI have been conducted that comprehensive meta-analyses of the heritability, the ratio of additive genetic to phenotypic variance ($h^2 = V_A/V_P$), of BMI are available (Elks et al., 2012; Min, Chiu, & Wang, 2013). More recently, tremendous attention has been placed on identifying molecular variants contributing to this heritability of BMI (Goodarzi, 2018; Locke et al., 2015; Loos & Yeo, 2014; Visscher et al., 2017).

While there are many critiques of BMI as a measure of obesity (eg, Müller, Bosy-Westphal, & Krawczak, 2010; Prentice & Jebb, 2001) and its application across human populations (Diverse Populations Collaborative Group, 2005), there has been little appreciation of the assumptions BMI introduces as a ratio or to alternative methods for genetic analysis of weight for a given height. Many problems with ratios are well-known to statisticians who have often expressed reservations about ratio analysis (Atchley, Gaskins, & Anderson, 1976; Curran-Everett, 2013; Jackson & Somers, 1991). However, consequences for quantitative genetic or genetic association studies have not been explored in any detail outside of the animal breeding literature. Early work showed that the heritability of a ratio could easily be predicted from statistics for the numerator and denominator variables with a first-order Taylor series approximation attributed to Pearson (1897). However, this ratio heritability was not useful in predicting evolutionary response to artificial selection (Gunsett, 1987; Sutherland, 1965; Taylor, 1959).

The approximation, as given by Sutherland (1965) but adapted to the weight/height ratio, is

$$h^2_{\mathrm{wt/ht}} = \frac{\left(h^2_{\mathrm{wt}}C^2_{\mathrm{wt}} + h^2_{\mathrm{ht}}C^2_{\mathrm{ht}} - 2r_{\mathrm{A}}h_{\mathrm{wt}}h_{\mathrm{ht}}C_{\mathrm{wt}}C_{\mathrm{ht}}\right)}{\left(C^2_{\mathrm{wt}} + C^2_{\mathrm{ht}} - 2r_{\mathrm{P}}C_{\mathrm{wt}}C_{\mathrm{ht}}\right)}, \qquad (1)$$

where h^2 is the trait heritability with h simply being their square roots, C is the trait coefficient of variation (variance/$\bar{x}^2$), r_{A} is the additive genetic correlation, and r_{P} is the phenotypic correlation. When multiplied by the squared ratio of their means $(\bar{x}_{\mathrm{wt}}/\bar{x}_{\mathrm{ht}})^2$, the numerator and the denominator of Equation (1) are the additive genetic variance and phenotypic variance, respectively, of the weight/height ratio. Note that heritability of weight/height and height/weight is identical. However, the heritability of BMI cannot be approximated from these raw variables' statistics. It will be very strongly correlated with this predicted weight/height heritability (see below) and could be approximated directly if height^2 is used as the denominator trait. Often, r_{A} and r_{P} are similar in sign and magnitude but they are not equivalent (Searle, 1961). Instead, they are related by the following equation where r_{R} is the residual correlation:

$$r_{\mathrm{P}} = r_{\mathrm{A}}h_{\mathrm{wt}}h_{\mathrm{ht}} + r_{\mathrm{R}}\left(1 - h^2_{\mathrm{wt}}\right)^{1/2}\left(1 - h^2_{\mathrm{ht}}\right)^{1/2}. \qquad (2)$$

While the heritability of BMI, weight, and height are frequently estimated, they are rarely treated in a multivariate framework such that r_{A} or even r_{P} is reported (cf., Elks et al., 2012). This is unfortunate given the crucial role these correlations play in determining the heritability of weight to height ratios. Because both correlations are positive in realistic circumstances, larger correlations will decrease genetic variance and the phenotypic variance of the weight/height ratio. The effect on the heritability of this ratio depends on the magnitude of the correlations and geometric mean of the heritabilities ($r_{\mathrm{P}}v{\cdot}r_{\mathrm{A}}h_{\mathrm{wt}}h_{\mathrm{ht}}$). The outcome is explored here through analysis of some simulated data under a range of different correlations with fixed coefficients of variation and heritabilities for weight and height.

The importance of these correlations requires more detailed exploration of how they influence heritability of BMI in human datasets. It also points to considering alternative metrics for assessing the genetic variance of weight for a given height. A simple methodological alternative to BMI and other ratios is a univariate model to estimate heritability of weight, using height as a covariate which should account for phenotypic variation in height among the measured individuals. Conceptually, this is akin to analyzing the residuals from regression of weight on height. The estimated heritability of this residual weight has a numerator and a denominator reduced by the phenotypic variation associated with height. However, because of the reliance on phenotypic association between weight and height, the resulting heritability will be strongly influenced by r_{P}, just like heritability of BMI or other weight-height ratios.

A second alternative is the *conditional heritability* of weight which is defined as the fraction of phenotypic variance in weight ($V_{\mathrm{P,wt}}$) that is due to additive genetic variance in weight *independent* of height: $h^2_{\mathrm{wt|ht}} = \left[V_{\mathrm{A,wt}} - \mathrm{Cov_A(wt,ht)}^2/V_{\mathrm{A,ht}}\right]/V_{\mathrm{P,wt}}$, where V_{A} is the genetic variance and $\mathrm{Cov_A(wt,ht)}$ is the genetic covariance between weight and height (Hansen, Armbruster, Carlson, & Pelabon, 2003; Jensen et al., 2003). These must be estimated in bivariate quantitative genetic models for weight and height. Comparison of these alternatives to weight/height heritability or BMI heritability is explored through simulated datasets below.

2 | METHODS

I used the GAW10 pedigree (MacCluer, Blangero, Dyer, & Speer, 1997; http://solar-eclipse-genetics.org/) in a series of simulations to explore the heritability of BMI and the weight/height ratio. The pedigree contains 1497 people in 23 extended families of up to 4 generations having 37-128 people in each family. I generated data for all pedigree members with the phensim() function from the pedantics package in *R*. Trait means, variances, and correlations were taken from four literature sources to capture the common range of height and weight heritabilities (Bastarrachea et al., 2007; Byars, Ewbank, Govindaraju, & Stearns, 2010; Choh, Gage, McGarvey, & Comuzzie, 2001; Coady et al., 2002; Jelenkovic, Poveda, & Rebato, 2011; Jelenkovic & Rebato,

2012). These observed values were used to parameterize simulations across a range of possible genetic and phenotypic correlations, while keeping the means, heritabilities, and phenotypic variances fixed (Table 1). Height and weight were measured by medical professionals in each sample (ie, not self-reported). Phenotypes were simulated with genetic and phenotypic correlations on a grid of possible positive values from .05 to .95. Many pairings implied residual correlations outside the −1 to 1 range and were dropped. The remaining 928 simulated datasets (185-271 for each study) were analyzed with restricted maximum likelihood in WOMBAT (Meyer, 2007) for univariate variance components and heritabilities of height, weight, weight/height, and BMI. The same simulated datasets were analyzed in WOMBAT in bivariate models for the trait variances and covariances that can be reformulated as heritabilities, genetic and phenotypic correlations, and conditional heritabilities. Sex-specific means were the only fixed effects in the WOMBAT models, and the additive genetic breeding value linked to the pedigree was the only random effect (Kruuk, 2004; Wilson et al., 2010). The only exception was a set of univariate models that included sex-specific *z*-scored height as a covariate for estimating variance components of weight.

Results were explored through plots and correlations within simulations for each study to uncover patterns. This included comparing the univariate weight/height heritability to that predicted by the approximation in Equation (1) from the bivariate model's statistics. I also compared the BMI heritability to the approximated weight/height heritability by analysis of covariance (ANCOVA) using population as a categorical variable and testing for population differences in the slope of the BMI heritability regression. *P* values are reported to assist interpretation, but these are dependent on the number of simulations run. The influence of changing r_A or r_P was assessed by plotting these against one another and examining the heritability of BMI, the heritability of weight adjusted by height as covariate, or the conditional heritability of weight. The difference in correlations ($r_A - r_P$) was also used in some correlations or plots. Smoothed surfaces were also created by linear interpolation with the interp() function from the Akima package. Simulated data and *R* code for analysis are available as Data S1.

3 | RESULTS

The univariate model heritability of weight/height and BMI are predicted very precisely from the bivariate approximation in Equation (1). Pearson's correlations within study sets are very high (weight/height range: 0.98-0.99, BMI range: 0.92-0.96). The BMI heritability is linearly related to the weight/height heritability but reaches more extreme values. The slope of the regression is ≈1.6 (range: 1.55-1.67) and does not differ significantly among study simulation sets ($P = 0.10$). However, the intercept does differ among studies because of variation in weight and height heritabilities and CVs (Table 2).

With fixed sex-specific means and phenotypic variances for each study, it is the covariances differing among the simulated datasets that determine these ratio heritabilities. The highest weight/height or BMI heritabilities are when phenotypic correlations exceed genetic ones ($r_P > r_A$) and they decline linearly as the difference r_A–r_P increases (Figures 1 and 2). The

TABLE 2 Common slope ANCOVA predicting heritability of BMI estimated in univariate models from the weight/height heritability ($h^2_{wt/ht}$) predicted from the bivariate model statistics

	β	SE	*P*
Intercept[a]	−.367	0.009	<.001
Samoa	.040	0.004	<.001
Bilbao	−.001	0.005	.760
Mexico	.138	0.006	<.001
$h^2_{wt/ht}$	1.620	0.019	<.001

[a]With Massachusetts as baseline and others as deviations.

TABLE 1 Phenotypic variances, heritabilities, phenotypic and genetic correlations, and sex-specific means for height and weight used for data simulations

	Height (cm)		Weight (kg)								
Study	♂	♀	♂	♀	$V_{P,ht}$	$V_{P,wt}$	h^2_{ht}	h^2_{wt}	r_P	r_A	h^2_{BMI}
Massachusetts[a]	173.80	160.35	81.17	65.74	40.96	176.89	0.84	0.52	0.35	0.46	0.37
Samoa[b]	170.84	160.13	90.49	89.52	33.29	318.27	0.58	0.46	0.35	0.45	0.41
Bilbao[c]	175.10	160.87	80.93	61.02	37.52	104.86	0.69	0.53	0.61	0.70	0.44
Mexico[d]	170.40	157.00	81.65	67.19	44.44	186.78	0.77	0.34	0.39	0.42	0.36

[a]Byars et al. (2010) and Coady et al. (2002).
[b]Choh et al. (2001).
[c]Jelenkovic et al. (2011) and Jelenkovic and Rebato (2012).
[d]Bastarrachea et al. (2007).

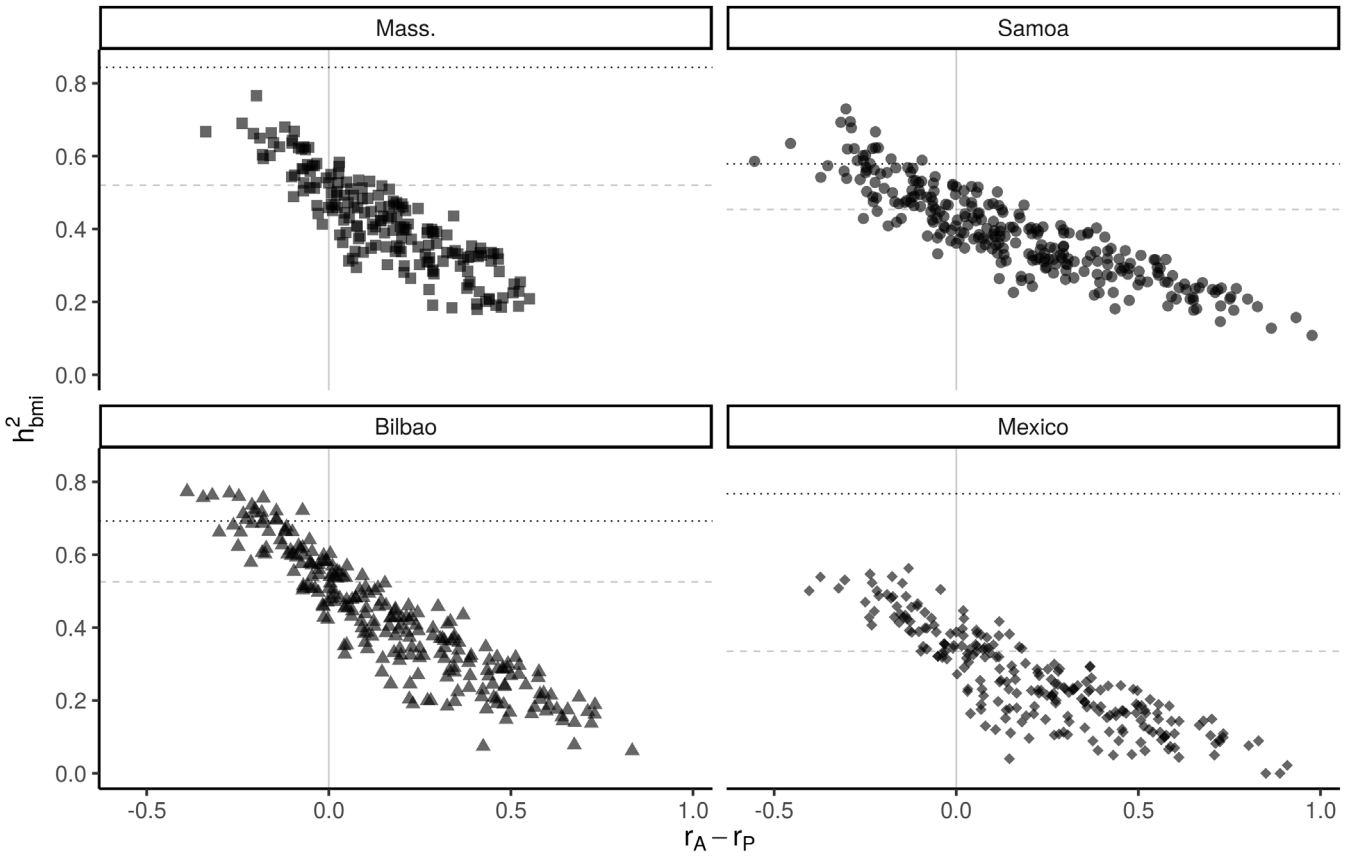

FIGURE 1 Estimated heritability of BMI compared to the difference in genetic (r_A) and phenotypic (r_P) correlations for the four study sets of simulations. Dotted and dashed horizontal lines indicate the height and weight heritabilities, respectively

resulting heritabilities for either ratio are almost always less than the height heritability and are usually lower than that for weight when genetic correlations exceed phenotypic ones ($r_P < r_A$). Whenever the correlations are equal, both ratio heritabilities are approximately equal to the heritability of weight. Comparing this with cases of $r_P < r_A$ causes large reductions in heritability of BMI. For example, when $r_P + 0.5 < r_A$ (the lower right tail of panels in Figure 1), the mean heritability of BMI is reduced to 35-50% of its value when the correlations are equal, depending on the study simulation set.

Heritability of weight with *z*-scored height as a covariate is also strongly correlated with heritability of BMI (range: 0.72-0.86) or the approximation from Equation (1) (range: 0.63-0.77). Conditional heritability of weight is strongly correlated with BMI heritability (range: 0.78-0.93), the approximation in Equation (1) (range: 0.71-0.89), or heritability of weight with height as a covariate (0.58-0.82). However, there are important systematic differences among these three metrics poorly captured by pairwise, linear correlations. In particular, the conditional heritability of weight is only affected by changes in the genetic correlation and is not influenced by the phenotypic correlation. The BMI heritability and heritability of weight with height as a covariate are both affected by change in either correlation. Indeed, controlling for variation in the genetic correlation, the partial correlation between BMI and conditional heritability of weight is much smaller (range: 0.33-0.57). In contrast, controlling for variation in the phenotypic correlation, the partial correlation between BMI and conditional heritability of weight always increases (range: 0.94-0.97).

Graphically, this can be seen in the smooth decline of the conditional heritability of weight with increasing r_A independent of r_P (right column, Figure 2) as a plane angled only along the *x*-axis. Heritability of BMI has a more complex dependence on the correlations. It has a peak with highest possible values of r_P and low r_A values and declines most steeply as r_A increases and r_P decreases (left column, Figure 2). Heritability of weight with *z*-scored height as covariate has an even more complex relationship with the correlations. It is highest with highest possible values of r_P and low to moderate r_A. Like heritability of BMI, it declines with increasing r_A and decreasing r_P, but then it increases again at low values of r_P and moderate to high r_A (center column, Figure 2).

4 | DISCUSSION

I have shown through a set of simulations based on literature values that the heritability of the weight/height ratio or BMI

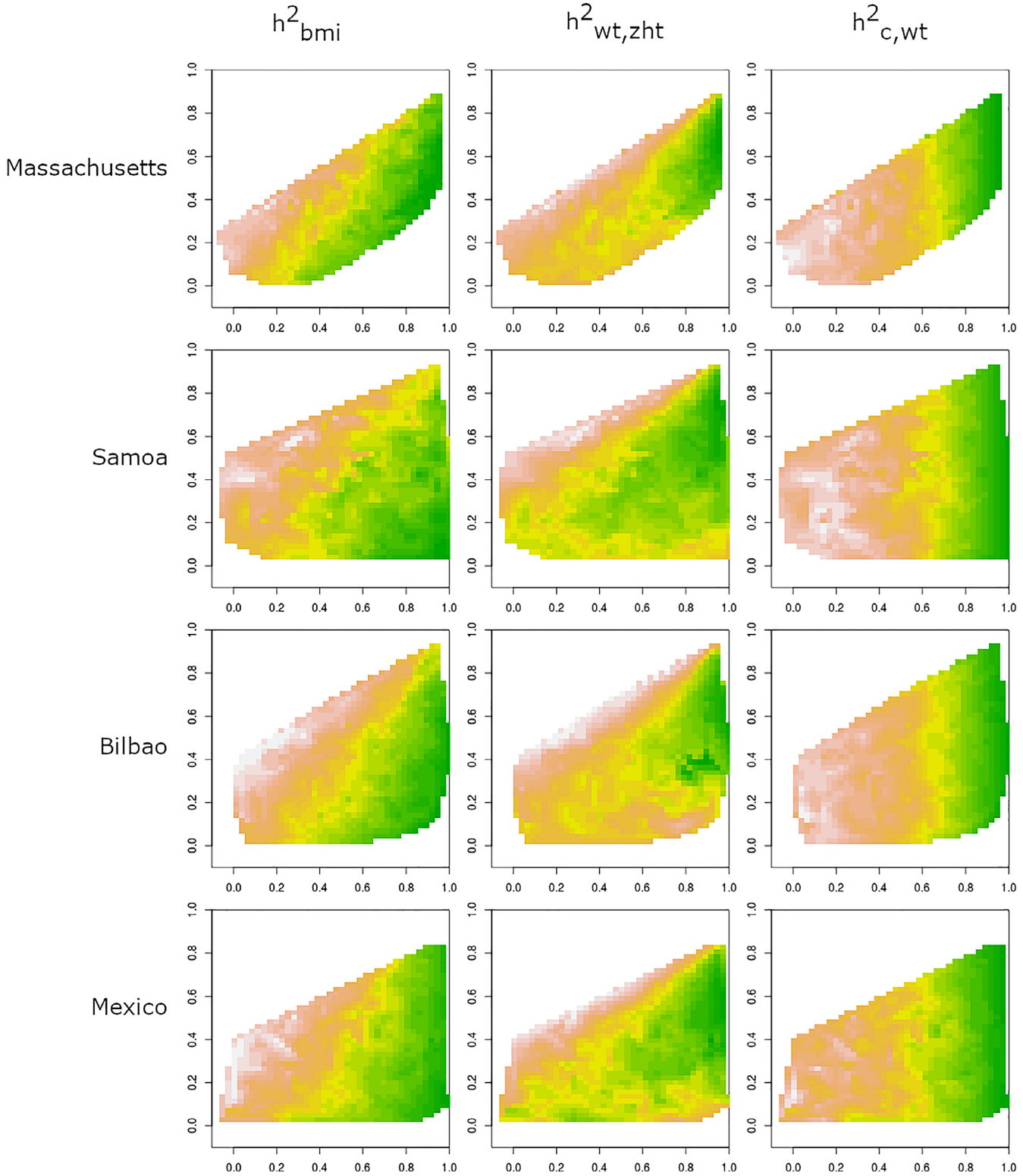

FIGURE 2 Surface plots of univariate BMI heritability (left column), heritability of weight with height covariate adjustment (center), and conditional heritability of weight (right) over the range of genetic correlations (*x*-axis) and phenotypic correlations (*y*-axis) for the four study samples (rows). Greens are lowest values; pink and white are the highest values

is well approximated by Equation (1). All terms of the equation can be estimated from a bivariate quantitative genetic model for weight and height (or weight and height^2). More importantly, the bivariate model offers more information on how height and weight are related to one another genetically and phenotypically and can be used for any dataset, a BMI

heritability might be estimated. The approximation from Equation (1) or a univariate model for BMI heritability should provide similar results. However, simulation results also demonstrate the complex dependence of BMI heritability, or the heritability of weight when using height as a covariate, on the phenotypic correlation and genetic correlation between weight and height.

The same bivariate quantitative genetic modeling approach could be taken with other commonly used anthropometric indices in obesity research, such as waist-hip or waist-height ratio. This may be biomedically important because these indices are better predictors of mortality than BMI in many cases (Kodama et al., 2012; Rost et al., 2018). Elsewhere, the abundant psychological and anthropological literature on second to fourth digit ratio could also be enhanced by direct assessment of digit lengths in a bivariate genetic model (Manning, 2002). This would be particularly advantageous as digit ratio has recently been shown an inadequate size-standardization, though raw digit lengths should still reflect hormone exposure during growth (Lolli et al., 2017). In contrast to the preponderance of ratios in these fields, the most comprehensive study of the evolutionary genetics of primate limb proportions includes complete phenotypic covariance and genetic covariance matrices and means for all major limb elements in several species (Hulsey, 2016). These can easily be transformed with Equation (1) into heritabilities of well-known limb indices (eg, crural, brachial, and humerofemoral). Moreover, they allow precise description of the phenotypic and genetic integration of limb element lengths. Similarly, construction and analysis of dental ratios by Hlusko, Schmitt, Monson, Brasil, and Mahaney (2016) rely on prior detailed description of phenotypic covariance and genetic covariance (Hlusko & Mahaney, 2009).

The influence of the weight-height phenotypic correlation on the heritability of BMI complicates its use as a measure of genetic variation in weight independent from height. Recognition of the influence of phenotypic correlations helps explain some results on the genetics of BMI. Many studies, including all those used in the simulations, report a descending series of height > weight > BMI heritability. BMI heritability is lowest due to genetic correlations exceeding phenotypic correlations, a very common pattern for morphological traits (Cheverud, 1988; Roff, 1995; Searle, 1961; Vattikuti, Guo, & Chow, 2012). Pleiotropic effects on height and weight are likely to be frequent because any vertical increase/decrease in skeletal frame will also affect weight. Environmental effects may perturb similar developmental pathways resulting in positive residual correlations, but they can also be quite distinct for each trait. In particular, environmental factors related to variation in adiposity (eg, physical activity, and smoking) are much less likely to be associated with changes in skeletal dimensions, resulting in lower phenotypic correlations.

An identical complaint could also be made against using height as a covariate to adjust heritability estimates for weight. However, this method is further complicated by unintuitive increase in heritability of weight when phenotypic correlations are very low. Because simulated phenotypes were constrained to have positive genetic correlations and phenotypic correlations, this region of increase in heritability of covariate-adjusted weight is due to negative residual correlations. Whether this is empirically relevant is unclear because there are very few published estimates of genetic and phenotypic correlations between height and weight. All four studies in Table 1 have positive residual correlations. However, it is biologically plausible there could be environmental triggers that would cause increased muscle or fat deposition at the expense of height growth or vice versa, and they would vary within populations. Early life stressors that have long-term effects on neuroendocrine control of appetite, satiety, and activity are obvious candidates (Charmandari, Kino, Souvatzoglou, & Chrousos, 2003). Ideally, phenotypes should be treated as phenotypes in a multivariate framework to accurately describe the genetic correlations and residual correlations rather than as covariates where a phenotypic regression reduces the genetic variance and residual variance by unknown amounts in a single modeled phenotype.

Changing BMI genetics can also be better contextualized through the bivariate model. Higher frequency of obesity has been associated in some studies with increased heritability of BMI or elevation of the effect of candidate loci (Albuquerque, Nóbrega, Manco, & Padez, 2017; McCaffery, Papandonatos, Bond, Lyons, & Wing, 2009). As increasing adiposity should diminish the phenotypic correlation between height and weight more than it reduces the genetic correlation (a shift to the right in Figure 1), the reported increases in BMI heritability must be due to relative increase in the genetic variance of weight. This genotype × environment interaction may reflect expression of cryptic genetic variance in novel obesogenic environments (Paaby & Rockman, 2014). In other cases, heritability of BMI is reported to remain stable despite increase in mean and phenotypic variance (Silventoinen et al., 2017). While this necessarily results from proportional changes in the genetic and residual variance in BMI, it could be accomplished through a variety of changes in the heritability of weight, heritability of height, or the phenotypic and genetic correlation between them. Following the speculation above, a stable BMI heritability could result from a phenotypic correlation reduced more than the genetic correlation offset by compensatory increase in the genetic variance. Distinguishing among alternatives would be simple in the bivariate model.

Genotype × sex or genotype × age interactions may also influence heritability of BMI. Adult sex differences in the phenotypic correlation between height and weight have been noted in some samples (eg, Micozzi, Albanes, Jones, &

Chumlea, 1986). Given the frequency of measurement in many biomedical studies, this is unlikely to be due entirely to inadequate controls for pregnancy and lactation. All else being equal, this should increase the denominator of Equation 1 and thereby depress the heritability of BMI in females. Without implementing a bivariate model of height and weight for each sex (Stearns, Govindaraju, Ewbank, & Byars, 2012), reported sex differences in the heritability of BMI could result from this or other component changes (Schousboe et al., 2003).

Heritability of height, weight, and BMI all typically increase from infancy to adulthood (Dubois et al., 2012). The contribution of changing variances vs correlations to the trajectory for BMI is currently unknown. Phenotypic correlations between height and weight are low at birth, rise through childhood and adolescence, and then fall again to modest values during adulthood (Tuddenham & Snyder, 1954). There may be a distinct advantage to this bivariate approach when analyzing height and weight across a large range of ages because both have theoretically justified nonlinear growth models that are commonly used (Hauspie, 1989). BMI has a complex age-specific pattern with no theoretical model (WHO Multicentre Growth Reference Study Group, 2006). There may be more mundane advantages, such as the less skewed distributions of height and weight compared to BMI.

Changes across adulthood in BMI heritability could also be related to changing correlations between height and weight, though these are rarely reported (Nan et al., 2012; Ortega-Alonso, Sipilä, Kujala, Kaprio, & Rantanen, 2009). Average BMI often increases in older adults but then declines in advanced old age, which suggests changing physiology of weight maintenance and opportunities for changes in its genetic variance and the covariance between weight and height (Rissanen, Heliövaara, & Aromaa, 1988). Moreover, evolutionary theories of aging all posit increasing genetic heterogeneity in late life (Charlesworth & Hughes, 1996; Kirkwood, 2017), but how this manifests in aged cohorts likely varies among phenotypes and will be strongly dependent on earlier mortality loss (Grafen, 1988).

The conditional heritability of weight is a metric more appropriate than heritability of BMI for describing polygenic effects on weight that are independent of height. It is simple to calculate from the results of bivariate or multivariate models. Precision of the conditional heritability or conditional genetic variance is easiest to compute by combining the Bayesian posterior distributions of the component terms (Boerner & Tier, 2016; Hadfield, 2010). The delta method can also be used with maximum likelihood estimates, provided the sampling (co)variances of the genetic covariance matrix are available (Hansen et al., 2003). Regardless of whether authors choose to compute conditional heritabilities, the simulation results and Equation (1) show the importance of reporting the phenotypic correlation and genetic correlations between height and weight.

Molecular studies will refine the polygenic information in the conditional heritability. Multi-trait genome-wide association study (GWAS) (Porter & O'Reilly, 2017; Zhou & Stephens, 2014) can offer richer understanding of the pleiotropic and independent effects of molecular variants on weight, height, and other commonly collected anthropometric and metabolic traits, though they require much larger samples to achieve adequate power. The inclusion of height, weight, and other direct measurements in such analyses is well-justified, while BMI and other anthropometric ratios will remain problematic (Ried et al., 2016).

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