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Revisiting heritability accounting for shared environmental effects and maternal inheritance

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Abstract

Heritability measures the proportion of phenotypic variation attributable to genetic factors. In addition to a shared nuclear genetic component, a number of additional variance components, such as spousal correlation, sibship, household and maternal effects, may have strong contributions to inter-individual phenotype variation. In humans, the confounding effects of these components on heritability have not been studied thoroughly. We sought to obtain unbiased heritability estimates for complex traits in the presence of multiple variance components and also to estimate the contributions of these variance components to complex traits. We compared regression and variance component methods to estimate heritability in simulations when additional variance components existed. We then revisited heritability for several traits in Framingham Heart Study (FHS) participants. Using simulations, we found that failure to account for or misclassification of necessary variance components yielded biased heritability estimates. The direction and magnitude of the bias varied depending on a variance structure and an estimation method. Using the best fitted models to account for necessary variance components, we found that heritability estimates for most FHS traits were overestimated, ranging from 4 to 47 %, when we compared models that considered necessary variance components to models that only considered familial relationships. Spousal correlation explained 14–36 % of phenotypic variation in several anthropometric and lifestyle traits. Maternal and sibling effects also contributed to phenotypic variation, ranging from 3 to 5 % and 4 to 7 %, respectively, in several anthropometric and metabolic traits. Our findings may explain, in part, the missing heritability for some traits.

Introduction

The goal of genetic studies is to unravel the genetic basis of a phenotype. As a summary statistic, heritability measures the proportion of phenotypic variation in a population that is attributable to genetic factors (Visscher et al. 2008). Heritability estimation is usually the initial step in planning genetic studies because subsequent linkage and association studies rely heavily on heritability estimates to determine power and necessary sample sizes to identify susceptibility genes. Therefore, it is important to obtain reliable heritability estimates. For a continuous phenotype of interest, the observed trait value can be partitioned into variance components that reflect unobserved genetic and environmental factors (Amos 1994; Visscher et al. 2008; Tenesa and Haley 2013). In addition to identifying underlying genetic components, it is important to understand and identify underlying environmental factors that contribute to phenotypes of interest to obtain accurate heritability estimates. The lack of knowledge of the variance components that contribute to a phenotype often leads to biased heritability estimation (Tenesa and Haley 2013).

Resemblance between relatives is determined by shared nuclear genetic components, non-nuclear genetic components, and environmental factors (Morton 1974; Morton and MacLean 1974; Wallace 1992; Lynch and Walsh 1998; Wong et al. 2005). Maternal and shared household effects in addition to spousal correlation are among the most important non-nuclear genetic and environmental factors that contribute to phenotypic variation. Shared environmental factors such as lifestyle or household conditions shared by close relatives can

have a strong effect on some phenotypes (Wong et al. 2005). Spousal correlation may result from assortative mating and/or living in the same environment for many years. Previous studies have reported significant correlations between spouses for several clinical measures including systolic and diastolic blood pressure (SBP and DBP), and body mass index (BMI) (Knuiman et al. 1996). A maternal effect refers to “the causal influence of the maternal genotype or phenotype on the offspring phenotype” (Wolf and Wade 2009; Burggren and Crews 2014). Maternal effects include uterine effects (Relton et al. 2012), maternal imprinting (Venkatraman et al. 2013) and mitochondrial inheritance (Wallace et al. 1988). Recent studies indicate that epigenetic modifications may occur in utero in response to maternal behaviors such as alcohol consumption, smoking, and physical activity, which may be associated with children’s health later in life (Relton et al. 2012). Maternal imprinting, another epigenetic phenomenon by which certain genes can be expressed when inherited from the mother, but not the father, is maternally heritable (Keverne 2013).

Another form of maternal inheritance involves transmission of mitochondrial DNA from the mother to her offspring. Mitochondria are essential for oxidative phosphorylation (OXPHOS), particularly the electron transport chain to generate energy for most cellular activities (Voet et al. 2013). It has been shown that mutations in the mitochondrial genome (mtDNA) can lead to a number of severe inherited rare diseases (Holt et al. 1988; Wallace et al. 1988; Taylor and Turnbull 2005) and may be involved in the development of common diseases, such as hypertension and metabolic disorders (Wilson et al. 2004; Li et al. 2009; Liu et al. 2009, 2012 Wang et al. 2011).

Previous studies in animals have demonstrated that statistical models that failed to account for maternal effects and shared environmental factors yielded larger heritability estimates when compared to models that considered such effects (Lynch and Walsh 1998; Maniatis and Pollott 2002; Willmore et al. 2006). In humans, shared environmental effects have been mainly studied in twins but not in extended families (Keller et al. 2010). In general, how maternal effects and environmental factors, as well as spousal correlation, affect heritability have not been studied extensively for most complex phenotypes in extended families (Tenesa and Haley 2013) with only a few exceptions (Schork and Guo 1993; Sun et al. 2003; Yang et al. 2007; Xing et al. 2008). Therefore, the primary goal of this study was to investigate how maternal effects, environmental factors, and spousal correlation affect heritability estimates and what is the best strategy to obtain unbiased heritability estimates in the presence of these factors. We first conduct simulation studies and then applied what we learned from simulation studies to several phenotypes in FHS. We found that heritability estimates for most FHS traits were overestimated, ranging from 4 to 42 %, when we compared models that considered necessary variance components to models that only considered familial relationships. Spousal correlation explained 14–36 % of phenotypic variation in several anthropometric and lifestyle traits. Maternal and sibling effects also contributed to phenotypic variation, ranging from 3 to 5 % and 4 to 7 %, respectively, in several anthropometric and metabolic traits. Our findings may explain, in part, the missing heritability for some traits.

Methods

Ethics statement

All participants provided written and informed consents for genetic research. This research received approval from the Institutional Review Boards (IRB) at the Boston University.

Genetic model

We assume that a quantitative trait is affected by nuclear genetic components (G_i) and non-nuclear genetic components (Schork and Guo 1993; Amos 1994; Yang et al. 2010).

$$Y_i = \mu + G_i + E_i. \quad (1)$$

In Eq. (1), let Y_i represents the trait value for the ith individual and μ be the overall trait mean. G_i represents any polygenic effects from unknown loci on the nuclear chromosome. The component E_i can represent any non-nuclear effects and can be further partitioned into several components in Eq. (2).

$$E_i = E_{\mathrm{U}} + E_{\mathrm{SP}} + E_{\mathrm{H}} + E_{\mathrm{M}} + e_i. \quad (2)$$

In Eq. (2), E_{U} is the 'sibling effect' shared by siblings (may result from uterine effects or being raised together in the same environment), E_{SP} is the spousal correlation (including positive assortment), E_{H} is the shared household effect by members from a nuclear families, E_{M} is the maternal inheritance and particularly refers to the effects that are inherited through maternal lines (e.g., maternal imprinting or mitochondrial inheritance),and e_i is the remaining environmental effect that is not linked to individuals' relationship. We further assume, without loss of generality, that $E(G_i) = E(E_{\mathrm{U}}) = E(E_{\mathrm{SP}}) = E(E_{\mathrm{H}}) = E(E_{\mathrm{M}}) = E(e_i) = 0$.

Let σ^2_{T} be the total phenotypic variance and let σ^2_{G} be the phenotypic variance due to unknown loci on the nuclear chromosome. In this study, we only consider the narrow-sense genetic effects (σ^2_{A}) due to the nuclear genome. The narrow-sense heritability is defined as $h^2_{\mathrm{A}} = \sigma^2_{\mathrm{A}} / \sigma^2_{\mathrm{T}}$. Let σ^2_{SP}, σ^2_U σ^2_H and σ^2_{M} be the phenotypic variance due to sibling effect, spouse correlation, shared household and maternal effects, respectively, and let σ^2_{e} be the residual variance. Thus, if we assume independence between all variance components, the total phenotypic variance can be partitioned into its contributing factors

$$\sigma^2_{\mathrm{T}} = \sigma^2_{\mathrm{A}} + \sigma^2_{\mathrm{SP}} + \sigma^2_{\mathrm{U}} + \sigma^2_{\mathrm{H}} + \sigma^2_{\mathrm{M}} + \sigma^2_{\mathrm{e}}. \quad (3)$$

Based on Eq. (3), the covariance for a pair of individuals in a pedigree is

$$\mathrm{Cov}\,(Y_i, Y_j) = \Phi_{ij}\sigma^2_{\mathrm{A}} + \Omega_{ij}\sigma^2_{\mathrm{SP}} + \Delta_{ij}\sigma^2_{\mathrm{U}} + \Psi_{ij}\sigma^2_{\mathrm{H}} + \Lambda_{ij}\sigma^2_{\mathrm{M}} \quad (4)$$

The diagonal elements of all matrices are equal to 1. In family data, Φ is twice the kinship coefficient matrix; Δ is a matrix that its off-diagonal element *ij*th is 1 for any pairs of siblings and 0 for otherwise; Ω is a matrix such that its off-diagonal element *ij*th is 1 for spousal pair and 0 otherwise; Ψ is a matrix such that its off-diagonal element *ij*th is 1 for a pair of members in a nuclear family and is 0 otherwise; Λ is a matrix such that its off-diagonal element *ij*th is 1 if family members *i* and *j* are in the same short-span maternal lineage (referred as maternal lineage) as described previously (Liu et al. 2013) and is 0 otherwise. For demonstration purposes, Supplementary Fig. 1 displays the covariance structures for Φ, Δ, Ω, Ψ, and Λ for a nuclear family that includes both parents and three offspring.

Simulations

The simulation studies aimed to investigate the best strategy to estimate heritability in the presence of multiple variance components in extended families.

We simulated a continuous phenotype Y_i according to Eq. (3). We assumed that Y_i is normally distributed with mean 0 and variance σ^2_{T}. Let $\sigma^2_{\mathrm{T}}=1$ and $h^2_{\mathrm{A}}=\sigma^2_{\mathrm{A}}/\sigma^2_{\mathrm{T}}=\sigma^2_{\mathrm{A}}$. We considered two scenarios for simulations of the genetic models (Table 1). In scenario 1, we set $h^2_{\mathrm{A}}=0.3$. This scenario included nine genetic models: (1) the simplest model (S) in which only h^2_A and σ^2_{e} were non-zero components; (2) spousal correlation model (SP) in which h^2_{A}, σ^2_{SP} and σ^2_{e} were non-zero; (3) sibling effect model (U) in which h^2_{A}, σ^2_{U} and σ^2_{e} were non-zero; (4) household effect model (H) in which h^2_{A}, σ^2_{H} and σ^2_{e} were non-zero; (5) A maternal inheritance model (M) in which h^2_{A}, σ^2_{M} and σ^2_{e} were non-zero; (6) a composite model (SP-U) with non-zero components h^2_{A}, σ^2_{SP}, σ^2_{U} and σ^2_{e}; (7) a composite model (SP-M) with non-zero components h^2_{A}, σ^2_{SP}, σ^2_{M} and σ^2_{e}; (8) a composite model (H-M) with non-zero components h^2_{A}, σ^2_{H}, σ^2_{M} and σ^2_{e}; and (9) a composite model (SP-U-M) with non-zero components h^2_{A}, σ^2_{SP}, σ^2_{U}, σ^2_{M} and σ^2_{e} are non-zero. In scenario 2, we set $h^2_A=0$ (i.e., the phenotypic variance due to nuclear DNA is 0) and also considered nine genetic models that are the same as in scenario 1. We used $\sigma^2_{\mathrm{SP}}=\sigma^2_{\mathrm{U}}=\sigma^2_{\mathrm{H}}=\sigma^2_{\mathrm{M}}=0.1$ whenever one or more of these variance components were not set to 0.

We simulated nuclear families and extended pedigrees to compare if we obtained the same conclusions for the genetic models we test (Table 1). We simulated 500 nuclear families with equal sizes of two parents and three siblings. Simulation of extended families was based on FHS family structure (Supplemental information). The Framingham Heart Study (FHS) contained extended family structures from three generation cohorts which were described in the section “Application to Framingham Heart Study Data”. We performed analysis using 1,000 simulation replicates to estimate heritability and other variance components. Because distribution of variance was skewed, median with interquartile range (IQR) was reported for all estimated variance components.

Analysis strategies

Two major methods, parent–offspring regression and variance component, have been used to estimate the additive heritability (Lynch and Walsh 1998). The β estimate was obtained from regression of the offspring values against one parent or mid-parent values, and the heritability was estimated as 2β or β, respectively. According to Eq. (4), the expected heritability estimate from the mother–offspring regression was $\sigma_A^2+2\sigma_H^2+2\sigma_M^2$, the father–offspring regression $\sigma_A^2+2\sigma_H^2$, and the mid-parent–offspring regression $\frac{(\sigma_A^2+2\sigma_H^2+\sigma_M^2)}{1+\sigma_{SP}^2+\sigma_H^2}$ (Supplementary Information for details). We compared heritability estimates obtained in simulations to expected values.

In addition to regression analysis to estimate heritability, we used variance component method to estimate heritability and other variance components simultaneously. For any genetic models listed in Table 1, we analyzed it using nine methods: (1) the S model in which only h_A^2 and σ_e^2 were included in the estimation process; (2) The SP model in which h_A^2, σ_{SP}^2 and σ_e^2 were included in the estimation process; (3) The U model in which h_A^2, σ_U^2 and σ_e^2 were included in the estimation process; (4) The H model in which h_A^2, σ_H^2 and σ_e^2 were included in the estimation process; (5) The M model in which h_A^2, σ_M^2 and σ_e^2 were included in the estimation process; (6) The SP-U model in which h_A^2, σ_{SP}^2, σ_U^2 and σ_e^2 were included in the estimation process; (7) The SP-M model in which h_A^2, σ_{SP}^2, σ_M^2 and σ_e^2 were included in the estimation process; (8) The HM model in which h_A^2, σ_H^2 σ_M^2 and σ_e^2 were included in the estimation process; and (9) The SP-U-M model in which h_A^2, σ_{SP}^2, σ_U^2, σ_M^2 and σ_e^2 were included in the estimation process. Using the analysis strategy described above, we conducted three type of analyses: (1) “simple” analysis—in which only h_A^2 is considered in the estimation process regardless of the simulation models; (2) concordance analysis—in which the same variance components that were simulated are included in the estimation process to test if variance components can be correctly estimated; and (3) discordant analysis—in which misclassified variance component (s) were considered in the estimation process to investigate the bias in heritability estimation and confounding effects among the variance components.

Linear mixed effect (LME) model was used for variance component analysis to estimate heritability (Abecasis et al. 2001) and additional components. Although variance components were known, we conducted log likelihood ratio (LR) test to evaluate if the selected best models based on LR test match the expected ones. In Eq. (5), $L(M_{null})$ represents the likelihood function of a null model without additional parameter (s) and $L(M_a)$ represents the likelihood function of an alternative model with additional parameter (s). LR is approximated by a Chi square distribution with $(df_1 - df_2)$ degrees of freedom. Symbols df_1 and df_2 represent the number of free parameters of M_{null} and M_a,

$$\begin{aligned} \mathrm{LR} &= -2 \times \log\left(\frac{L(M_{\mathrm{null}})}{L(M_{\mathrm{a}})}\right) \\ &= 2 \times (\log L(M_{\mathrm{a}}) - \log L(M_{\mathrm{null}})). \end{aligned} \quad (5)$$

All statistical analyses were performed using R software (http://cran.r-project.org). The R functions *lm* () and *lmekin* () (http://cran.r-project.org/src/contrib/Archive/kinship/) were used for simple linear regression and linear mixed models, respectively.

Application to Framingham Heart Study data

The FHS began in 1948 with recruitment of an original cohort of 5,209 participants (55 % were women) with an average age of 44 years. In 1971, the offspring of the original cohort and spouses of the offspring were recruited, including 5,124 individuals (52 % of women) with a mean age of 37 years. A third-generation cohort was recruited in 2002, including 4,095 participants (53 % of women) with an average age of 43 years. Details of study design and follow-up were described previously (Dawber et al. 1951; Feinleib et al. 1975; Kannel et al. 1979; Splansky et al. 2007). At each clinical visit, participants underwent medical examination. Demographic measures such as height and weight, and clinical variables such as blood pressure, were recorded. Blood samples were collected and saved for further analyses. A medical history that focused on cardiovascular diseases and risk factors was obtained.

Supplementary Table 1 displays the characteristics for the continuous traits for which the heritability was revisited in this investigation. The examination cycles from which these measurements were obtained were described in the details of the Supplementary Information. Standardized and normalized residuals of all traits are obtained adjusting for age, or weight and/or BMI in a sex- and cohort- specific manner (Supplementary Table 2) and used for estimating variance components.

We applied the genetic models listed in Table 1 to the traits described in Supplementary Table 1. Estimation to heritability and other variance components were detailed in the Supplementary information. The LR test was used to evaluate model fit (Eq. 5): the LR test was performed between each of the SP, U, H, M, SP-U, SP-M, H-M, and SP-U-M models and the S model. We defined the best model to be the most parsimonious model with the largest LR test value. The bias in heritability was calculated by $\Delta h_{\mathrm{A}}^2\% = \left(\frac{\hat{h}_{\mathrm{A}}^2 - \hat{h}_{\mathrm{A}}^2 *}{\hat{h}_{\mathrm{A}}^2 *}\right)\%$, where $\hat{h}_{\mathrm{A}}^2$ was the heritability estimate using the S model (i.e., only including $\hat{h}_{\mathrm{A}}^2$ and σ_{e}^2) and $\hat{h}_{\mathrm{A}}^2 *$ was the heritability estimate using the best fitted model.

Results

We first compared heritability between expected values and estimates in simulations using the parent–offspring regression methods. Then, we presented results from variance component method when simulation and analysis models were concordant and discordant. Next, we reported heritability estimates for three categories of FHS traits with the best fitted

model to account for environmental and/or maternal effects. We reported median values with IQRs for all variance component estimates.

Heritability estimates in parent–offspring regression

Supplementary Table 3 displays expected and estimated values of heritability for scenarios listed in Table 1 using the three types of parent–offspring regressions that take the parent–offspring relationship into consideration and may give rise to biased heritability estimates. In all scenarios, the heritability estimates in simulations matched the respective expected values. The sibling effect (σ^2_U) did not affect the estimation of heritability in any of the three regressions because it was not used in any of the parent– offspring regressions. However, the common household effect (σ^2_H) gave rise to inflated heritability estimates in all of the three regression methods. The maternal effect (σ^2_M) gave rise to inflated heritability estimates in both mid-parent–offspring and mother–offspring regressions but were not affect heritability estimates in father–offspring regression. The bias in the mother–offspring regression was larger than that in the mid-parent–offspring regression. Differently, the spouse correlation (σ^2_{SP}) only caused a deflated heritability estimate in mid-parent–offspring regression at $h^2_A=0.3$. If in composite models, two or more of these variance components may jointly affect heritability estimates in the three regressions, which depends on which variance structures are combined.

Heritability and additional variance estimates in variance component method

We performed simulations to estimate heritability and additional variance components using both nuclear (results not shown) and extended family structures (Table 2; Supplementary Tables 4). Results obtained from both family structures were similar with a few differences: the heritability estimates seemed to have slightly wider IQRs in extended families than in nuclear families for some scenarios. However, extended families appear to yield more accurate estimates for additional variance structures than nuclear families in some scenarios. In subsequent paragraphs, we present results obtained from the extended family structure.

When simulation and analysis of genetic models were concordant (cells highlighted in gray), heritability and additional variance components were, in general, properly estimated. When simulation and analysis of genetic models were discordant (non-highlighted cells), situations varied in several ways as reported in the following several paragraphs.

Failure to account for necessary variance components gave rise to a biased heritability estimate, but the direction and magnitude of the bias were different based on the type of a variance structure that should be but is not accounted for (Table 2; Supplementary Tables 4). In summary, heritability estimates were biased upwardly if σ^2_U, σ^2_H and σ^2_M were not accounted for, which was clearly shown when we analyzed Y_i that generated by the U, H, and M models with the S model at $h^2_A=0.3$ or $h^2_A=0$. It appeared that failure to account for σ^2_H or σ^2_M gave rise to a more inflated heritability value than that for σ^2_U: the analysis of the U model with the S model at $h^2_A=0.3$ yields $\hat{h}^2_A=0.34$ (IQR: 0.31, 0.36); but the analysis of the

H or M mode with the S model gave rise to $\hat{h}^2_A = 0.50$ (IQR: 0.45, 0.52) or 0.51 (IQR: 0.49, 0.54) at $h^2_A = 0.3$, respectively; On the contrast, failure to account for σ^2_{SP} did not cause a bias in a heritability estimate at $h^2_A = 0$, but biases a heritability estimate downwardly at $h^2_A = 0.3$: the analysis of the SP model with the S model yields $\hat{h}^2_A = 0.28$ (IQR: 0.25, 0.31) $< h^2_A = 0.3$. Furthermore, failure to account for two or more variance components in a composite model gave rise to a biased heritability estimate that results from the joint effects of these variance components (Supplementary Tables 4). For examples, analysis of the SP-U-M model with the S model yielded $\hat{h}^2_A = 0.42$ (IQR: 0.39, 0.44), which was $> \hat{h}^2_A - 0.34$ (in analysis of U model with S model) but $< \hat{h}^2_A = 0.50$ (in analysis of M model with S model).

Misclassification of variance components in analysis, in general, gave rise to a biased heritability estimate. A heritability estimate was greatly inflated if we analyzed Y_i that is generated by the H or M model (or a composite model with σ^2_H and/or σ^2_M) by other models at $h^2_A = 0.3$ or $h^2_A = 0$. Differently, the analysis of Y_i that was generated by the SP model with the U or M model gave rise to an unbiased heritability estimate at $h^2_A = 0$ but yielded a slightly deflated heritability estimate at $h^2_A = 0.3$: $\hat{h}^2_A = 0.27$ (IQR; 0.25, 0.29) and 0.26 (0.23, 0.29), respectively. If the SP model was analyzed by the H model, a heritability estimate was not biased at $h^2_A = 0$ but greatly deflated at $h^2_A = 0.3$: $\hat{h}^2_A = 0.11$ (IQR: 0.04, 0.17). The result also varied if the U model was analyzed with a different model: if the U model was analyzed with the SP model, the heritability estimate was inflated: $\hat{h}^2_A = 0.35$ (IQR: 0.32, 0.37) and 0.07 (IQR: 0.04, 0.09) at $h^2_A = 0.3$ and $h^2_A = 0$, respectively; but if analyzed with the H or M model, the heritability estimate was deflated or only slightly deflated/inflated at $h^2_A = 0.3$ and $h^2_A = 0$.

Inclusion of unnecessary variance component (s) in addition to all necessary variance structure (s) in analysis of Y_i yielded correct estimates for both true variance components and the unnecessary variance components (Table 2; Supplementary Tables 4). For example, in analysis of Y_i generated by the S model at $h^2_A = 0.3$, inclusion of both σ^2_M and σ^2_H in analysis (i.e., the H-M model) yielded $\hat{h}^2_A = 0.29$ (IQR = 0.25, 0.32), $\hat{\sigma}^2_M = 0$ (IQR = 0, 0.007) and $\hat{\sigma}^2_H = 0$ (IQR = 0, 0.01). In general, over-fitted modeling seemed better than under-fitted modeling in estimating heritability when it was unclear what variance structure was underlying the traits.

In terms of differentiation ability, It seemed that LME can differentiate σ^2_{SP} from σ^2_U or σ^2_M, or differentiate σ^2_H from σ^2_U or σ^2_M well in most cases. However, LME cannot differentiate σ^2_{SP} from σ^2_H well. For example, the analysis of the H model by the SP model gave rise to $\hat{\sigma}^2_{SP} = 0.10$ (IQR: 0.08, 0.13); the analysis of the SP model by the H model yielded $\hat{\sigma}^2_H = 0.04$ (IQR: 0.03, 0.05). In addition, LME can only partially differentiate σ^2_U from σ^2_M or vice versa.

For example, the analysis of the M model with the U model yielded $\hat{\sigma}^2_{\mathrm{U}}=0.05$ (IRQ: 0.03, 0.06).

Supplementary Fig. 2 displays log likelihood ratio (LR) tests between the simplest model (S) that only accounted for familial correlation and the model that accounted for other variance components in simulations. Comparing the LR values across models with known variance components provides valuable information which is useful in identifying necessary variance component (s) to account for in practice. In Supplementary Fig. 2, the title of each plot denotes the genetic model that simulates Y_i and the *y*-axis represents the LR test between the S model and each of the models (on the *x*-axis) that were used to analyzed Y_i. A LR test was significant if the median LR value for a test $>\lambda_{0.05,1}$ or $\lambda_{0.05,2}$ or $\lambda_{0.05,3}$ = 3.84 or 6.0 or 7.8, respectively. In general, the LR tests were significant for models with the necessary component (s) compared to the S model or to the models without the necessary component (s). When the variance component (s) was misclassified or unnecessarily included, the LR test was not significant between the model with the misclassified or unnecessary component (s) and the S model (Supplementary Fig. 2). Despite these general conclusions, we found that LME cannot differentiate σ^2_{SP} and σ^2_{H} well using the LR, which was consistent with the results reported in the precedent paragraph.

Revision of heritability estimates using the FHS extended pedigrees

We revisited heritability for three types of continuous traits (anthropometric, metabolic, and lifestyle traits) measured in FHS extended families. Supplementary Table 1 summarizes characteristics for these traits. Among all traits we analyzed, five included $N > 14{,}000$ individuals across the three generation cohorts. The rest included two generation cohorts (N between ~4,000 and 8,000). The smallest sample sizes were from the lifestyle traits ($N \sim$ 4,000).

Table 3 displays median point estimators for heritability and other necessary variance components identified along with proportions of bias in heritability (Δh^2_{A}) when heritability estimates are compared between the S models that only consider familial relationship and the best model (identified by LR tests) that accounts for additional variance component (s). Supplementary Table 5 and Fig. 3 display detailed results for estimates of variance components using the nine models in Table 1 and LR tests between models with additional component (s) and the S model. The FHS traits were classified into five categories depending on the type of additional variance component(s) that affected the traits: (1) phenotypes affected by maternal effect: total cholesterol and low-density cholesterol; (2) phenotypes affected by sibling effect: fasting blood glucose, fasting blood insulin, high-density cholesterol and protein intake; (3) phenotypes affected by spousal correlation: weight, BMI, and carbohydrate intake; (4) phenotype affected by both spousal correlation and maternal effect: height and fat intake; and (5) phenotypes affected by both spousal correlation and sibling effect: systolic blood pressure, diastolic blood pressure, triglyceride, and alcohol consumption.

The bias in heritability estimates was small or moderate for most of the traits we revisited: nine traits demonstrated low bias ($\Delta h^2_A < 10\%$), four demonstrated moderate bias ($10\% < \Delta h^2_A \leq 20\%$), and two show relatively large bias ($\Delta h^2_A \geq 20\%$). The largest biases were observed for two lifestyle traits, protein intake ($\Delta h^2_A \sim 42\%$, upwardly) and fat intake ($\Delta h^2_A \sim 47\%$, upwardly).

Spousal correlation explained a relatively large proportion of phenotypic variation. The largest spousal effect was observed for three lifestyle traits: 36, 27, and 35 % for alcohol consumption, fat intake and carbohydrate intake, respectively. For the three anthropometric traits, 14, 16 and 14 % is observed for height, weight, and BMI, respectively. Three metabolic traits were also moderately affected by spousal correlation: ~6 % for SBP, DBP, and triglyceride. Compared to spousal correlation, the sibship and maternal effects only explained small or moderate amount of phenotypic variation: 4–6 % by sibling effect and 3–5 % by maternal effect.

Discussion

We systematically investigated the issue of bias in heritability estimates and phenotypic variance that may result from spousal correlation, as well as sibling or maternal effects using simulated data and actual FHS data from extended families. This study demonstrated that identifying sources that are likely to contribute to phenotypic variance is essential to avoid bias in heritability estimates. Fitting models with familial correlation and additional variance component (s) that are likely to contribute to a trait and conducting likelihood ratio tests between models are the best strategy to identify necessary variance component (s) and to avoid bias in estimating heritability. Applying such a strategy, we revisited heritability for several FHS traits and demonstrated that most heritability estimates are biased upwardly, the overestimation of heritability ranged from 3 to 47 % across the traits we revisited.

In this manuscript, we only considered the narrow-sense heritability and did not consider the nuclear genetic effects that are due to non-additive genetic values including dominance and epistasis among genes. Previous results showed that the additive genetic variance contributes mostly to complex trait resemblance between relatives compared to other nuclear genetic variances (Hill et al. 2008). Nevertheless, the non-additive genetic values may cause inflation in h^2_A estimation if using closely related individuals such as monozygotic MZ or dizygotic DZ twins (Visscher et al. 2008; Zuk et al. 2012). More accurate estimates can be obtained using data from extended pedigrees than from simpler relationships such as twins or siblings alone (Xiang et al. 2002; Visscher et al. 2008). In application of FHS data, all traits included participants from at least two trans-generational cohorts (Supplementary Table 1) with extended relationships. Such extended pedigree structure helps discrimination for different variance components, which was clearly demonstrated in estimating h^2_A for most FHS phenotypes.

Spousal correlation can explain a large proportion of phenotypic variance for several anthropometric and lifestyle traits in the FHS, demonstrating that long-married spouses are

more likely to develop similar habits and also to be exposed to the same risk factors for certain diseases. Among these traits, 'height' for founder parents was largely established prior to marriage, clearly indicating positive assortment in FHS extended family data. Our investigation did not find supporting evidence that household effect was a significant variance component in any of the FHS traits, reflecting the fact that most FHS participants were adults when they were recruited therefore siblings in nuclear families were unlikely to still live in the same household with their parents. Unlike spousal correlation that explained a large proportion of phenotypic variance in several traits, either sibling or maternal effect only explained a moderate proportion of phenotypic variance. Interestingly, several traits were found to be affected by the joint effects of spousal correlation and sibling effect/maternal inheritance. Pedigree errors (which were not likely in the FHS families which have been carefully recorded and checked by identity by descent information estimated using genome-wide SNP data), non-paternity and X chromosome linkage may also give rise to non-zero values in estimating maternal inheritance. However, our data were not sufficient to allow good estimates of all these effects simultaneously.

We applied the standard likelihood ratio test in evaluating model fit among nested models in analysis of the simulation data and FHS traits. In our simulation data, the LR test cannot disentangle spousal correlation from shared household effect, or sibling effect from maternal effect (Supplementary Fig. 2). However, in the analysis of the FHS traits, LR test can clearly differentiate these variance structures without any ambiguity (Supplementary Fig. 3). Two reasons may have contributed to these findings. First, the effect sizes were set to be the same for additional variance structures ($\sigma^2_{SP}=\sigma^2_{H}=\sigma^2_{U}=\sigma^2_{M}=0.1$) in simulations. In FHS, the estimated effect sizes were very different (Supplementary Table 5). Second, the number of families in simulations was much fewer than that in real FHS data. In addition, the family structure used in simulations was also simpler than that in the actual FHS extended families. Although the standard LR test is a common practice in evaluating model fit between nested models, previous study (Visscher 2006) demonstrated that this test may be conservative because the test statistic is assumed to follow a Chi square distribution asymptotically, with degrees of freedom equal to the number of parameters tested. However, when the null hypothesis is true, the distribution of the likelihood ratio test is a mixture of Chi square distributions with different degrees of freedom. Due to the conservativeness in using the standard likelihood ratio test, there was a possibility that we failed to identify some weak variance components when we analyzed the FHS traits. On the other hand, the variance components that were identified by the standard LR test were most likely to be true effects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Parameters in simulation models

Genetic model	h_A	σ^2_U	σ^2_{SP}	σ^2_H	σ^2_M	σ^2_e
Scenario 1						
Simplest model (S)	0.3					0.7
Sibling effect (U)	0.3	0.1				0.6
Spousal correlation (SP)	0.3		0.1			0.6
Household effect (H)	0.3			0.1		0.6
Maternal inheritance (M)	0.3				0.1	0.6
Spousal correlation + sibling effect (SP-U)	0.3	0.1	0.1			0.5
Spousal correlation + maternal effect (SP-M)						
Household + maternal effects (H-M)	0.3			0.1	0.1	0.5
Spousal correlation + sibling effect + maternal effect (SP-U-M)	0.3	0.1	0.1		0.1	0.4
Scenario 2						
Simplest model (S)	0					1
Sibling effect (U)	0	0.1				0.9
Spousal correlation (SP)	0		0.1			0.9
Household effect (H)	0			0.1		0.9
Mitochondrial inheritance (M)	0				0.1	0.9
Spousal correlation + sibling effect (SP-U)	0	0.1	0.1			0.8
Spousal correlation + maternal effect (SP-M)						
Household + maternal effects (H-M)	0			0.1	0.1	0.8
Spousal correlation + sibling effect + maternal effect (SP-U-M)	0	0.1	0.1		0.1	0.7

Table 2

Variance component estimations when simulation and analysis of models are concordant or discordant

Simulated genetic model	Estimation of variance components with S, SP, U, H and M models								
	S	**SP**		**U**		**H**		**M**	
	$\hat{h}^2_{\mathrm{A}}$	$\hat{h}^2_{\mathrm{A}}$	$\hat{\sigma}^2_{\mathrm{SP}}$	$\hat{h}^2_{\mathrm{A}}$	$\hat{\sigma}^2_{\mathrm{U}}$	$\hat{h}^2_{\mathrm{A}}$	$\hat{\sigma}^2_{\mathrm{H}}$	$\hat{h}^2_{\mathrm{A}}$	$\hat{\sigma}^2_{\mathrm{M}}$
S	**0.30 (0.27, 0.33)**	0.29 (0.27, 0.33)	0 (0, 0.02)	0.30 (0.27, 0.33)	0 (0, 0.01)	0.30 (0.26, 0.33)	0 (0, 0.01)	0.30 (0.26, 0.33)	0 (0, 0.01)
SP	0.28 (0.25, 0.31)	**0.30 (0.27, 0.32)**	**0.10 (0.07, 0.13)**	0.27 (0.25, 0.29)	0 (0, 0.03)	0.11 (0.04, 0.17)	0.04 (0.03, 0.05)	0.26 (0.23, 0.29)	0.006 (0, 0.03)
U	0.34 (0.31, 0.36)	0.35 (0.32, 0.37)	0.03 (0.02, 0.06)	**0.30 (0.27, 0.32)**	**0.10 (0.08, 0.12)**	0.29 (0.23, 0.33)	0.03 (0, 0.06)	0.27 (0.23, 0.31)	0.06 (0.04, 0.08)
H	0.50 (0.47, 0.52)	0.50 (0.48, 0.53)	0.10 (0.08, 0.13)	0.46 (0.44, 0.48)	0.01 (0, 0.03)	**0.31 (0.28, 0.37)**	**0.10 (0.08, 0.13)**	0.49 (0.46, 0.52)	0 (0, 0.004)
M	0.51 (0.49, 0.54)	0.42 (0.40, 0.45)	0.02 (0, 0.04)	0.40 (0.38, 0.41)	0.05 (0.03, 0.06)	0.50 (0.47, 0.53)	0 (0, 0.01)	**0.31 (0.31, 0.38)**	**0.10 (0.08, 0.13)**
SP-U	0.32 (0.30, 0.34)	0.36 (0.33, 0.38)	0.12 (0.10, 0.16)	0.27 (0.25, 0.30)	0.11 (0.09, 0.13)	0.10 (0.04, 0.16)	0.13 (0.10, 0.16)	0.23 (0.20, 0.27)	0.08 (0.05, 0.10)
SP-M	0.44 (0.42, 0.46)	0.42 (0.40, 0.45)	0.11 (0.09, 0.14)	0.36 (0.34, 0.39)	0.06 (0.05, 0.08)	0.19 (0.14, 0.25)	0.12 (0.09, 0.14)	0.25 (0.21, 0.29)	0.12 (0.09, 0.14)
H-M	0.64 (0.61, 0.66)	0.63 (0.59, 0.65)	0.12 (0.09, 0.15)	0.55 (0.52, 0.57)	0.07 (0.05, 0.08)	0.47 (0.44, 0.52)	0.11 (0.09, 0.14)	0.52 (0.48, 0.55)	0.11 (0.09, 0.14)
SP-U-M	0.42 (0.39, 0.44)	0.49 (0.46, 0.50)	0.15 (0.12, 0.18)	0.37 (0.34, 0.39)	0.16 (0.14, 0.18)	0.18 (0.13, 0.23)	0.15 (0.12, 0.18)	0.21 (0.18, 0.24)	0.19 (0.17, 0.21)

Simulated genetic model	Estimation of variance components with SP-U, SP-M, H-M and SP-U-M models												
	SP-U			**SP-M**			**H-M**			**SP-U-M**			
	$\hat{h}^2_A$	$\hat{\sigma}^2_{SP}$	$\hat{\sigma}^2_U$	$\hat{h}^2_A$	$\hat{\sigma}^2_{SP}$	$\hat{\sigma}^2_M$	$\hat{h}^2_A$	$\hat{\sigma}^2_H$	$\hat{\sigma}^2_M$	$\hat{h}^2_A$	$\hat{\sigma}^2_{SP}$	$\hat{\sigma}^2_U$	$\hat{\sigma}^2_M$
S	0.29 (0.26, 0.32)	0 (0, 0.01)	0 (0, 0.02)	0.29 (0.26, 0.33)	0 (0, 0.03)	0 (0, 0.02)	0.29 (0.25, 0.32)	0 (0, 0.01)	0 (0, 0.007)	0.29 (0.26, 0.33)	0 (0, 0.03)	0 (0, 0.01)	0 (0, 0.01)
SP	0.29 (0.27, 0.32)	0 (0, 0.02)	0.10 (0.07, 0.13)	0.29 (0.25, 0.32)	0.09 (0.06, 0.13)	0 (0, 0.01)	0.10 (0.03, 0.15)	0.09 (0.07, 0.11)	0 (0, 0.02)	0.28 (0.24, 0.31)	0.09 (0.06, 0.12)	0 (0, 0.01)	0 (0, 0.02)
U	0.31 (0.28, 0.33)	0 (0, 0.03)	0.10 (0.08, 0.12)	0.28 (0.25, 0.32)	0.02 (0, 0.05)	0.06 (0.04, 0.08)	0.26 (0.24, 0.29)	0.01 (0, 0.04)	0.06 (0.04, 0.08)	0.30 (0.26, 0.32)	0 (0, 0.03)	0.09 (0.07, 0.11)	0 (0, 0.03)
H	0.50 (0.47, 0.53)	0.10 (0.07, 0.12)	0 (0, 0.01)	0.49 (0.46, 0.52)	0.10 (0.07, 0.12)	0 (0, 0.02)	0.31 (0.29, 0.35)	0.11 (0.08, 0.13)	0 (0, 0.007)	0.49 (0.47, 0.52)	0.10 (0.07, 0.13)	0 (0, 0.01)	0 (0, 0.02)
M	0.41 (0.38, 0.43)	0.006 (0, 0.03)	0.05 (0.03, 0.07)	0.31 (0.27, 0.35)	0 (0, 0.03)	0.09 (0.07, 0.12)	0.31 (0.28, 0.36)	0 (0, 0.01)	0.11 (0.08, 0.13)	0.31 (0.27, 0.35)	0 (0, 0.03)	0 (0, 0.02)	0.09 (0.07, 0.11)
SP-U	**0.30 (0.27, 0.33)**	**0.10 (0.08, 0.12)**	**0.10 (0.07, 0.12)**	0.29 (0.25, 0.33)	0.12 (0.09, 0.15)	0.06 (0.04, 0.08)	0.06 (0.002, 0.11)	0.11 (0.08, 0.14)	0.06 (0.03, 0.08)	0.29 (0.25, 0.32)	0.11 (0.07, 0.13)	0.09 (0.07, 0.12)	0 (0, 0.03)
SP-M	0.40 (0.37, 0.43)	0.10 (0.07, 0.13)	0.05 (0.03, 0.07)	**0.30 (0.26, 0.34)**	**0.10 (0.07, 0.13)**	**0.10 (0.08, 0.12)**	0.10 (0.04, 0.16)	0.05 (0.03, 0.07)	0.10 (0.08, 0.12)	0.30 (0.25, 0.34)	0.10 (0.07, 0.13)	0 (0, 0.02)	0.09 (0.07, 0.12)
H-M	0.60 (0.57, 0.63)	0.10 (0.07, 0.13)	0.05 (0.03, 0.07)	0.50 (0.46, 0.54)	0.10 (0.08, 0.13)	0.10 (0.08, 0.12)	**0.30 (0.30, 0.41)**	**0.11 (0.09, 0.13)**	**0.10 (0.09, 0.14)**	0.50 (0.46, 0.54)	0.10 (0.07, 0.12)	0 (0, 0.02)	0.09 (0.07, 0.12)
SP-U-M	0.40 (0.37, 0.43)	0.10 (0.07, 0.15)	0.15 (0.13, 0.17)	0.28 (0.25, 0.33)	0.11 (0.09, 0.14)	0.16 (0.14, 0.18)	0.06 (0.01, 0.17)	0.10 (0.08, 0.14)	0.15 (0.13, 0.18)	**0.30 (0.27, 0.34)**	**0.10 (0.07, 0.12)**	**0.10 (0.07, 0.13)**	**0.11 (0.08, 0.13)**

S simplest model, *SP* spousal correlation model, *U* sibling effect model, *H* household effect model, *M* maternal inheritance model, *SP-U* a composite model with both SP and U, *SP-M* a composite model with both SP and M, *H-M* a composite model with both H and M, *SP-U-M* a composite model with SP, U and M

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Table 3

Revision of heritability for traits in the Framingham Heart Study family data

Traits	Kinship only	Significant variance components[a]				$\Delta h^2_A(\%)$	Source of effect[b]	LR, *df* (*p* value)[b]
	$\hat{h}^2_A$	$\hat{h}^2_A$	$\hat{\sigma}^2_{SP}$	$\hat{\sigma}^2_U$	$\hat{\sigma}^2_M$			
Anthropometric								
Height	0.82	0.84	0.13	0	0.03	−2	SP + M	171, 2, <0.0001
Weight	0.43	0.46	0.16	0	0	−6	SP	51, 1, <0.0001
Body mass index	0.44	0.46	0.14	0	0	−4	SP	38, 1, <0.0001
Metabolic								
Systolic blood pressure	0.40	0.39	0.06	0.06	0	3	SP + U	36, 2, <0.0001
Diastolic blood pressure	0.33	0.32	0.06	0.05	0	3	SP + U	30, 2, <0.0001
Fasting blood glucose	0.33	0.29	0	0.06	0	14	U	12, 1, 0.005
Fasting blood insulin	0.26	0.22	0	0.05	0	18	U	7, 1, 0.006
Total cholesterol	0.49	0.45	0	0	0.03	9	M	5, 1, 0.025
HDL cholesterol	0.46	0.44	0	0.04	0	5	U	8, 1, 0.005
LDL cholesterol	0.49	0.44	0	0	0.04	11	M	6, 1, 0.014
Triglyceride	0.41	0.39	0.06	0.05	0	5	SP + U	20, 2, <0.0001
Life style								
Alcohol consumption	0.25	0.22	0.36	0.06	0	14	SP + U	101, 2, <0.0001
Protein intake	0.17	0.12	0	0.05	0	42	U	3, 1, 0.08
Fat intake	0.22	0.15	0.27	0	0.05	47	SP + M	16, 2, 0.0003
Carbohydrate intake	0.27	0.28	0.35	0	0	−4	SP	20, 1, <0.0001

[a] $\hat{\sigma}^2_R$, estimated variance components. R stands for spousal correlation (SP), sibling effect (U), maternal inheritance (M)

[b] Detailed information on the estimates of all variance components using the nine models, likelihood ratio (LR) tests (with degree of freedom, *df*) between the models with additional component (s) and the model with only familial correlation are demonstrated in Supplementary Table 5 and Fig. 3