Calculating power to detect maternal and offspring genetic effects in genetic association studies

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Abstract

Offspring outcomes are a function of maternal genetics operating on the intrauterine and postnatal environment, offspring genetics and environmental factors. Partitioning genetic effects into maternal and offspring components requires genotyped mother-offspring pairs or genotyped individuals with phenotypic information on themselves and their offspring. We performed asymptotic power calculations and data simulations to estimate power to detect maternal and offspring genetic effects under a range of different study designs and models. We also developed the "Maternal and offspring Genetic effects Power Calculator" (M-GPC), an online utility which allows users to estimate the power to detect maternal and offspring genetic effects in their own studies. We find that approximately 50,000 genotyped mother-offspring pairs will be required to detect realistically sized maternal or offspring genetic effects (>0.1% variance explained) with appreciable power (power >90%, $\alpha=5x10^{-8}$, two degree of freedom test), whereas greater than 10,000 pairs will be required to determine whether known genetic loci have maternal and/or offspring genetic effects (power >78%, $\alpha=0.05$). The structural equation modelling framework espoused in this manuscript provides a natural method of combining different data structures including those present in large scale biobanks in order to maximize power to detect maternal and offspring genetic effects. We conclude that the sample sizes required to detect maternal or offspring genetic effects that explain realistic proportions of the trait variance with appreciable power are achievable and within the range of current research consortia.

Keywords: genetic association; GWAS; maternal effects; offspring effects; fetal effects; power

Introduction

Offspring phenotypes, including perinatal outcomes such as birthweight, length at birth and other anthropometric measurements, are thought to be a product of maternal genetics, offspring genetics and environmental factors. In this manuscript, we define maternal genetic effects as the causal influence of the maternal genotype on the offspring phenotype (Wolf and Wade 2009). Maternal genetic effects arise when the mother makes a contribution to the phenotype of her progeny over and above that which results from the genes she contributes to the zygote (Mather and Jinks 1982). Thus, our definition focuses on the effect of the maternal genome and is distinct from mitochondrial inheritance and genetic effects due to imprinting. In contrast, we define offspring genetic effects as those genetic effects on the offspring's phenotype that are directly mediated by the offspring's genome, which is comprised of 50% of alleles inherited from their mother and 50% from their father.

Across many perinatal phenotypes it has been shown that the offspring genome contributes more to offspring trait variance than the maternal genome; however estimates of the relative contributions vary greatly (Eaves et al. 2014; Horikoshi et al. 2016; Lunde et al. 2007; Magnus 1984a; Magnus 1984b). Maternal genetic effects on offspring phenotypes can be mediated through the intrauterine environment (likely to be most important for perinatal traits like birthweight) but also through maternal behaviors influencing the offspring's post-natal environment (likely more important for offspring traits later in life). For example, recent studies have shown how parental polygenic risk scores for educational attainment consisting of alleles not transmitted to children are also associated with child's educational attainment (Bates et al. 2018; Kong et al. 2018) highlighting the importance of parental genomes in influencing offspring phenotypes.

Partitioning genetic effects into maternal and offspring genetic components is not straight-forward because maternal and offspring genotypes are correlated. In general, such partitioning requires either genotyped mother-offspring pairs or genotyped individuals providing phenotype information on themselves and their offspring (Warrington et al. 2018). Traditionally, maternal and offspring genetic effects have been estimated using genotyped mother-offspring pairs where the offspring has phenotype information. Specifically, offspring phenotype is regressed on both the maternal and offspring genotypes, and consequently estimates of the maternal genetic effect are obtained conditional on offspring genotype. However, there is a dearth of cohorts worldwide with large numbers of genotyped mother-offspring pairs, meaning that studies using just these individuals may be underpowered. Recently, we have shown how maternal genetic effects can also be estimated in large cohorts of unrelated genotyped mothers where phenotypic information is available on both them and their offspring, like in the case of birthweight in the UK Biobank Study (Beaumont et al. 2018; Sudlow et al. 2015; Warrington et al. 2018). Our approach uses the technique of structural equation modelling to partition genetic effects into maternal and offspring components of variation. Importantly, our method yields asymptotically unbiased estimates of maternal and offspring genetic effects, is robust to missing data and random measurement error, and can be used to analyze individual level or summary results data (Warrington et al. 2018).

In the current manuscript, we investigate the power to detect maternal and offspring genetic effects using a variety of different study designs. We investigate the power of a two degree of freedom test, where the focus is on locus detection (i.e. that a locus is associated with a trait of interest regardless of whether this association is mediated through the maternal or the offspring genome), and also the power of a one degree of freedom test where the focus is on demonstrating an effect of the maternal or offspring genome on the trait of interest. Whilst Warrington et al (Warrington

et al. 2018) presented some initial power estimates via simulation, we explore a greater range of study designs via asymptotic distribution theory and subsequently confirm our results via simulation. We also develop a web-based utility, the “Maternal and offspring Genetic effects Power Calculator” (M-GPC; http://evansgroup.di.uq.edu.au/MGPC/), which allows investigators to explore the power to detect maternal and offspring genetic effects using a range of different study designs.

Methods

The Structural Equation Model

We used an extension of the structural equation model (SEM) described in Warrington et al (Warrington et al. 2018) to perform the asymptotic power calculations described in this manuscript. The overall SEM consisted of five different components as depicted by the path models in Figure 1. The path diagram illustrated in Figure 1A represents genotyped individuals who have phenotypic information on themselves and their offspring. The path model in Figure 1B represents genotyped individuals who have phenotypic information on themselves only. In Figure 1C, the path model represents genotyped individuals who provide phenotypic information on their offspring only. These three components of the model were introduced in Warrington et al (Warrington et al. 2018). In Figure 1D, the path model represents genotyped mother-offspring pairs where the offspring has phenotypic information. Finally, in Figure 1E, the path model represents genotyped mother-offspring pairs where both the mother and offspring have phenotypic information. These five components depicted in the path models are fitted simultaneously in a SEM and the parameters (i.e. the coefficients estimating the maternal and offspring genetic effects) are constrained to be equal across the different components. We note that in order for the model to be empirically identified (i.e. maternal and offspring genetic effects and other unknown parameters estimated uniquely), the data must at a minimum include some genotyped individuals who have phenotype information on themselves, and some genotyped individuals who have information on their offspring's phenotype (although these individuals do not need to be overlapping).

Asymptotic power calculations

Asymptotic power calculations (Neale 1992) were performed using the openMX package (Boker et al. 2011; Hunter 2018; Neale et al. 2016; Pritikin et al. 2015) in R studio (RStudioTeam 2015) (version 1.1.419). Briefly, asymptotic covariance matrices were generated assuming certain underlying values for the parameters of the model depicted in Figure 1 (see below for details on the range of underlying values we tested). The full model was then fitted to the covariance matrices to confirm a perfect fit to the data and to check that the parameter values were correctly estimated. Secondly, a reduced model where the parameter(s) of interest was constrained to zero was fitted to the same covariance matrices. We examined the effect of constraining the maternal genetic effect, offspring genetic effect or both of these parameters to zero. The difference in minus twice the log-likelihood chi-square between the full and reduced models is equal to the non-centrality parameter of the test for association, with the degrees of freedom equal to the difference in the number of free parameters between the models. Power was then calculated as the area under the curve of a non-central chi-square distribution to the right of the significance threshold of interest (equation 1).

$$Power = \int_{X_{\alpha}^{'2}(v,0)}^{\infty} dX^{'2}(v, \varsigma), \tag{1}$$

where $X_{\alpha}^{'2}(v, 0)$ is the quantile of the 100 * (1-α) percentage point of the central χ^2 distribution with v degrees of freedom, and ς is the non-centrality parameter.

Simulations

We simulated data to confirm the results of our asymptotic power calculations under the different scenarios, with 10,000 replications (see below for details on the range of underlying values we tested). For each simulation the following variables were generated: offspring phenotype, mother's

phenotype (not generated for genotyped mother-offspring pairs in Scenario 6), a latent variable (U) to model the residual correlation between maternal and offspring phenotypes (not generated for genotyped mother-offspring pairs in Scenario 6), offspring genotype, maternal genotype, paternal genotype and grandparental genotype on the mother's side (not generated for mother-offspring pairs in Scenario 6). Individuals' genotypes were simulated from a binomial distribution, with 0, 1 or 2 copies of the minor allele and a minor allele frequency of 0.5. Each genotype was associated with a value of -1.41, 0, or 1.41 so that all genotypes were scaled to have unit variance. We assumed autosomal Mendelian inheritance and simulated the transmission of genotypes from parents to offspring. For mother-offspring pair *i*, standardized values for the maternal phenotype and offspring phenotype were generated using the following equations:

$$Maternal\ Phenotype_i = \beta_m * SNP_{Grandmother_i} + \beta_o * SNP_{mother_i} + \beta_{U,m} * U_i + \varepsilon_i \quad (2)$$

$$Fetal\ Phenotype_i = \beta_m * SNP_{mother_i} + \beta_o * SNP_{offspring_i} + \beta_{U,O} * U_i + \varepsilon_{Oi} \quad (3)$$

where $\beta_{U,m}$ is the effect of the standard normal latent factor U on the individual's own phenotype and $\beta_{U,O}$ on the offspring's phenotype. The residual error terms ε and ε_O were drawn from normal distributions with mean zero and variance chosen so that the maternal and offspring phenotypes had unit variance.

Power was defined as the proportion of replications with *p*-values for the effect of interest (maternal genetic effect, offspring genetic effect or the two degree of freedom test of both effects) lower than the significance threshold. Genotyped mother-offspring pair simulations in Scenario 6 were run with conditional linear regression. Example R code for the simulations is available for

download from our website (http://evansgroup.di.uq.edu.au/SOFTWARE/POWER_CALCULATOR/).

Effect size, sample size and residual correlation values for power calculations

In both the asymptotic power calculations and the simulations, we assumed SNPs exerted maternal and/or offspring genetic effects that explained either 0.05% or 0.1% of the trait variance. To provide some reference points for the reader as to the likely size of genetic effects, the top loci for height and body mass index are thought to exert offspring genetic effects that explain roughly 0.3% of the variance in these phenotypes (Weedon et al. 2008; Willer et al. 2009). In contrast, a recent genome-wide association study (GWAS) of birthweight reported that the most strongly associated maternal SNPs explained between 0.04% to 0.1% of the variance in birthweight after conditioning on offspring genotype (Beaumont et al. 2018). Indeed the relatively small maternal effect sizes reported in this latter study was the motivation for performing power calculations involving loci explaining 0.05% and 0.1% of the phenotypic variance in the present manuscript. We also examined conditions where maternal/offspring genetic effects explained 0% of the trait variance (to ensure that the type 1 error rate was appropriate) and also allowed for the possibility that maternal and offspring genetic effects might exert effects on the phenotype in opposite directions. We examined three levels of residual correlation between the maternal and offspring phenotypes (ρ = 0, 0.25, 0.50) (technically ρ is a residual covariance, but since SNP effects are very small, practically speaking this parameter can be thoughts of as the observational correlation between phenotypes to aid with intuition). For the asymptotic power calculations, we assumed a sample size of 1) N=10,000, 20,000, 30,000, 40,000, and 50,000 genotyped mothers with phenotypic information on themselves, their offspring or both or 2) N=10,000, 20,000, 30,000, 40,000, and 50,000 genotyped mother-offspring pairs. The simulations were performed with N =

50,000 genotyped mothers with phenotype information on themselves, their offspring or both or N=50,000 genotyped mother-offspring pairs.

We estimated the power of a one degree of freedom test to detect maternal or offspring genetic effects and the power of a two degree of freedom test to detect any effect at the locus. We present the results using N=50,000 mother-offspring pairs (referring to either genotyped mother-offspring pairs or genotyped mothers with phenotypic information on themselves, their offspring or both) in the main text of this article, as we estimate this to be the number of genotyped mother-offspring pairs that we currently have access to across the world through our collaborations as part of the Early Growth Genetics (EGG) and EArly Genetics and Life course Epidemiology (EAGLE) Consortia (Middeldorp et al. Submitted). The results of the other sample sizes are presented in the Supplementary Material.

The different study designs

We examined six different scenarios for each of the sample sizes (Table I). Scenario 1 (complete overlap) consisted of 100% of the genotyped individuals with their own and their offspring's phenotype. Scenario 2 (no overlap) involved 50% of the genotyped individuals with their own phenotype only and 50% of the genotyped individuals with their offspring's phenotype only (i.e. no individuals with both their own and their offspring's phenotype). Scenario 3 (partial overlap #1) involved 50% of the genotyped individuals with their own and their offspring's phenotype, 25% of the genotyped individuals with their own phenotype only, and 25% of the genotyped individuals with their offspring's phenotype only. Scenario 4 (partial overlap #2) involved 50% of the genotyped individuals with their own and their offspring's phenotype and 50% of the genotyped individuals with their own phenotype only. Scenario 5 (partial overlap #3) involved 50% of the genotyped individuals with their own and their offspring's phenotype, and 50% of the

genotyped individuals with their offspring's phenotype only. Scenario 6 (genotyped mother-offspring pairs with information on offspring phenotype only) involved 100% genotyped mother-offspring pairs where phenotypic information was available on the child only. This scenario involves genotyping twice the number of individuals with phenotype information. Scenario 7 involved 100% genotyped mother-offspring pairs with phenotype information available on both mother and offspring.

Online web utility

We developed the "Maternal and offspring Genetic effects Power Calculator" (M-GPC), an online power calculator that allows investigators to explore the power to detect maternal and offspring genetic effects in their own studies (http://evansgroup.di.uq.edu.au/MGPC/). The power associated with genotyped mother-offspring pairs as well as genotyped individuals who have their own or their offspring's phenotype available (or both) can be assessed. Our power calculator is built using the R shiny app (https://shiny.rstudio.com/) running the R studio software (RStudioTeam 2015) and the openMX package (Boker et al. 2011; Hunter 2018; Neale et al. 2016; Pritikin et al. 2015) in the background. The R code for the web utility can be downloaded from our website (http://evansgroup.di.uq.edu.au/SOFTWARE/POWER_CALCULATOR/).

Results

The results from the asymptotic power calculations, along with the confirmatory results from the simulations (for N=50,000), are shown in Supplementary Table I. In all cases the results of the simulations agreed closely with the power predicted from the asymptotic calculations. In the following sections, we highlight some general features of our results.

Effect of study design on power

In general, genotyped mother-offspring pairs (Scenarios 6 and 7) provided the greatest power to detect maternal/ offspring genetic effects compared to the other study designs (Figure 2, Supplementary Table I). The Scenario 6 design was also the most efficient in terms of the number of individuals with phenotypic information, since genotyped mother-offspring pairs where the offspring only is phenotyped, involve the phenotyping of only one individual per pair whereas other scenarios where only the mother is genotyped (Scenarios 1 through 5) involve the collection of two phenotypes per pair. However, if one compares power as a function of the number of individuals genotyped, then the most effective design is Scenario 1 (complete data), genotyped mothers who also have phenotypic information on themselves and their offspring. This is because genotyped mother-offspring pairs require the genotyping of two individuals per pair, whereas the other scenarios only involve the genotyping of one individual per pair.

We also confirm the finding in Warrington et al (Warrington et al. 2018) that power to detect maternal and offspring genetic effects is very low when there is no overlap between individuals who report their own and their offspring's phenotype (Scenario 2 (no overlap)), and that power to detect maternal genetic effects increases when some individuals with their own phenotype also

report their offspring's phenotype, and power to detect an offspring genetic effect increases when some genotyped individuals with their offspring's phenotype report their own phenotype also.

The influence of locus effect size and direction of effect on the power of one and two degrees of freedom tests

Figure 3 displays the power to detect maternal genetic effects, offspring genetic effects or any genetic effect at a locus in genotyped individuals who have phenotype information on themselves and their offspring (i.e. Scenario 1). Power to detect association was greater for the two degree of freedom test compared to the one degree of freedom tests when maternal and offspring genetic effects produced effects on the trait in the same direction. This was also the case when either the offspring or maternal genetic effect was zero. In contrast, when the SNP produced opposing maternal and offspring genetic effects on the phenotype, the power of the two degree of freedom test decreased rapidly and in some cases was less powerful than the one degree of freedom tests Similar results were obtained in the case of genotyped mother-offspring pairs (i.e. Scenarios 6 and 7) (see Supplementary Table 1).

The effect of varying the residual correlation between maternal and offspring phenotypes (ρ)

Figure 4 displays power to detect maternal genetic effects as a function of the residual correlation between maternal and offspring phenotypes. The power to detect offspring genetic effects in this setting is the same when the maternal genetic effect is 0% and the offspring genetic effect is 0.1%. This figure presents calculations for 50,000 genotyped mother-offspring pairs (Scenario 6), 50,000 genotyped individuals who have their own and their offspring's phenotype (Scenario 1), and 25,000 genotyped individuals who have their own phenotype only together with 25,000 genotyped individuals with their offspring's phenotype only (Scenario 2). We illustrate both power to identify

a maternal genetic effect in Figure 4a (one degree of freedom test) and power to detect an effect at the locus in Figure 4b (two degrees of freedom test).

For both the one and two degree of freedom tests, power to detect association was independent of the residual correlation in the case of genotyped mother-offspring pairs where only the offspring has been phenotyped (Scenario 6), and also for designs involving genotyped individuals who have their own phenotype only together with genotyped individuals with their offspring's phenotype only (i.e. the no overlap condition in Scenario 2). This is not surprising as when there is no sample overlap the residual correlation is not modelled in the SEM. For the one degree of freedom test, power to detect maternal genetic effects increased with the residual correlation in the case of Scenario 1. Interestingly, when the residual correlation was 0.5, the power to detect maternal genetic effects was the same between genotyped mother-offspring pairs and genotyped individuals with their own and their offspring's phenotype. In the case of the two degrees of freedom test, power to detect association in Scenario 1 decreased as the residual correlation increased, except when maternal and offspring genetic effects on the phenotype were in opposite directions, in which case power increased with increasing residual correlation (Supplementary Table 1).

Effect of the addition of maternal phenotype information on the power of genotyped mother-offspring pairs

Phenotyping mothers as part of the genotyped mother-offspring pairs design (i.e. Scenario 7) increased power to detect offspring genetic effects (one degree of freedom test) and locus detection in general (two degree of freedom test) compared to just phenotyping offspring (Scenario 6). In contrast, the power to detect maternal genetic effects (one degree of freedom test) did not change when the residual phenotypic correlation between maternal and offspring phenotypes was zero.

However, when the residual phenotypic correlation increased, power to detect maternal genetic effects increased also (Supplementary Table 1).

Can maternal or offspring *genetic effects be identified and characterized in realistically sized samples?*

Finally, we were interested in whether loci that exerted maternal or offspring genetic effects could be detected using genetic studies of the size that were currently available across the world. We were interested in the power to detect novel loci that exerted maternal genetic or offspring genetic effects on offspring traits in genome-wide association studies (two degree of freedom test, $\alpha = 5x10^{-8}$), and also the power to partition genetic effects at known loci into maternal and offspring components (one degree of freedom test, $\alpha = 0.05$). Figure 5 shows how many genotyped mothers with phenotype information on themselves, their offspring or both, or genotyped mother-offspring pairs are required for locus detection (two degree of freedom test, $\alpha = 5x10^{-8}$) and how many are needed to partition a known locus into maternal and offspring genetic effects (one degree of freedom test, $\alpha = 0.05$) assuming that the maternal genetic effect explains 0.1% and offspring genetic effects explain 0% of the phenotypic variance. The same number of individuals would be required (to detect an offspring genetic effect) assuming an offspring genetic effect of 0.1% and a maternal genetic effect of 0%. Sample sizes are provided for genotyped mother-offspring pairs (Scenarios 6), and for genotyped individuals where phenotypes are available for both mother and offspring (Scenario 1, $\rho = 0.25$). Both designs require 40,000 to 50,000 pairs in order to detect novel loci exerting maternal genetic effects on offspring phenotypes with high power (>70% - 80%) in genome-wide association studies. In contrast, much lower numbers (N > 10,000 pairs) are required in order to partition known genetic loci into maternal and offspring sources of variation with similar amounts of power.

Discussion

We have used a flexible SEM (Warrington et al. 2018) to estimate the power to detect maternal and offspring genetic effects under a variety of experimental designs. We also provide an online utility that researchers can use to perform asymptotic power calculations which showed good concordance with estimates from simulated datasets. Our results show that when maternal and offspring genetic effects affect offspring phenotypes in the same direction, the two degree of freedom test to detect any effect of the locus on the phenotype was always more powerful than a one degree of freedom test which assessed the evidence for either a maternal or offspring genetic effect. Intuitively, this is because the two degree of freedom test is picking up both effects which when combined have a larger impact on the phenotype so it's easier to detect than the smaller individual effects. Also, when both maternal and offspring effects are constrained to zero in the two degree of freedom test, the SEM contains no paths that can adequately model the observed SNP-outcome covariance(s). The result is that the reduced model tends not to fit the data very well resulting in a large difference in fit between the full and reduced models and consequently a larger non-centrality parameter and greater power to detect association. In contrast, when only one parameter is constrained to zero (i.e. the maternal genetic effect β_m or the offspring genetic effect β_o), the SEM still contains a path from the SNP to the outcome that can model the observed SNP-outcome covariance, albeit imperfectly. Thus under this reduced model, the decrement in model fit is not quite as bad, and therefore power is not as great. The corollary is that (assuming the same type 1 error rate) the two degree of freedom test usually requires fewer individuals to identify SNPs that affect outcomes (i.e. locus detection) than the number of individuals required to determine whether the particular SNP exerts its effect through the maternal or offspring genomes.

In contrast, when maternal and offspring genetic effects act in opposite directions the observed SNP-outcome covariance is low. In this situation, constraining the maternal and/or offspring paths to zero has little effect on model fit. In these situations, the difference in degrees of freedom between the models is more important than model fit and consequently the two degree of freedom test often has less power than the one degree of freedom test. Loci that exert maternal and offspring genetic effects in the opposite direction do exist in nature and are particularly relevant for perinatal phenotypes such as offspring birthweight (Beaumont et al. 2018). One example is a rare variant in the *GCK* gene that is associated with type 2 diabetes and offspring birthweight (Hattersley et al. 1998). The rare variant in the *GCK* gene predisposes the mother to high circulating blood glucose which on average increases offspring's birthweight, but only if the offspring does not inherit the variant. If the mother and the offspring both have the variant then the baby on average is of normal birth weight as maternal hyperglycemia compensates for the offspring defect in glucose sensing. However, if the variant is transmitted from the father to the offspring, then it predisposes to reduced glucose sensing and consequent reduced insulin secretion, leading to a decrease in offspring birthweight (Hattersley et al. 1998; Hattersley and Tooke 1999).

We also examined the effect of varying the residual correlation between maternal and offspring phenotypes on the power to detect association. Whilst the residual correlation did not affect the power to detect association in the case of genotyped mother-offspring pairs where only the offspring had been phenotyped (Scenario 6), it did have a major effect on designs where genotyped mothers had their own and their offspring's phenotype (i.e. Scenarios 1, 3, 4, 5, and 7). Specifically power to detect loci (2 degree of freedom test) decreased as the residual phenotypic correlation increased (in contrast power increased as the residual phenotypic correlation increased when maternal and offspring genetic effects affected the trait in opposite directions). In contrast, the

power to detect maternal genetic effects (1 degree of freedom test) increased as the residual phenotypic correlation increased. The implication is that the level of residual correlation between maternal and offspring phenotypes, as well as whether the focus is on locus discovery (i.e. 2 degree of freedom test) or demonstration of maternal/ offspring genetic effects (1 degree of freedom test), are important considerations when choosing the optimal experimental design (see below).

In order to partition genetic effects into maternal and offspring components, our calculations show that large genotyped cohorts will be required. Importantly our calculations show that designs that involve mother and offspring phenotypes/genotypes from the same family (i.e. genotyped mother offspring pairs or mothers reporting their own and their offspring's genotype) have substantially higher power than study designs where one group of mothers report their own phenotype and another mutually exclusive group of mothers report their offspring's phenotype. As an example of the added power provided by overlapping samples, M-GPC estimates that approximately 24,000 genotyped mothers with offspring phenotypes combined with 24,000 genotyped offspring with their own phenotype (i.e. 48,000 individuals genotyped in total) would be required to demonstrate a maternal effect responsible for 0.1% of the phenotypic variance with 90% power (1df test, β_o = 0, α = 0.05, ρ = 0.25). In contrast, only 14,000 genotyped mother-offspring pairs or 19,000 genotyped mothers who provide their own and their offspring's phenotype would be required to achieve the same level of statistical power. Likewise for locus discovery, M-GPC estimates that approximately 39,000 genotyped mothers with offspring phenotypes combined with 39,000 genotyped offspring with their own phenotype (i.e. 78,000 individuals genotyped in total) would be required to detect a maternally mediated locus responsible for 0.1% of the phenotypic variance with 90% power (two degree of freedom test, $\beta_o = 0$, $\alpha = 5\text{x}10^{-8}$, $\rho = 0.25$). In contrast, only 49,000

genotyped mother-offspring pairs or 46,000 genotyped mothers who provide their own and their offspring's phenotype would be required to achieve the same statistical power

In a cohort of genotyped mother-offspring pairs, investigators are required to collect and analyse two DNA samples per offspring outcome. Although this design is generally more powerful in terms of partitioning genetic effects into maternal and offspring components (if you count the number of phenotypes), it is both a time consuming and costly design. In contrast, a cohort study where only mothers are genotyped, but where phenotypic data are available for both mothers and their offspring, can provide good power, but the cost of genotyping may be drastically reduced. For phenotypes that are easily and cheaply measured (e.g. the mother self-reporting her offspring's phenotype) this may be a more efficient choice, whereas genotyped mother-offspring pairs are better used when the cost of genotyping is low compared to the cost of phenotyping. Importantly, as shown in Scenario 3 (partial overlap #1), using this SEM it is possible to combine different study designs to increase power. Therefore, researchers can incorporate all types of data, including genotyped mother-offspring pairs and genotyped mothers with phenotypes on both mother and offspring from different studies, to gain maximal power. Including genotyped mother-offspring pairs where both have been phenotyped is uniformly the most powerful study design.

Previous studies by our group (Beaumont et al. 2018) have shown that maternal genetic effects of common genetic variants associated with offspring birthweight typically do not explain more than ~0.1% of the trait variance. Assuming that this effect size is representative of maternal genetic effects associated with other perinatal and offspring phenotypes, then our power calculations suggest that at least 40,000-50,000 genotyped mother-offspring pairs (or genotyped individuals with their own and their offspring's phenotype) will be required to achieve at least 80% power for locus detection (two degree of freedom test) at genome-wide levels of significance. In the case of

perinatal phenotypes, it has been estimated that there are approximately 50,000 genotyped mother-offspring pairs with GWAS that are currently available for such analyses across the world (Evans et al. Submitted; Middeldorp et al. Submitted). The implication is that the detection of loci that exert maternal genetic effects on offspring phenotypes will be possible assuming collaboration across different cohorts and the sharing of summary statistics. In addition, the availability of publicly available resources like the UK Biobank (Horikoshi et al. 2016; Sudlow et al. 2015; Warrington et al. 2018) makes it possible to identify loci that exert maternal genetic influences on phenotypes like birthweight because of the large number of genotyped individuals reporting both their own and their offspring's phenotype.

Once a genetic variant has been associated with an offspring phenotype, the next question is whether it exerts its effect via the maternal genome, offspring genome or both. It can be argued that for this goal, a less stringent type one error rate may be more appropriate to evaluate significance (e.g. $\alpha = 0.05$) since the focus is typically on a few genetic variants rather all SNPs across the genome. Our power calculations show that in this situation, approximately 10,000 genotyped mother-offspring pairs (or genotyped individuals with maternal and offspring phenotypes) would be sufficient to partition genetic effects into maternal and offspring sources of variation with appreciable power (assuming $\alpha = 0.05$). This number of individuals is much easier to achieve, and indeed several of the larger population based birth cohort studies already contain close to or more than this number of mother-offspring pairs (Boyd et al. 2013; Fraser et al. 2013; Magnus et al. 2016). The implication is that known loci for many perinatal traits, could be partitioned into maternal and offspring genetic effects using current sample sizes that are available in several cohorts (Beaumont et al. 2018; Horikoshi et al. 2016; Taal et al. 2012; van der Valk et al. 2015).

It is important to realize that the inclusion of additional genotyped individuals with their own phenotype, will in general not affect the power to detect maternal genetic effects (although it will still increase power to detect offspring genetic effects and detect loci). In other words, the inclusion of large publicly available GWAS data (typically individuals reporting their own phenotype) in an existing analysis of e.g. genotyped mother-offspring pairs will not increase power to detect maternal genetic effects. In general, in order to increase power to detect maternal effects, genotyped mothers with their offspring's phenotype must be added to the analysis.

Finally, we acknowledge that the statistical models underlying the power calculations presented in this manuscript make several assumptions including that at the SNPs under investigation, the only type of genetic effects that affect the offspring phenotype of interest are (additive) maternal and offspring genetic effects. The presence of other effects such as genetic dominance, parent of origin effects (e.g. due to imprinting), and/or paternal genetic effects may mean that estimates of maternal and/or offspring genetic effects from our models are biased. For example, in the case of genotyped mothers who report their own and their offspring's phenotype, paternal genetic effects will bias estimates of maternal and offspring genetic effects when paternal genotype is not included in the structural equation model. Whilst it could be argued that paternal genetic effects may have limited influence on perinatal offspring phenotypes (e.g. birthweight, gestational age etc), the same is probably not true for other offspring traits. For example, a recent study by the deCODE group showed that untransmitted alleles for educational attainment from both parents were associated with a range of offspring traits (Kong et al. 2018). In general, the resolution of paternal genetic effects and the ability to account for them so that they do not bias estimates of maternal and offspring genetic effects will require paternal genotypes to be included in the analysis. Unfortunately, there is a paucity of cohorts around the world that have collected large numbers of

paternal genotypes, meaning that it may be difficult to conduct these sorts of analyses on a large scale.

Conclusion

We have developed the "Maternal and offspring Genetic effects Power Calculator" (M-GPC), a freely available online web utility that can be used to estimate power to detect maternal and offspring genetic effects in genetic association studies. We show that genotyped mother-offspring pairs are the most powerful study design for detecting maternal or offspring genetic effects, but that collections involving genotyped individuals who provide information on both their own and their offspring's phenotype are likely to be more efficient when the cost of genotyping is high and phenotype collection is low. We conclude that the samples sizes required to detect maternal and/or offspring genetic effects that explain realistic proportions of offspring trait variance with appreciable power are achievable and within the range of current research consortia.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Authors contributions:

GHM, NMW and DME designed the research; GHM conducted the research and analysed data; GH assisted with implementation of the R shiny app. GHM and DME wrote the paper. All authors read and approved the final manuscript.

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Figure legends

Figure 1: Path diagrams illustrating the SEM used to perform asymptotic power calculations. Squares denote observed variables whereas circles denote latent variables. Causal paths are represented by unidirectional arrows and bidirectional arrows represent covariances. The variance of the genotypes (both latent and observed) are set to Φ (i.e. variance in grandmaternal genotype = Φ, variance in maternal genotype = 0.75Φ + 0.25Φ and variance in offspring genotype = 0.75Φ + 0.25Φ as can be easily verified by path analysis/covariance algebra), which is estimated from the data. The causal path between the individual's own genotype and both their mother and offspring's latent genotype is set at 0.5 according to quantitative genetics theory. Small letters over the arrows represent path coefficients; β_m: maternal genetic effect; β_o: offspring genetic effect; ρ: covariance between residual error terms; ε: residual error in the maternal phenotype; ε_O: residual error in the offspring phenotype. Panel A illustrates the model component where mothers are genotyped, but the phenotype is available for both mother and offspring; panel B illustrates the model component where mothers are genotyped and phenotype information is available only on themselves; panel C illustrates the model component where mothers are genotyped but phenotype information is only available on their offspring; panel D illustrates the model component representing genotyped mother-offspring pairs where the offspring phenotype is available; and panel E illustrates the model component representing genotyped mother-offspring pairs where both mother and offspring are phenotyped. The different components (A to E) are combined into one overall model with each parameter (i.e. β_m, β_o, var(ε), var(ε_O), Φ, ρ) constrained equal across the different components. The likelihood associated with the different components is then weighted by their sample size and added together to calculate an overall likelihood.

Figure 2: Power (y-axis) to detect maternal (lower panel) and offspring **(upper panel) genetic effects as a function of variance explained (x-axis) according to the different study designs.** Variance explained in the phenotype was fixed at 0.1% for maternal genetic effects (upper panel) and 0.1% for offspring genetic effects (lower panel). The residual correlation (ρ) between maternal and offspring phenotypes was set to 0.25. The x-axes display the variance explained in the phenotype by either maternal or offspring genetic effects. The negative values represent situations where the maternal or offspring genetic effect decreases the offspring's phenotype (i.e. maternal and offspring genetic effects act in the opposite directions). N = 50,000 genotyped mother-offspring pairs or genotyped mothers with phenotypic information on themselves, their offspring or both if not otherwise specified. $\alpha = 5 \times 10^{-8}$, 1 degree of freedom test. Power for the other sample sizes, effect sizes and residual correlations are presented in Supplementary Table 1.

Figure 3: The influence of locus effect size and direction on power to detect maternal and offspring genetic effects. The upper panel displays power to detect an offspring genetic effect (y-axis) as a function of offspring genetic effect size (x-axis) assuming the maternal genetic effect explained 0.1% of the phenotypic variance. The lower panel shows power to detect a maternal genetic effect (y-axis) as a function of maternal genetic effect size (x-axis) assuming the offspring genetic effect explained 0.1% of the phenotypic variance. All calculations assume 50,000 genotyped mothers with phenotype information on themselves and their offspring, and a residual correlation of $\rho = 0.25$ between maternal and offspring phenotypes. df: degrees of freedom; $\alpha = 5 \times 10^{-8}$.

Figure 4: Power (y-axis) to detect maternal genetic effects (one degree of freedom test) is shown in the upper panel or any effect at a locus (two degree of freedom test) in the lower panel as a function of ρ, the residual correlation between maternal and offspring phenotypes

(x-axis). Power is shown for N=50,000 genotyped individuals with their own and their offspring's phenotype (Complete overlap, Scenario 1); N=50,000 genotyped mothers where 50% report their own phenotype and 50% report their offspring's phenotype (No overlap, Scenario 2). For illustration the variance explained is set to 0.1% for the maternal genetic effect and 0% for the offspring genetic effect. df: degrees of freedom; $\alpha = 5 \times 10^{-8}$. Power of genotyped mother-offspring pairs (Scenario 6) included as a comparison even though ρ does not affect power in this situation.

Figure 5: Power to detect association at different sample sizes for either genotyped mother-offspring pairs or genotyped mothers with their own and their offspring's phenotype. Results for two degree of freedom tests ($\alpha = 5 \times 10^{-8}$) where the aim is locus detection are compared against the power of one degree of freedom tests of maternal genetic effects ($\alpha = 0.05$) where the aim is to partition known loci into maternal and offspring genetic components. For all conditions, maternal genetic effects at the locus explain 0.1% of the phenotypic variance (offspring genetic effects explain 0% of the phenotypic variance). The residual correlation (ρ) between maternal and offspring phenotypes was set to 0.25.

Table 1: Overview of the six different scenarios

	Mothers genotyped	**Offspring genotyped**	**Proportion of total sample who have genotyped mothers with their own and their offspring's phenotype**	**Proportion of the total sample who have genotyped mothers with their own phenotype only**	**Proportion of the total sample who have genotyped mothers with their offspring phenotype only**	**Proportion of the total sample who have genotyped mother-offspring pairs where offspring phenotype is available**
Scenario 1 Complete Overlap	Yes	No	100%	-	-	-
Scenario 2 No overlap	Yes	No	-	50%	50%	-
Scenario 3 Partial Overlap #1	Yes	No	50%	25%	25%	-
Scenario 4 Partial Overlap #2	Yes	No	50%	50%	-	-
Scenario 5 Partial Overlap #3	Yes	No	50%	-	50%	-

Scenario 6 Mother-offspring pairs (Offspring only phenotyped)	Yes	Yes	-	-	-	100%
Scenario 7 Mother-offspring pairs (Mother and offspring phenotyped)	Yes	Yes	100%	-	-	100%