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Quantitative Genetics in the Postmodern Family of the Donor Sibling Registry

by

Joseph Christopher Lee

DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

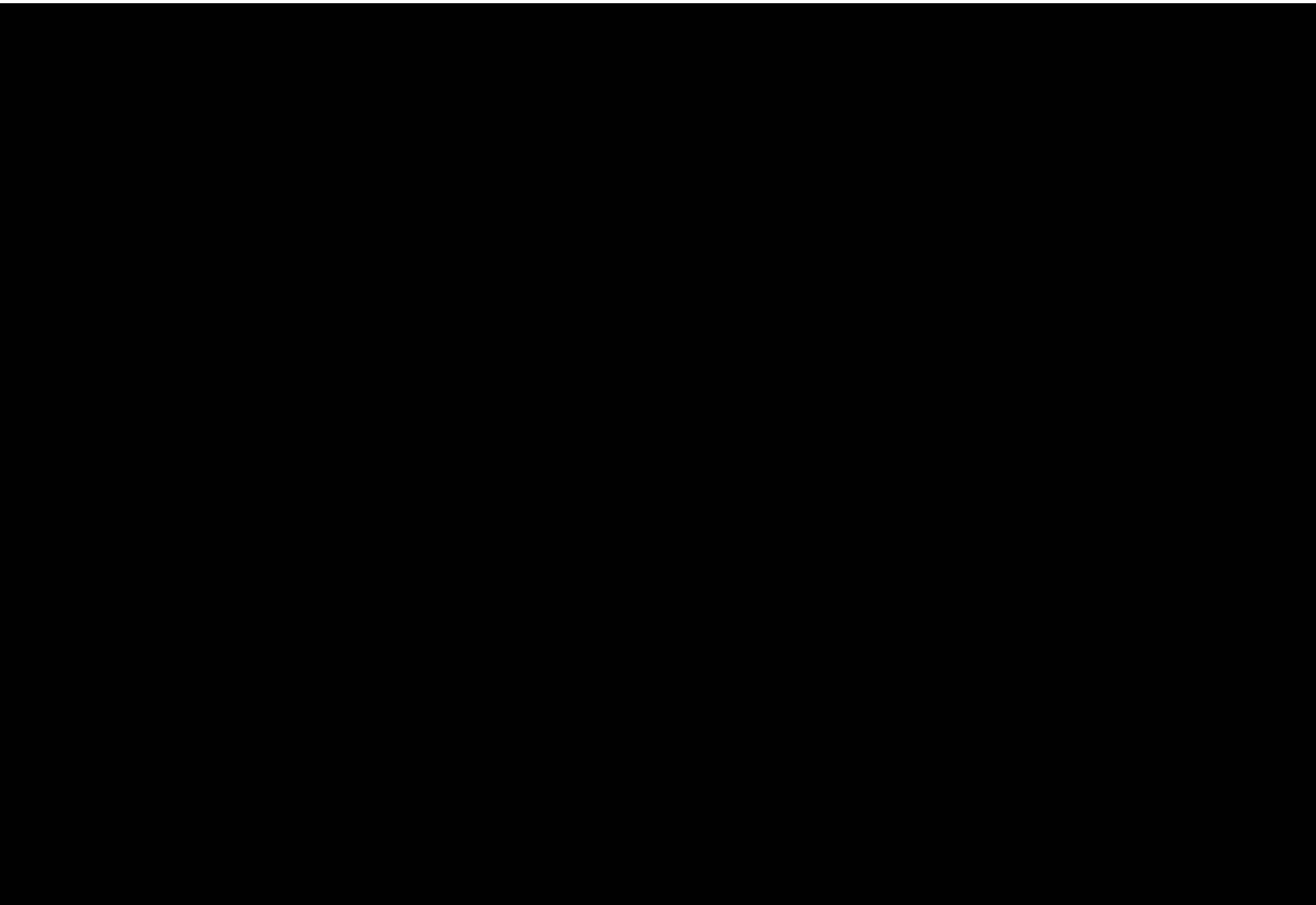
DOCTOR OF PHILOSOPHY

in

Pharmaceutical Sciences and Pharmacogenomics

in the

GRADUATE DIVISION



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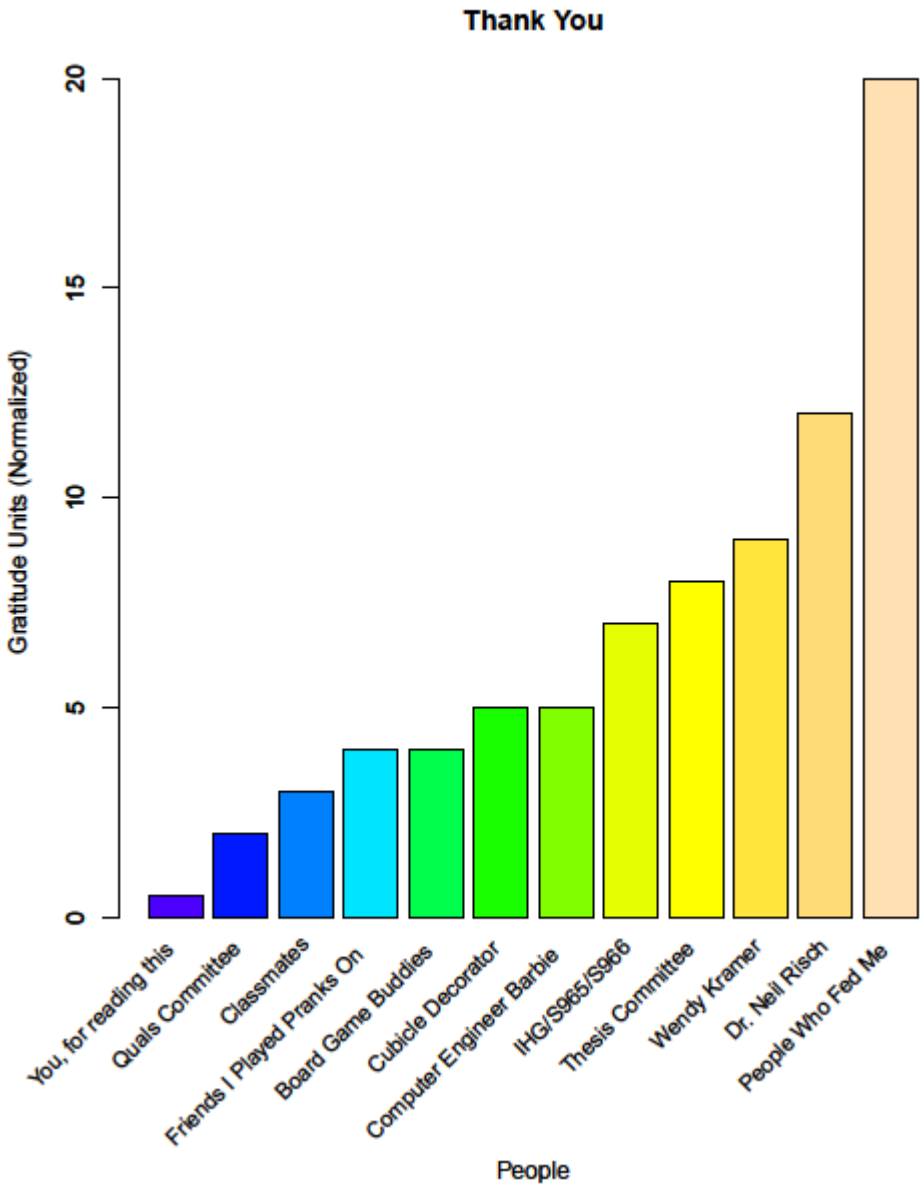

Figure A Gratitude units vs. people who have supported me. These capstone results represent many people, many memories, and many thanks.

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Quantitative Genetics in the Postmodern Family of the Donor Sibling Registry

Joseph Christopher Lee

Abstract

Quantitative genetics is primarily concerned with two subjects: the correlation between relatives and the response to selection. The correlation between relatives is used to determine the heritability of a trait -- the key quantity that addresses the question of nature vs. nurture. Heritability, in turn, is used to predict the response to selection -- the main driver of improvements in crops and livestock. The theory of quantitative genetics has been thoroughly tested and applied in plants and animals, but heritability and selection remain open questions in humans due to limited natural experimental designs.

The Donor Sibling Registry (DSR) is an organization that helps individuals conceived as a result of sperm, egg, or embryo donation make contact with genetically related individuals. Families who conceived children via anonymous sperm donation join the DSR and match with other families who used the same donor ID at the same sperm bank. The resulting donor pedigree consists of heterosexual, lesbian, and single mother families who are connected through the common anonymous sperm donor used to conceive their children.

Here, we introduce a new quantitative genetic study design based on the unprecedented family relationships found in the donor pedigree. We surveyed 945 individual families constituting 159 donor pedigrees from the Donor Sibling Registry and used their demographic, physical, and behavioral characteristics to conduct a quantitative genetic study of selection and heritability. A direct measurement of phenotypic assortment showed mothers actively selected mates for height, eye color, and religion.

Artificial selection for donor height increased mean child height in a manner consistent with the selection differential. Reared-apart donor-conceived paternal half-siblings provided unbiased heritability estimates for traits influenced by maternal and contrast effects. Maternal effects were important in determining the variance of birth weight while eliminating contrast effects revealed sociability to be a highly heritable childhood temperament. Thus, the unprecedented family relationships in the donor pedigree enable a universal model for quantitative genetics.

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1 Introduction to Quantitative Genetics

Fisher established the field of quantitative genetics in 1918 with "The Correlation between Relatives on the Supposition of Mendelian Inheritance" (*1*). This seminal paper reconciled continuous variation with Mendelian genetics by proposing a polygenic model in which a large number of individual loci exert an additive effect on the value of a quantitative trait. Fisher then used the correlation between relatives to estimate the proportion of additive genetic variance. This proportion, formalized as the heritability h^2, forms the basis for quantitative genetics (*2*).

1.1 Heritability

The phenotypic variation of a quantitative trait (V_P) can be decomposed into the sum of genetic (V_G) and environmental (V_E) components.

$$V_P = V_G + V_E \tag{1.1}$$

Genetic variation consists of additive (V_A) and dominance (V_D) components. Environmental variation consists of shared (V_{ES}) and random (V_{ER}) components.

$$V_P = V_A + V_D + V_{ES} + V_{ER} \tag{1.2}$$

The narrow-sense heritability h^2 is the proportion of phenotypic variance due to additive genetic effects. It is the key value that addresses the question of nature vs. nurture.

$$h^2 = \frac{V_A}{V_P} \tag{1.3}$$

Heritability is measured using the correlation between relatives (*3*). Consider two relatives whose phenotypes P_1 and P_2 are determined by:

$$\begin{aligned} P_1 &= M_1 + F_1 + D_1 + E_S + E_{R1} \\ P_2 &= M_2 + F_2 + D_2 + E_S + E_{R2} \end{aligned} \tag{1.4}$$

where M and F are the additive effects of the maternally and paternally derived alleles, D is the dominance effect, E_S is the shared environmental effect, and E_R is the random environmental effect. Assuming no gene-environment interactions:

$$\begin{aligned} Cov\{P_1, P_2\} = & Cov\{M_1, M_2\} + Cov\{F_1, F_2\} \\ & + Cov\{M_1, F_2\} + Cov\{F_1, M_2\} \\ & + Cov\{D_1, D_2\} + Cov\{E_S, E_S\} \end{aligned} \tag{1.5}$$

The value of this phenotypic covariance depends on the mean number of alleles shared identical-by-descent (IBD) between the two relatives. Two alleles are IBD if they are descended from the same ancestral allele in a previous generation. With probability r_0 the two relatives share zero alleles IBD and all of the allelic covariances are zero. With probability r_1 the two relatives share one allele IBD and the covariance corresponding to the shared allele is $V_A/2$. With probability r_2 the two relatives share two alleles IBD and the covariance corresponding to the shared alleles is $V_A + V_D$.

$$Cov\{P_1, P_2\} = r_0 \times 0 + r_1 \times \frac{V_A}{2} + r_2 \times V_A + r_2 \times V_D + V_{ES} \tag{1.6}$$

For a pair of relatives, the coefficient of relatedness r is one-half the mean number of alleles shared IBD:

$$r = r_0 \times 0 + r_1 \times 1/2 + r_2 \tag{1.7}$$

Combining equations (1.6) and (1.7),

$$Cov\{P_1, P_2\} = rV_A + r_2 V_D + V_{ES} \tag{1.8}$$

Dividing equation (1.8) by the total phenotypic variance V_P and assuming a negligible dominance component yields:

$$Corr\{P_1, P_2\} = rh^2 + \rho_{ES} \quad (1.9)$$

Thus, the correlation between relatives is a function of the coefficient of relatedness, the heritability, and the shared environmental component. Twin and adoption studies routinely manipulate this equation to estimate heritability (*4, 5*).

1.1.1 Twin Studies

Monozygotic (MZ) twins share all of their genes, while dizygotic (DZ) twins share half of their genes on average. Subtracting the DZ correlation from the MZ correlation yields an indirect estimate of the heritability.

Twin studies assume the shared environmental component ρ_{ES} is the same for MZ and DZ twins. Although this "equal environment assumption" is largely valid, it does not hold in all cases. For instance, same-sex adult MZ twins are in more frequent contact with each other than their DZ counterparts. This increases MZ twin similarity and artificially inflates heritability estimates for self-reported psychiatric symptoms, alcoholic intake, and personality (*6*).

1.1.2 Adoption Studies

Adoption can be viewed in genetic terms as a social intervention that randomizes environment. In an indirect adoption study, biological relatives share genes and environment while adoptive relatives share environment only. Subtracting the adoptive relative correlation from the biological relative correlation yields an indirect estimate of the heritability.

In the more powerful direct adoption study, biological relatives are separated by the adoption process and do not share common environment. The correlation of these reared-apart relatives provides a direct estimate of the heritability.

Caveats for the adoption study designs include:

- Biased populations – Adoptive parents typically come from the high end of the social stability spectrum while biological parents come from the low end (*7*).
- Selective placement – Adoptive and biological parents can be matched based on variables such as ethnicity, religion, and social background, potentially confounding biological and environmental influences (*6*).
- Privacy – It is increasingly difficult to carry out an adoption study in the United States due to adoption's private nature (*6, 8*).

1.1.3 Specialty Designs

Specialty study designs explore a wide range of family relationships:

- Twins reared apart – Studies of twins reared apart fuse twin and adoption methodologies to eliminate shared environment. Twins separated at birth are extremely rare (*9, 10*).
- Children of MZ twins – Nominally cousins, children of MZ twins are genetic half-siblings who are reared apart in different households (*11, 12*).
- Half-siblings – In an indirect study, half-siblings are compared with full-siblings to eliminate the effect of shared environment (*13-17*). The more powerful direct study examines half-siblings who have been reared apart. Such half-siblings may vary in their exposure to a common environment or biological parent (*8*).
- Exact genetic relationship – Genome-wide DNA markers can be used to

determine the exact coefficient of relatedness. The variation in r between full siblings enables a direct estimate of the heritability (*18*). This approach can be taken to its logical extreme using SNPs to calculate distant genetic relationships between putatively unrelated individuals, but this method cannot yet fully account for observed heritability (*19*).

Table 1.1 summarizes the components of phenotypic variance captured in the family relationships described above. $V_{EMaternal}$ is an additional environmental component that comes from sharing the same maternal womb.

Table 1.1 Components of phenotypic variance for family relationships commonly used to estimate heritability

Relationship	Components of Phenotypic Variance
Twin Studies	
Monozygotic Twins	$V_A + V_D + V_{ES} + V_{EMaternal}$
Dizygotic Twins	$\frac{1}{2}V_A + \frac{1}{4}V_D + V_{ES} + V_{EMaternal}$
Adoption Studies	
Biological Full-Siblings	$\frac{1}{2}V_A + \frac{1}{4}V_D + V_{ES} + V_{EMaternal}$
Adoptive Full-Siblings	V_{ES}
Biological Full-Siblings, Adopted Away	$\frac{1}{2}V_A + \frac{1}{4}V_D + V_{EMaternal}$
Twins Reared Apart	
Monozygotic Twins	$V_A + V_D + V_{EMaternal}$
Dizygotic Twins	$\frac{1}{2}V_A + \frac{1}{4}V_D + V_{EMaternal}$
Half-Siblings	
Paternal Half-Siblings	$\frac{1}{4}V_A + V_{ES}$
Maternal Half-Siblings	$\frac{1}{4}V_A + V_{ES} + V_{EMaternal}$
Half-Siblings, Reared Apart	$\frac{1}{4}V_A$

1.2 Selection

Predicting the phenotypic response to selection is one of the most important applications of quantitative genetics. Heritability determines how fast a population will change in response to selection.

1.2.1 Response to Selection

The response to selection R is the change in the population mean produced by selection. It is measured as the difference between the phenotypic mean of the parental generation and the mean of the offspring of the selected parents. The selection differential S is the strength of the applied selection. It is measured as the difference between the phenotypic mean of the parental generation and the mean of the selected parents. R and S are related through the heritability by:

$$R = h^2 S \tag{1.10}$$

Given a selection differential and a prior estimate of the heritability in the base population, equation (1.10) can be used to predict the response to selection. When equation (1.10) is rewritten as

$$h^2 = \frac{R}{S} \tag{1.11}$$

h^2 is referred to as the realized heritability. The realized heritability describes how the response is related to the cumulative selection differential applied over the course of many generations. It can estimate the heritability as described by equation (1.3), but it tends to be biased after the first generation of selection (*20*).

1.2.2 Selection in Humans

Selection remains a difficult topic to study in humans. Research is restricted to observational studies of natural selection because selective breeding experiments are unethical. Since natural selection operates through differential reproductive success, the human reproductive time scale limits the availability of high-quality multi-generational data sets. When such records are available, the data typically lends itself to an evolutionary biology analysis of Bateman gradients rather than a quantitative genetic

prediction of the phenotypic response to selection (*21, 22*). In rare cases where phenotypic predictions are possible, as in the Framingham Heart Study (*23*), the results are inconclusive because natural selection measured at the phenotypic level does not necessarily imply a causal relationship between the trait and reproductive fitness (*24*).

Without a proper experimental structure, even the relatively simple act of determining which traits undergo active selection in humans is challenging. Asking spouses how they selected their partner "will not be fruitful, since there is no necessary connection between the causes of behavior and the causes to which such behavior is attributed" (*25*).

1.3 Statement of Purpose

The theory of quantitative genetics has been thoroughly tested and applied in plants and animals, but the genetic architecture of complex traits and the response to selection are open questions in humans. Here, we introduce a new family study design to address these issues.

The donor pedigree is a historically unprecedented family structure made possible by modern reproductive medicine. It consists of heterosexual, lesbian, and single mother families who are connected through the common anonymous sperm donor used to conceive their children. We used the unique gender and kinship arrangements found in the donor pedigree to conduct a quantitative genetic study with three aims: (i) to examine female mate choice preferences and determine which traits undergo active selection in humans, (ii) to describe the response to selection as a realized heritability, and (iii) to establish donor-conceived reared-apart paternal half-siblings as a model to measure the heritability of traits intractable to other study designs.

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2 The Donor Sibling Registry

2.1 Introduction

The Donor Sibling Registry (DSR) is an organization that helps individuals conceived as a result of sperm, egg, or embryo donation make contact with genetically related individuals. Families who conceived children via anonymous sperm donation join the DSR and match with other families who used the same donor ID at the same sperm bank. The resulting "donor family" consists of heterosexual, lesbian, and single mother families who are connected through the common sperm donor used to conceive their children. Thus far, the DSR has been the subject of a number of sociological research studies:

- Single mothers and lesbian couples were more likely to search for their donor than heterosexual couples; the primary motivation was to enhance their child's sense of identity. Parents searched for donor siblings because they were curious about similarities in appearance and personality (*1-3*).
- Compared with heterosexual couples, single mothers and lesbian couples informed their children of their sperm donor origin at an earlier age. Later age of disclosure was associated with increased negative feelings; in heterosexual couples this led to increased negative feelings towards the mother but not the father (*2-4*).
- A retrospective survey of egg donors found 30.3% experienced some degree of ovarian hyperstimulation syndrome and 26.4% experienced infertility or other menstrual changes following donation. Prospective studies are necessary to understand the long-term health risks of egg donation (*5*).

- Fewer children from heterosexual couple families told their father they were searching for their donor, as compared to children from lesbian couple families who told their non-biological mother (*6*).
- Donors' main reasons for donating were to help others and for financial payment. Donors who had contact with their donor-conceived children generally reported having positive experiences (*7, 8*)
- Non-biological parents chose a donor to match their physical characteristics. Non-biological mothers were more interested than non-biological fathers in meeting the donor (*9*).
- Compared with North American parents, UK/Australian parents who used egg donation told their children of their donor conception at an earlier age (*10*). Parents generally supported early disclosure (*11*).

Here, we characterize the DSR with respect to the parameters and phenotypes used in our quantitative genetic study of donor pedigrees.

2.2 Materials and Methods

Subjects were recruited from the Donor Sibling Registry (DSR). All DSR members were sent an email inviting them to participate in the study. The invitation letter and a link to the study website were posted on the DSR homepage. Recruitment was initiated in June 2010 and lasted five months. Eligibility criteria included having a familial or biological connection to a registered member of the DSR. The UCSF Committee on Human Research approved the study protocol before the study was initiated. Subjects provided electronically signed informed consent before participating.

Study data was collected and managed using REDCap electronic data capture tools hosted at UCSF (*12*). Subjects self-identified as either a biological mother of a donor-conceived child, a donor, a donor-conceived child (age 7-12), a donor-conceived adolescent (age 13-18), a donor-conceived adult (age 18+), or a non-biological parent of a donor-conceived child. Subjects completed surveys tailored to their self-identified group.

We restricted our analysis to data from biological mother reports due to the low absolute number of self-reports from donors, donor-conceived children, donor-conceived adolescents, donor-conceived adults, and non-biological parents. We further restricted our analysis to complete paternal half-sibling pedigrees that included a biological mother, a sperm donor with a known ID and clinic, donor-conceived children, and a non-biological parent (if applicable). The complete pedigree requirement excludes mothers who used egg donation, mothers who did not have full donor ID/clinic information, and mothers who did not advance far enough into the survey to complete the parent report on their child.

Biological mothers completed self-report surveys regarding demographic, physical, and behavioral characteristics. They provided information about their donor and partner (if applicable) and then completed a parent report about their donor-conceived child's physical characteristics, medical history, temperament, symptoms of mental disorders, and birth and early development. Temperament was evaluated using the Emotionality, Activity, and Sociability (EAS) Temperament Survey for Children (*13*). Symptoms of mental disorders were measured using the Strengths and Difficulties Questionnaire (SDQ) (*14*). Birth and early development events were assessed using the NCS-A birth

and early development questionnaire (*15*). Variable definitions for survey responses are shown in Table 2.1.

Table 2.1 Variable definitions for survey options

Survey Option	Variable Definition
Factors Important in Donor Choice	
Unimportant Somewhat Unimportant Neight Important Nor Unimportant	Not Important
Somewhat Important Very Important	Important
Eye Color	
Gray Blue	Blue
Amber Hazel Green	Green
Brown	Brown
Race/Ethnicity - Since subjects could mark more than one race/ethnicity on the survey, we assigned them to a single category in order of increasing priority: White, Black, Hispanic, Other, and Asian.	
White Middle Eastern Ashkenazi Jewish	White
African-American African Afro-Caribbean	Black
Mexican Central/South American Puerto Rican Cuban Other Latino/Hispanic	Hispanic
South Asian Chinese Japanese Korean Filipino Vietnamese	Asian

Other Southeast Asian	
Native Hawaiian Samoan Other Pacific Islander Native American Indian Other Don't Know	Other

Religion

Christian Catholic Roman Catholic Eastern Orthodox Protestant Baptist Methodist Unitarian	Christian
Agnostic Atheist	Atheist
Jewish	Jewish
Buddhist Hindu Muslim Other	Other

Education Level

Grade School Some High School High School or GED	High School
Technical/Trade School	Technical/Trade School
Some College	Some College
College	College
Graduate/Professional School	Graduate/Professional School

Employment Status

Full-Time Employed	Full-Time Employed
Part-Time Employed	Part-Time Employed
Full-time Student	Full-time Student
Homemaker	Homemaker
Retired Disabled	Other

Unemployed Other	

Marital Status

Never married	Never married
Married or living as married	Married or living as married
Separated Divorced Widowed	Other

Sexual Orientation

Heterosexual, straight	Heterosexual
Homosexual, gay	Homosexual
Bisexual Other	Other

Household Income

< $10000 / yr $10000 - 14999 / yr $15000 - $19999 / yr	< $19999 / yr
$20000 - $39999 / yr	$20000 - $39999 / yr
$40000 - $59999 / yr	$40000 - $59999 / yr
$60000 - $100000 / yr	$60000 - $100000 / yr
$100000 - $199999 / yr	$100000 - $199999 / yr
> $200000 / yr	> $200000 / yr

2.3 Results

2.3.1 Descriptive Statistics

At the start of the study there were approximately 28000 registered members of the DSR, consisting of donors, parents, and donor-conceived people. We consented a total of 1845 subjects (1344 biological mothers, 107 donors, 150 donor-conceived adults, 47 donor-conceived adolescents, 30 donor-conceived children and 167 non-biological parents), yielding an approximate 6.6% survey response rate.

Biological mothers provided information on 945 complete pedigrees consisting of a biological mother, a sperm donor with a known ID and clinic, donor-conceived

children, and a non-biological parent (if applicable). Figure 2.1 shows all family relationships observed in our sample. The variance components and sample size for each relationship are listed in Table 2.2.

Descriptive statistics for adults in these complete pedigrees are shown in Table 2.3. DSR parents were largely white and well-educated. The proportion of single mothers, lesbian mothers, and heterosexual mothers was similar to previous survey results (*1*).

Parent age, height, and body mass index (BMI) distributions are shown in Figure 2.2. Male partners displayed greater positive skew for age than mothers or female partners. Donors were taller and had lower BMIs than male partners.

The complete pedigrees contain a total of 1213 children. Descriptive statistics for these children are shown in Table 2.4. The prevalence of multiple births in the DSR was higher than the US national average of 3.3% due to the use of assisted reproductive technology (*16*).

Child age, height, and BMI distributions are shown in Figure 2.3. Donor-conceived children were taller and had higher BMIs compared to median CDC growth curves (*17*). Cross-tabulation tables for mother/donor/child eye and hair color are shown in Table 2.5 and Table 2.6, respectively. These tables are symmetric across the main diagonal, demonstrating internal consistency with regards to eye and hair color genetics.

Table 2.7 shows the distribution of the number of children per biological mother. Approximately 25% of mothers had more than one donor-conceived child, either as a result of multiple births or from multiple donor-assisted conceptions. Based on shared donor ID and clinic information, 576 out of the 1213 children matched with a half-sibling

internally within our sample, capturing 8.1% of the 7155 children who had matched with a half-sibling in the DSR at the start of the study. The 576 children who matched with a half-sibling formed 159 donor pedigrees in which each child shares the same sperm donor. The distribution of the number of children in each donor pedigree is shown in Table 2.8; the largest donor pedigree contains 10 children, with a median size of three children.

We assessed the reliability of the donor ID/clinic half-sibling matching process by measuring the inter-rater reliability of mother-reported physical characteristics for the donors. Krippendorff alpha (*18*) values for height (α =0.67), weight (α =0.76), eye color (α =0.78), and hair color (α = 0.79) support the claim that mothers in each donor pedigree used the same donor.

2.3.2 Adjusting for Covariates

In our heritability analysis, each phenotype was adjusted for covariates. Mother height was adjusted for age by linear regression. Donor height was calculated by averaging the mother-reported heights for each donor and then adjusted by subtracting the mean of all donors. Mother BMI was derived from the raw height and weight values for each individual, log transformed, and then adjusted for age by linear regression. Donor BMI was derived by averaging the mother-reported heights and weights for each donor, calculating a BMI from the average values, and then log-transforming them.

Child height was adjusted for age and sex by taking the residuals from a local regression (LOESS) of height versus age, stratified by sex (Figure 2.3B-C). Only children two years or older were included in the analysis to ensure a standing height measurement. Child BMI was derived from the raw height and weight values for each

individual, and then adjusted for age and sex by taking the residuals from a LOESS regression of BMI versus age, stratified by sex (Figure 2.3D-E). The residuals were then log transformed to increase normality. Similar to height, only children two years or older were included in the BMI analysis.

Child birth weight (Figure 2.4A) was adjusted by taking the residuals from a multiple linear regression of birth weight on sex (Figure 2.4B), birth order (Figure 2.4C), biological mother BMI (Figure 2.4D), and weeks premature (Figure 2.4E), stratified by whether the child was a singleton or part of a multiple birth. Inclusion criteria for singletons were less than seven weeks premature, birth weight less than 15 pounds, and maternal BMI between 15 and 55. Inclusion criteria for multiple births were the same as for singletons, but children were included if they were less than ten weeks premature. Birth order was derived from the children's ages. Birth order was a tie in the case of twins, e.g. if a mother had a child age 7 and twins age 4, then the birth orders were 1, 2, and 2, respectively.

Figure 2.5 shows maternal age at time of birth. Although maternal age was not a significant covariate for birth weight, the spike at age 38 illustrates the inevitability of the biological clock.

The SDQ questionnaire assesses five scales: emotional problems, conduct problems, hyperactivity/inattention, peer relationship problems, and prosocial behavior. The first four scales are then combined into a total difficulties score. Only children aged 4-17 were included in the SDQ analysis. Figure 2.6 shows the distribution of SDQ scores in the DSR vs. normative data from the United States; no clinically meaningful differences were detected.

Each SDQ scale was adjusted for statistically significant covariates by taking the residuals from a multiple linear regression. The emotional problems score was adjusted for child sex (Figure 2.7A), child age (Figure 2.7B), twin status (Figure 2.7C), and mother employment status (Figure 2.7D). The conduct problems score was adjusted for child sex (Figure 2.8A), twin status (Figure 2.8B), and household income (C). The hyperactivity score was adjusted for child sex (Figure 2.9A), mother employment status (Figure 2.9B), mother sexual orientation (Figure 2.9C), and household type (Figure 2.9D). The peer problems score was adjusted for child sex (Figure 2.10A) and child age (Figure 2.10B). The prosocial behavior score was adjusted for child sex (Figure 2.11A) and twin status (Figure 2.11B). The total difficulties score was adjusted for child sex (Figure 2.12A), child age (Figure 2.12B), twin status (Figure 2.12C), and mother employment status (Figure 2.12D).

The EAS temperament survey measures four dispositions: emotionality, activity, sociability, and shyness. Figure 2.13 shows the distribution of temperament scores in the DSR. Children aged 1-17 were included in the temperament analysis.

Each disposition was adjusted for statistically significant covariates by taking the residuals from a multiple linear regression. Emotionality was adjusted for child age (Figure 2.14A), mother employment status (Figure 2.14B), and mother sexual orientation (Figure 2.14C). Activity was adjusted for child age (Figure 2.15A), twin status (Figure 2.15B), and household type (Figure 2.15C). Sociability was adjusted for child sex (Figure 2.16A), child age (Figure 2.16B), and mother education level (Figure 2.16C). Shyness was adjusted for child age (Figure 2.17A) and twin status (Figure 2.17B).

Table 2.2 Relationships in the donor family.

Parent/Parent Relationships	Assortative Mating Covariance	Examples in	n
Biological Mother/Non-Biological Parent			
Female Partner (Lesbian Couple)	$V_{PA} + V_{SH}$	I-4/I-5, I-6/I-7	308
Male Partner (Heterosexual Couple)	$V_{PA} + V_{SH}$	I-8/I-9, I-10/I-11	163
Donor/Biological Mother			
Single Mother	V_{PA}	I-1/I-2, I-1/I-3	466
Lesbian Couple		I-12/I-4, I-12/I-5, I-12/I-6	328
Heterosexual Couple		I-12/I-8, I-12/I-10	170
Donor/Non-Biological Parent			
Female Partner		I-12/I-4, I-12/I-5, I-12/I-7	324
Male Partner		I-12/I-9, I-12/I-11	171
Child/Parent Relationships	**Phenotypic Covariance**	**Examples in**	**n**
Biological Mother	$\frac{1}{2}V_A + V_{ES}$	I-2/II-1, I-3/II-2, I-3/II-3, I-4/II-4, etc.	1213
Donor	$\frac{1}{2}V_A$	I-1/II-1, I-1/II-2, I-12/II-3, I-12/II-4, etc.	1213
Non-Biological Parent	V_{ES}	I-5/II-4, I-4/II-5, I-9/II-8, I-9/II-9, etc.	649
Child/Child Relationships	**Phenotypic Covariance**	**Examples in**	**n**
Reared Apart			
Paternal Half-Siblings	$\frac{1}{4}V_A$	II-1/II-2, II-3/II-4, II-3/II-5, II-3/II-6, etc.	535
Reared Together			
Paternal Half-Siblings	$\frac{1}{4}V_A + V_{ES}$	II-4/II-5	2
Maternal Half-Siblings	$\frac{1}{4}V_A + V_{ES} + V_{EMaternal}$	II-2/II-3	24
Full-Siblings	$\frac{1}{2}V_A + \frac{1}{4}V_D + V_{ES} + V_{EMaternal}$	II-6/II-7	122
Dizygotic Twins	$\frac{1}{2}V_A + \frac{1}{4}V_D + V_{EC} + V_{EMaternal}$	II-8/II-9	70
Monozygotic Twins	$V_A + V_D + V_{EC} + V_{EMaternal}$	II-10/II-11	6

Table 2.3 Demographic and physical characteristics for parents.

Characteristic	Biological Mother	Donor	Non-Biological Parent	
			Male	Female
	(n = 945)	(n = 686)	(n = 163)	(n = 308)
Age - yrs	43.7 ± 6.7		47.3 ± 10.0	43.8 ± 7.4
Height - (in)	65.1 ± 2.7	72.2 ± 2.3	70.6 ± 3.2	65.6 ± 2.6
BMI	28.0 ± 6.6	23.9 ± 2.4	27.7 ± 4.9	27.5 ± 6.1
Eye Color				
Blue	296 (31.7)	297 (44.8)	63 (39.1)	106 (35.1)
Green	310 (33.2)	181 (27.3)	55 (34.2)	79 (26.2)
Brown	328 (35.1)	185 (27.9)	43 (26.7)	117 (38.7)
Hair Color				
Blonde	135 (14.5)	160 (24.2)	19 (11.9)	51 (17.2)
Brown	728 (78.3)	451 (68.1)	115 (71.9)	208 (70)
Black	39 (4.2)	29 (4.4)	19 (11.9)	26 (8.8)
Red	28 (3)	22 (3.3)	7 (4.4)	12 (4)
Race - no. (%)				
White	845 (89.9)	590 (88.5)	152 (93.3)	266 (86.6)
Black	12 (1.3)	13 (1.9)	3 (1.8)	3 (1)
Hispanic	39 (4.1)	28 (4.2)	2 (1.2)	21 (6.8)
Asian	12 (1.3)	9 (1.3)	2 (1.2)	4 (1.3)
Other	32 (3.4)	27 (4)	4 (2.5)	13 (4.2)
Religion - no. (%)				
Christian	601 (64.3)	440 (75.3)	114 (69.9)	204 (67.1)
Atheist	153 (16.4)	36 (6.2)	25 (15.3)	49 (16.1)
Jewish	119 (12.7)	46 (7.9)	15 (9.2)	19 (6.3)
Other	61 (6.5)	62 (10.6)	9 (5.5)	32 (10.5)
Education - no. (%)				
High School or GED	14 (1.5)	9 (1.4)	19 (11.7)	22 (7.2)
Technical/Trade School	24 (2.6)	8 (1.2)	10 (6.1)	11 (3.6)
Some College	92 (9.8)	94 (14.5)	33 (20.2)	46 (15)
College	284 (30.2)	283 (43.7)	43 (26.4)	113 (36.8)
Graduate/Professional School	527 (56)	254 (39.2)	58 (35.6)	115 (37.5)
Employment - no. (%)				
Full-Time Employed	656 (69.7)	243 (47.8)	137 (84)	244 (79.7)
Part-Time Employed	128 (13.6)	32 (6.3)	5 (3.1)	18 (5.9)
Full-Time Student	10 (1.1)	205 (40.4)	0 (0)	6 (2)
Homemaker	89 (9.5)	0 (0)	2 (1.2)	18 (5.9)
Other	58 (6.2)	28 (5.5)	19 (11.7)	20 (6.5)

Marital Status - no. (%)				
Never Married	365 (38.8)	405 (78.9)		
Married or Living as Married	436 (46.4)	90 (17.5)		
Other	139 (14.8)	18 (3.5)		
Sexual Orientation - no. (%)				
Heterosexual, Straight	532 (56.3)			
Homosexual, Gay	325 (34.4)			
Other	82 (8.7)			
Household Type - no. (%)				
Heterosexual-Couple Family	162 (17.1)			
Single-Mother Family	459 (48.6)			
Lesbian-Couple Family	312 (33)			
Household Income - no. (%)				
$19999 or less / yr	40 (4.4)			
$20000 - $39999 / yr	64 (7)			
$40000 - $59999 / yr	124 (13.5)			
$60000 - $99999 / yr	284 (30.9)			
$100000 - $199999 / yr	325 (35.4)			
$200000 or more / yr	81 (8.8)			

Table 2.4 Demographic and physical characteristics for children.

Characteristic	Child
	(n = 1213)
Sex	
Male	624 (52)
Female	577 (48)
Race	
White	1046 (87.7)
Black	25 (2.1)
Hispanic	58 (4.9)
Asian	26 (2.2)
Other	38 (3.2)
Eye Color	
Blue	589 (49.4)
Green	250 (21)
Brown	353 (29.6)
Birthweight	7.4 (1.1 - 11.9)
Twin	
Singleton	975 (82.9)
DZ	166 (14.1)
MZ	13 (1.1)

Triplet+	22 (1.9)
Temperament	
Emotionality	2.6 (1 - 5)
Activity	4 (1 - 5)
Sociability	3.6 (1 - 5)
Shyness	2.2 (1 - 5)
SDQ	
Emotional	1 (0 - 10)
Conduct	1 (0 - 9)
Hyperactivity	3 (0 - 10)
Peer	1 (0 - 9)
Prosocial	8 (0 - 10)
Total	6 (0 - 29)

Table 2.5 Child eye color given mother and donor eye color

Mother	Child	Donor		
		Blue	Green	Brown
Blue	Blue	199 (94.3)	65 (72.2)	22 (34.9)
	Green	12 (5.7)	22 (24.4)	10 (15.9)
	Brown	0 (0)	3 (3.3)	31 (49.2)
Green	Blue	99 (62.7)	57 (43.8)	23 (24.5)
	Green	53 (33.5)	55 (42.3)	23 (24.5)
	Brown	6 (3.8)	18 (13.8)	48 (51.1)
Brown	Blue	40 (32)	29 (25.7)	19 (13.6)
	Green	25 (20)	26 (23)	10 (7.1)
	Brown	60 (48)	58 (51.3)	111 (79.3)

Table 2.6 Child hair color given mother and donor hair color

Mother	Child	Donor			
		Blonde	Brown	Black	Red
Blonde	Blonde	49 (94.2)	77 (74)	2 (18.2)	0 (0)
	Brown	1 (1.9)	24 (23.1)	9 (81.8)	1 (20)
	Black	0 (0)	0 (0)	0 (0)	0 (0)
	Red	2 (3.8)	3 (2.9)	0 (0)	4 (80)
Brown	Blonde	113 (59.8)	167 (27.6)	6 (12.8)	16 (57.1)
	Brown	72 (38.1)	421 (69.5)	36 (76.6)	6 (21.4)
	Black	0 (0)	1 (0.2)	5 (10.6)	0 (0)
	Red	4 (2.1)	17 (2.8)	0 (0)	6 (21.4)
Black	Blonde	0 (0)	3 (10.3)	0 (0)	0 (0)
	Brown	4 (100)	22 (75.9)	2 (50)	2 (100)
	Black	0 (0)	4 (13.8)	2 (50)	0 (0)
	Red	0 (0)	0 (0)	0 (0)	0 (0)
Red	Blonde	5 (71.4)	9 (45)	0 (0)	0 (0)
	Brown	0 (0)	9 (45)	4 (100)	0 (0)
	Black	0 (0)	0 (0)	0 (0)	0 (0)
	Red	2 (28.6)	2 (10)	0 (0)	2 (100)

Table 2.7 Distribution of the number of children per mother

Number of Children per Mother	1	2	3	4	5
n (%)	722 (76.4)	187 (19.8)	28 (3)	7 (0.7)	1 (0.1)

Table 2.8 Distribution of number of children in each donor pedigree

Donor Pedigree Size	2	3	4	5	6	7	8	9	10
n	57	42	20	14	11	6	5	2	2

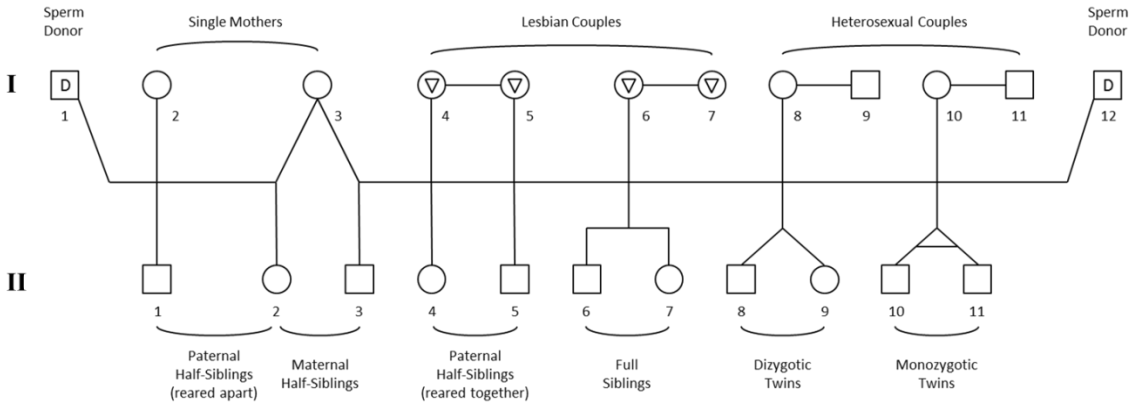

Figure 2.1 Pedigree displaying all gender and kinship arrangements contained in donor families ascertained from the Donor Sibling Registry (DSR).

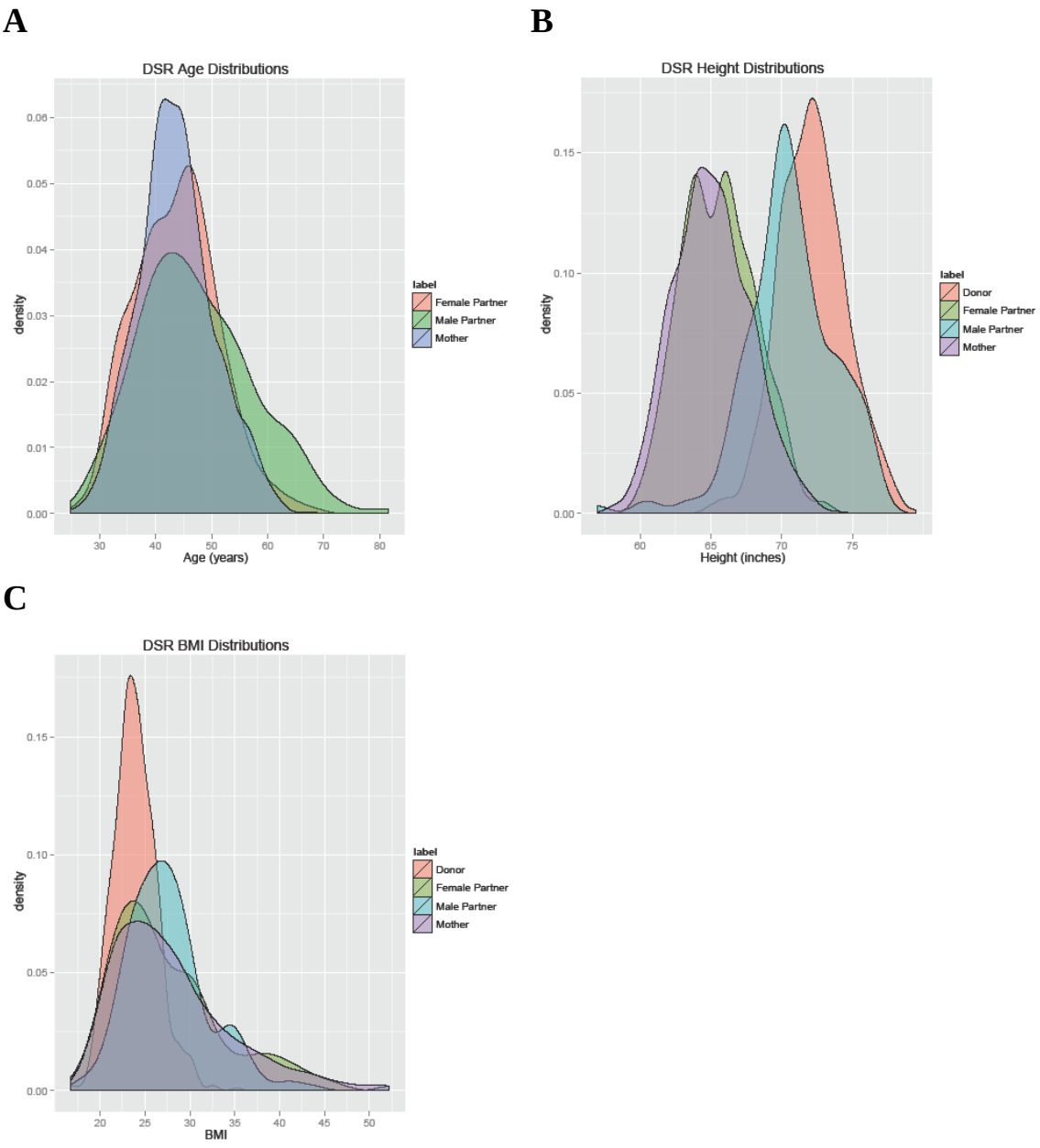

Figure 2.2 Distributions for parental phenotypes
(A) age (B) height (C) BMI

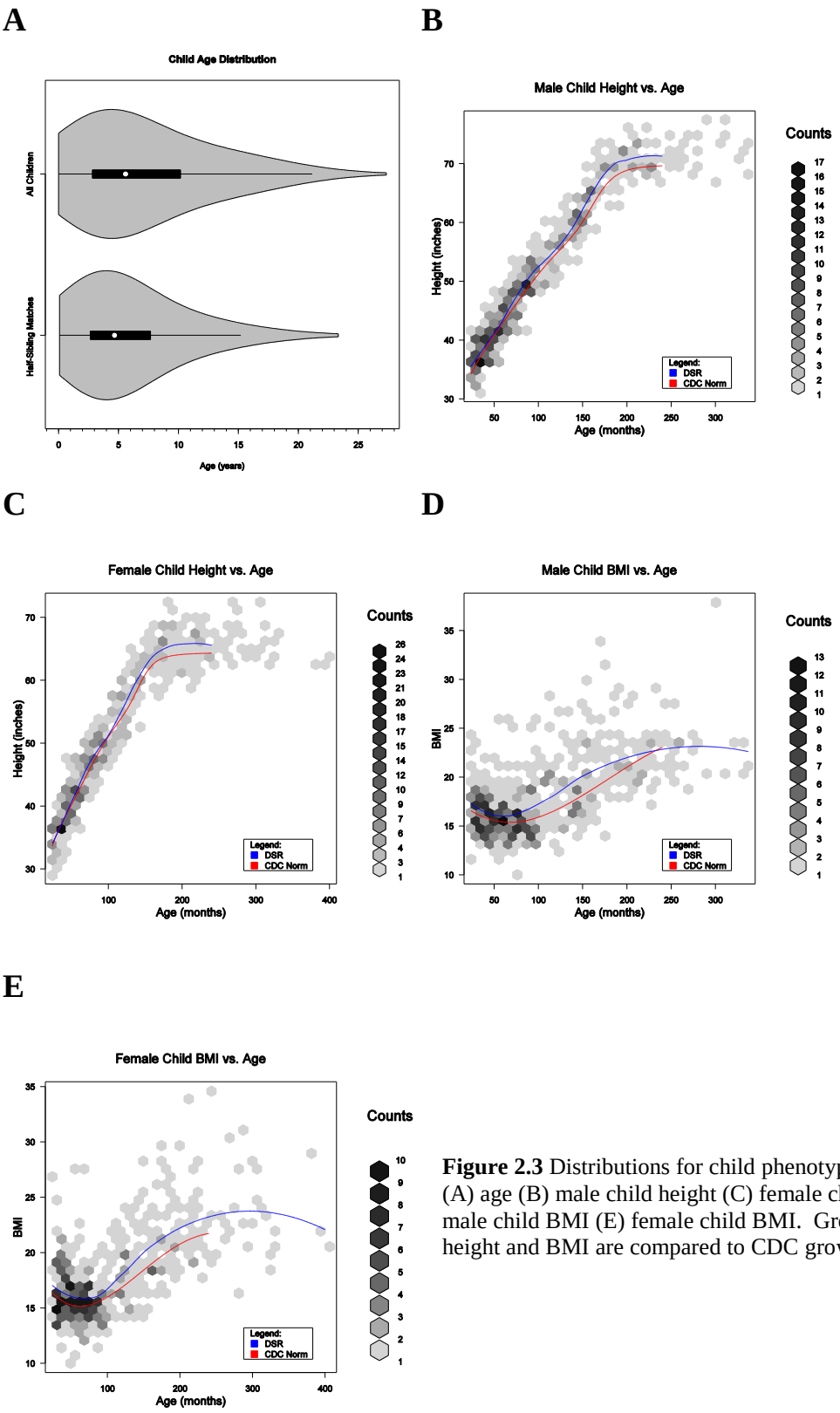

Figure 2.3 Distributions for child phenotypes (A) age (B) male child height (C) female child height (D) male child BMI (E) female child BMI. Growth curves for height and BMI are compared to CDC growth curves

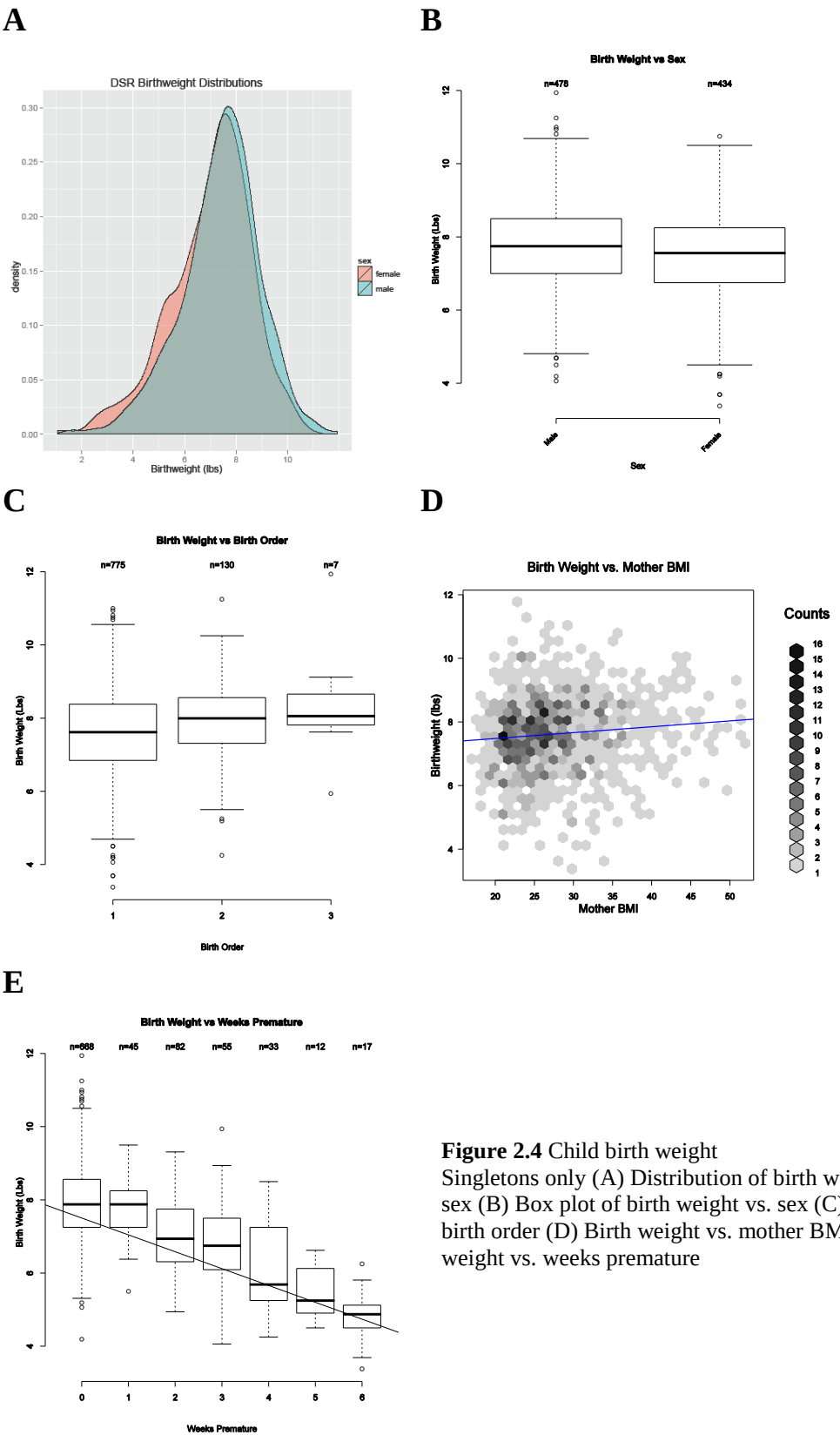

Figure 2.4 Child birth weight
Singletons only (A) Distribution of birth weight stratified by sex (B) Box plot of birth weight vs. sex (C) Birth weight vs. birth order (D) Birth weight vs. mother BMI (E) Birth weight vs. weeks premature

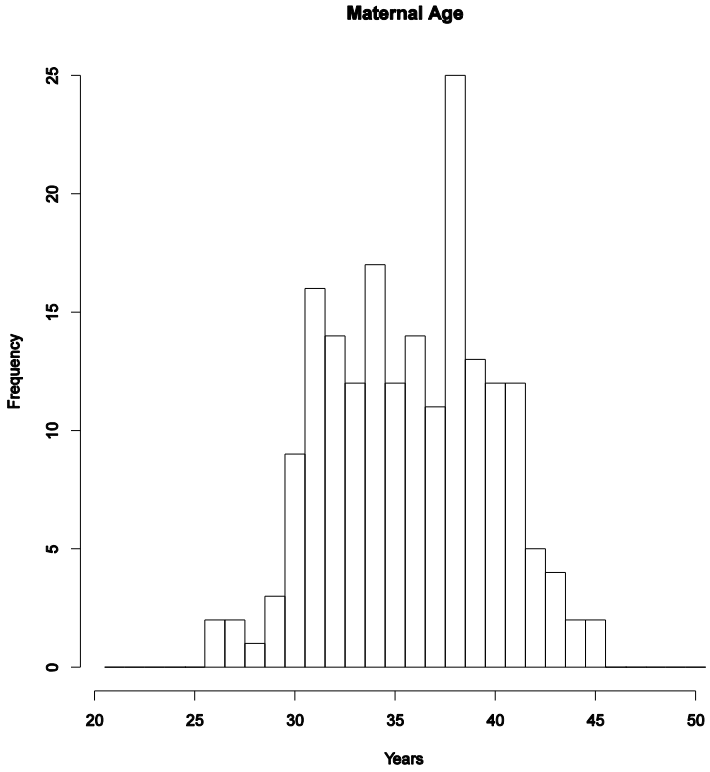

Figure 2.5 Maternal age at time of birth

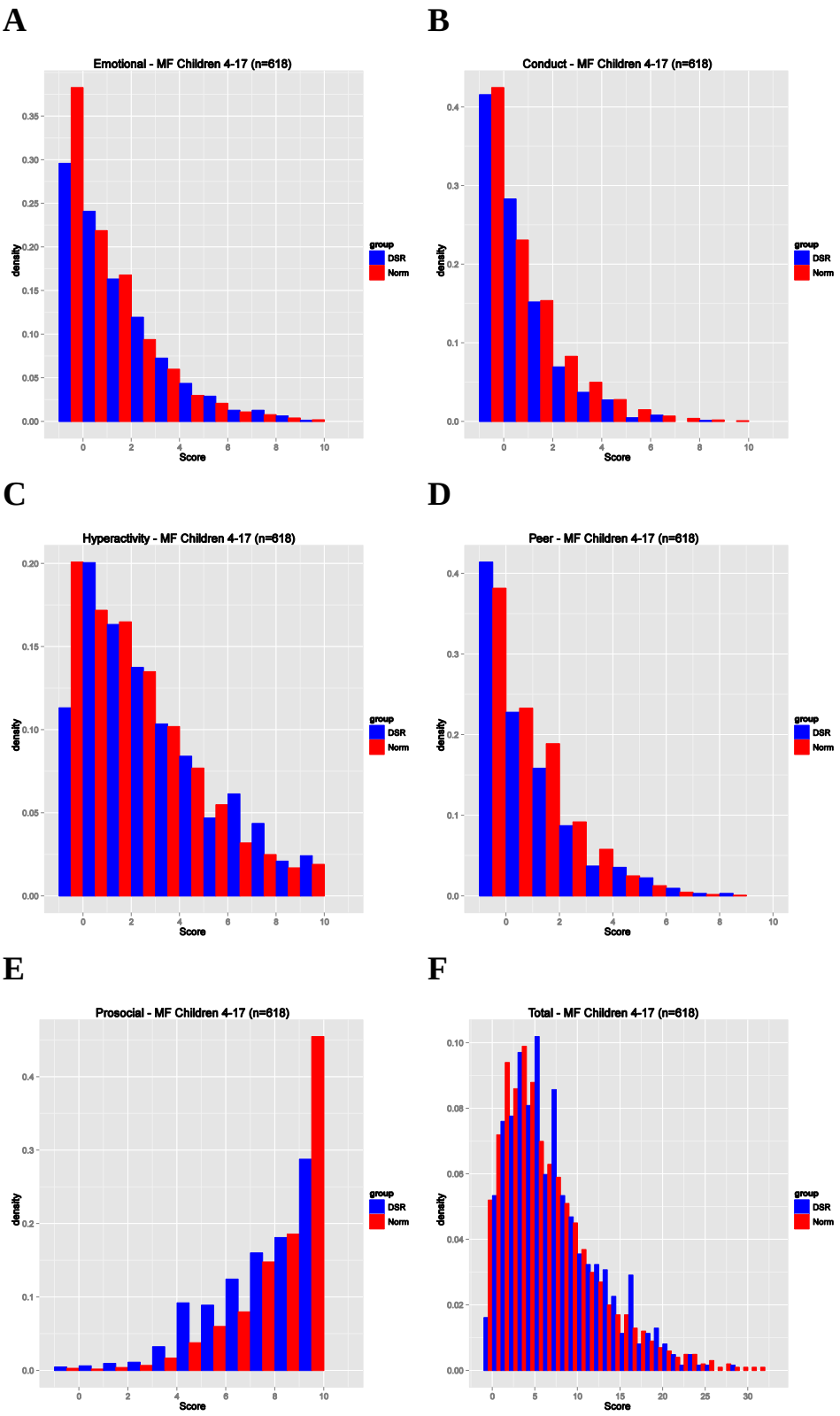

Figure 2.6 Distribution of SDQ scores in the DSR vs. US norms.
(A) Emotional problems (B) Conduct problems (C) Hyperactivity (D) Peer problems (E) Prosocial (F) Total score

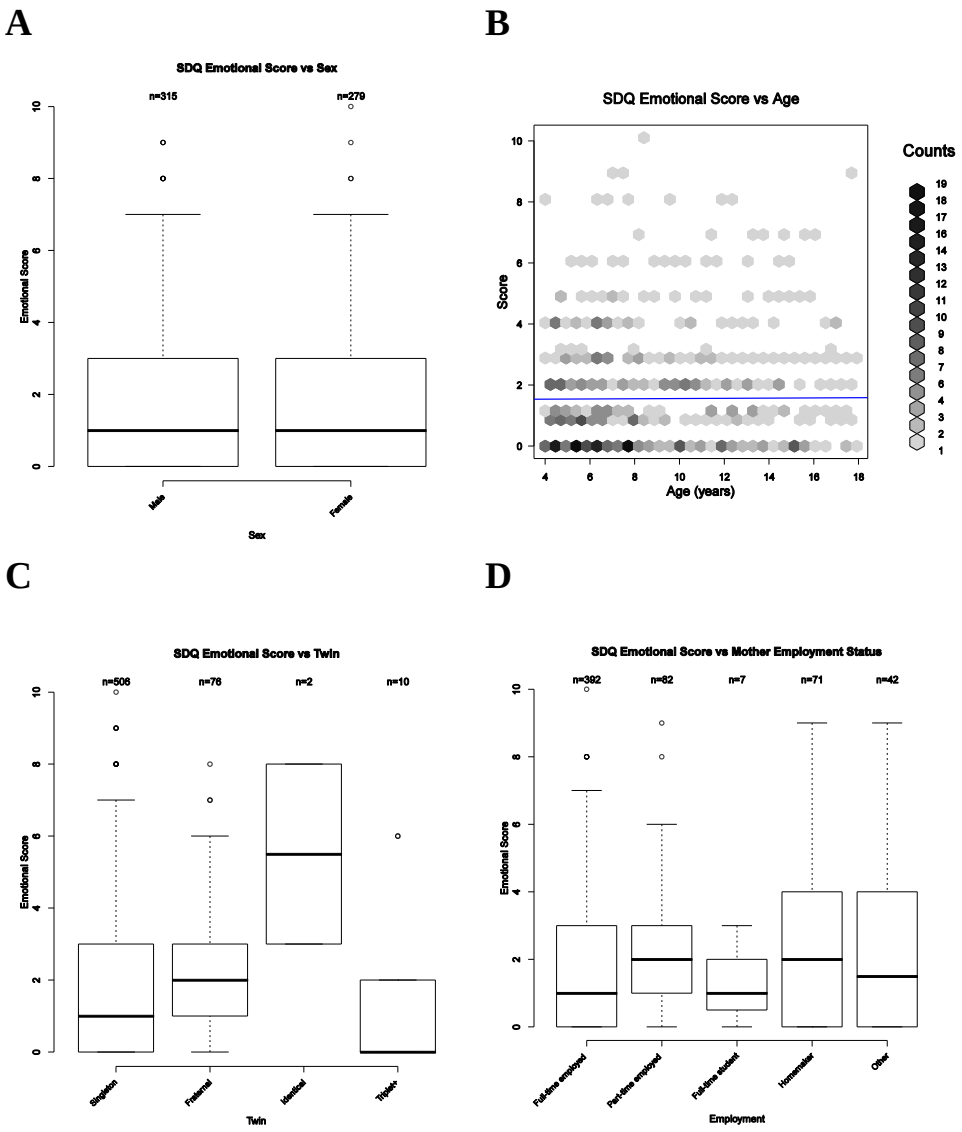

Figure 2.7 SDQ emotional problems subscale vs. covariates
(A) sex (B) age (C) twin status (D) mother employment status

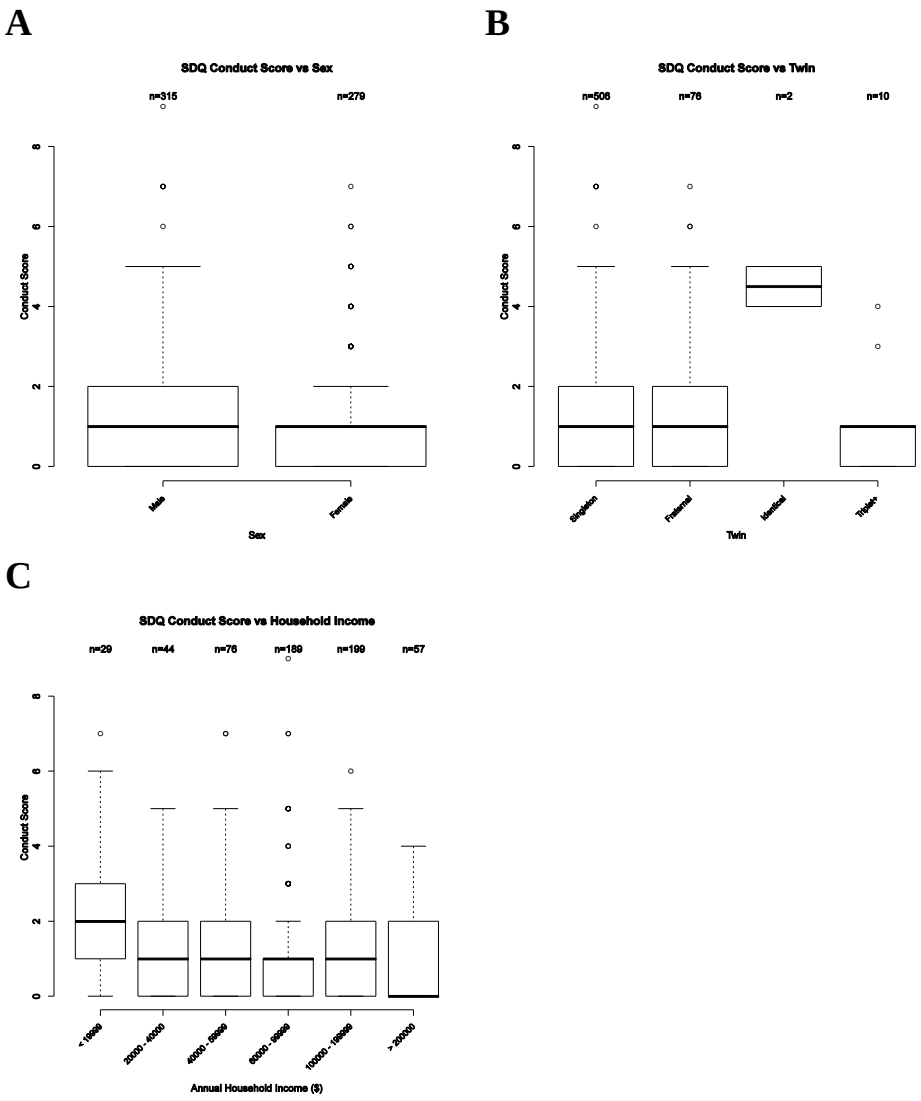

Figure 2.8 SDQ conduct problems subscale vs. covariates
(A) sex (B) twin status (C) household income

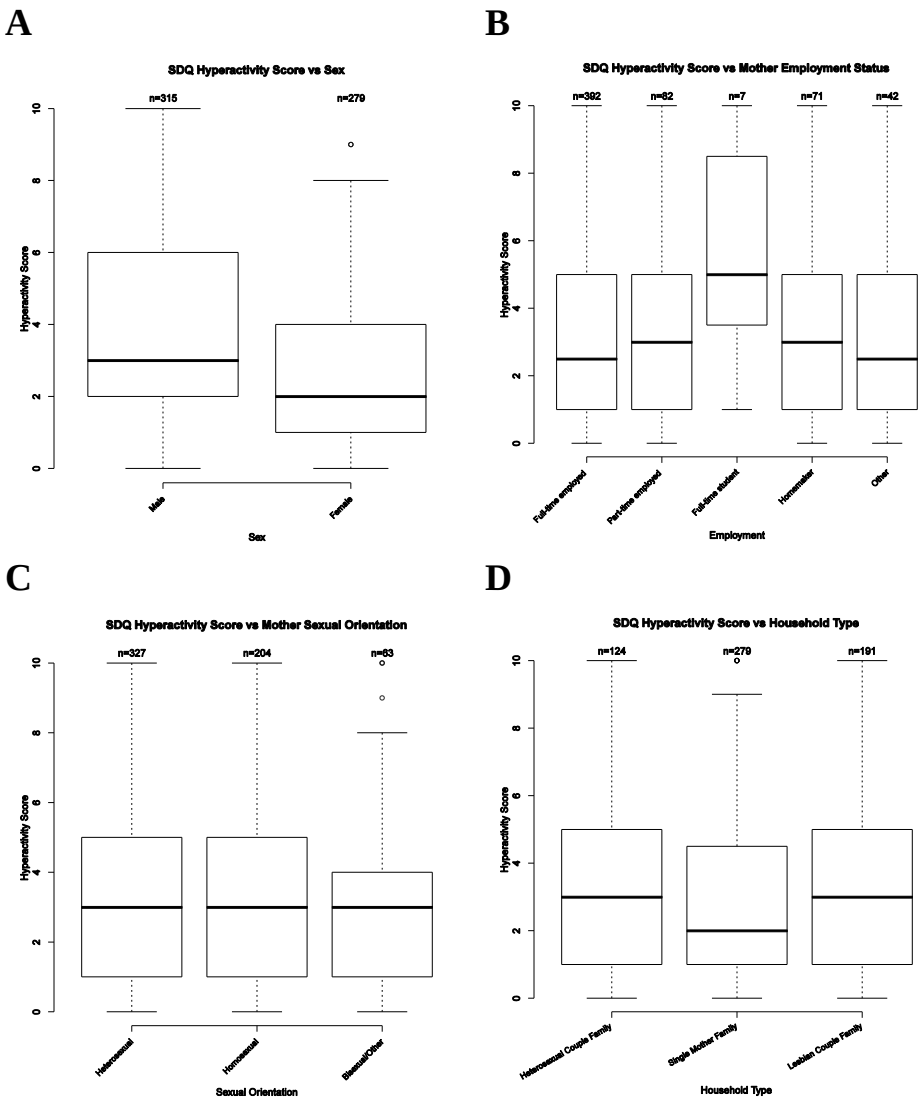

Figure 2.9 SDQ hyperactivity subscale vs. covariates
(A) sex (B) mother employment status (C) mother sexual orientation (D) household type

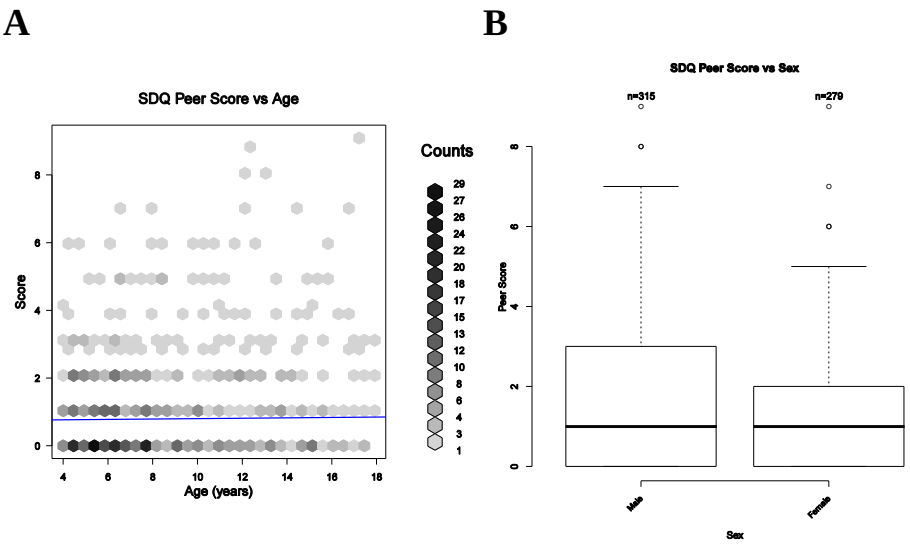

Figure 2.10 SDQ peer problems subscale vs. covariates
(A) age (B) sex

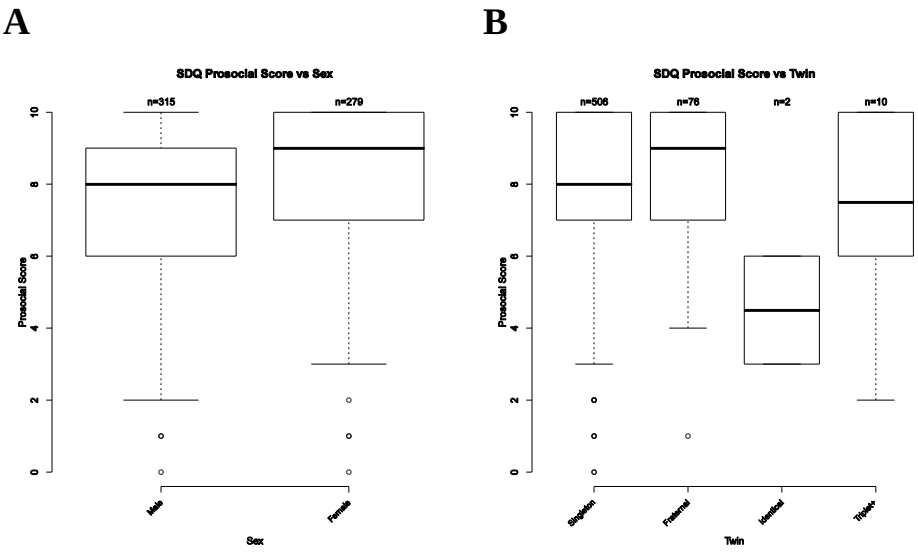

Figure 2.11 SDQ prosocial subscale vs. covariates
(A) sex (B) twin status

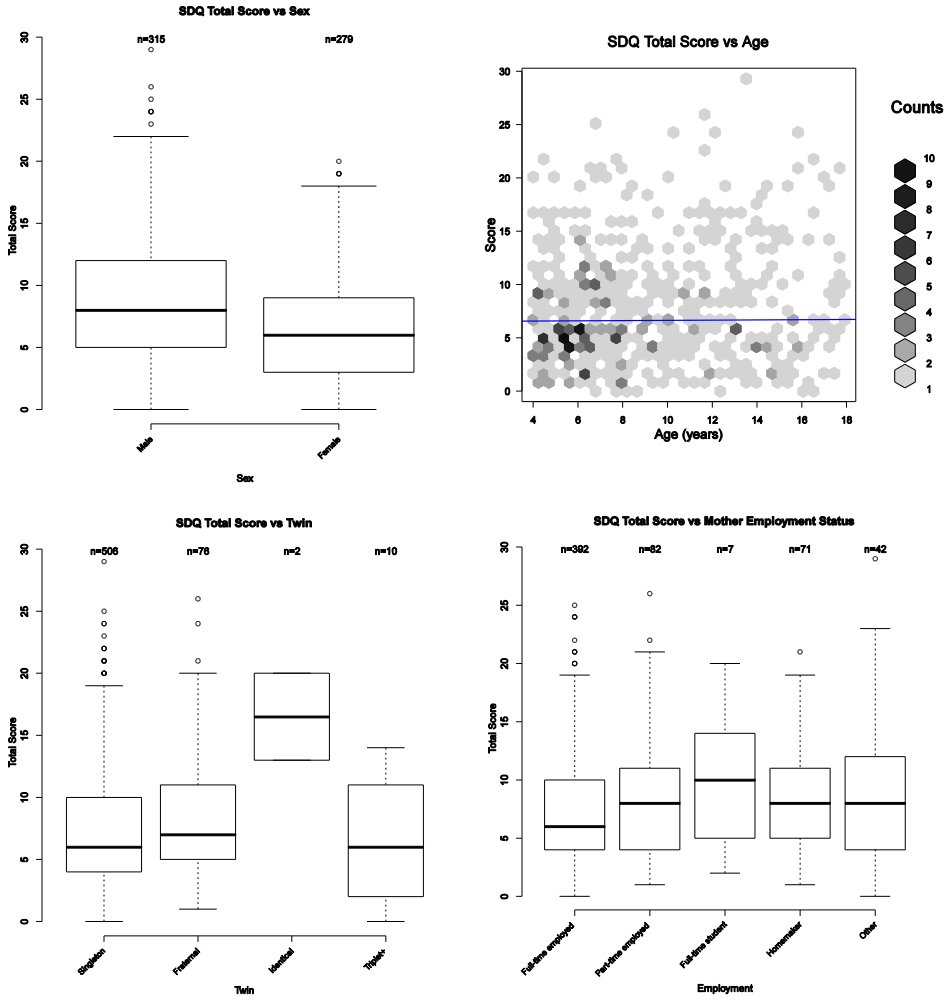

Figure 2.12 SDQ total score vs. covariates
(A) sex (B) age (C) twin status (D) mother employment status

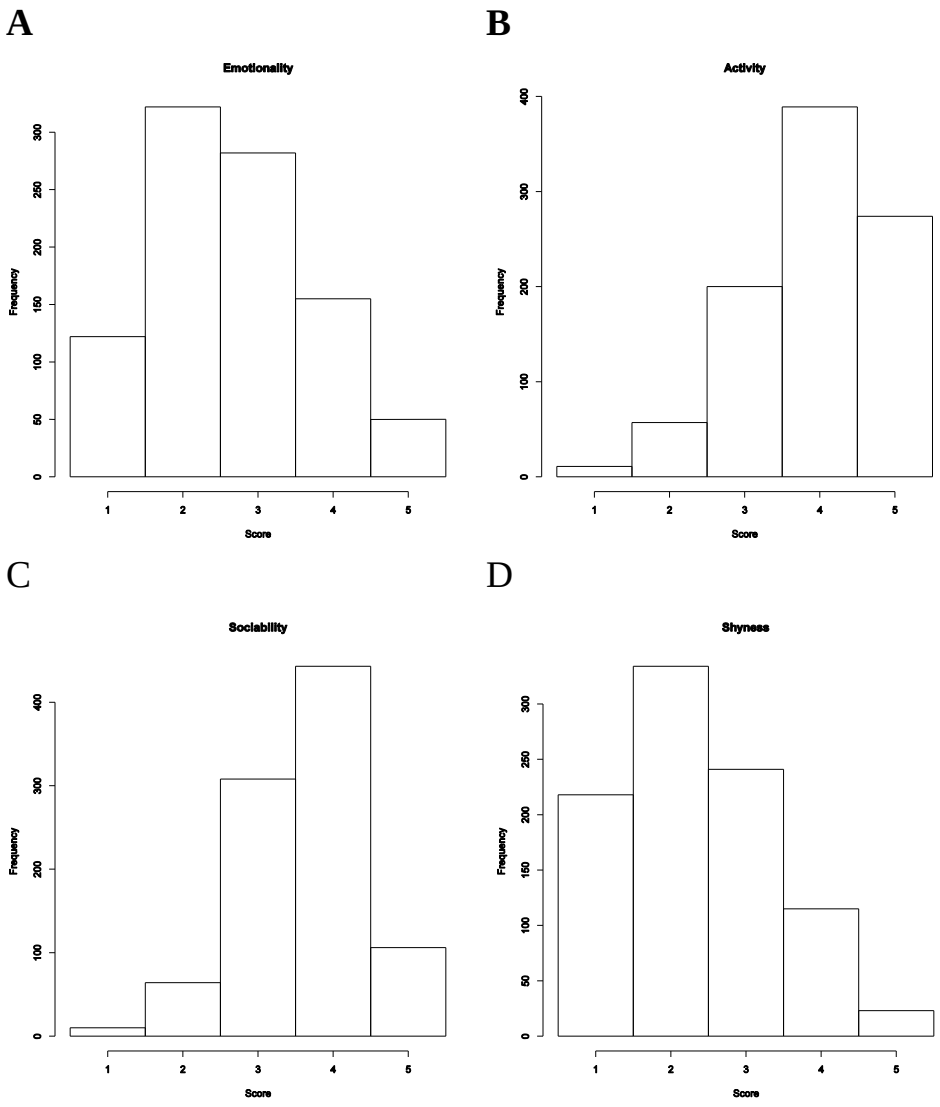

Figure 2.13 Distribution of EAS temperament scores in the DSR
(A) Emotionality (B) Activity (C) Sociability (D) Shyness

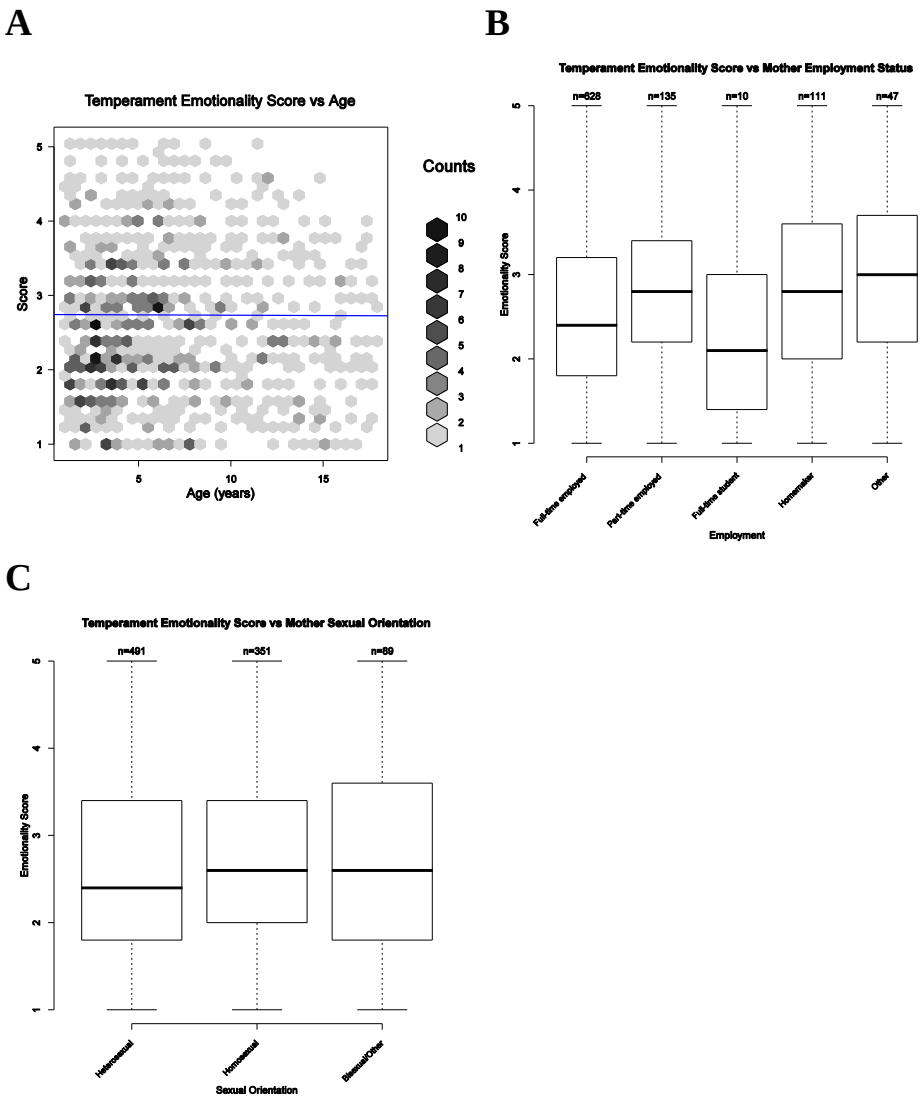

Figure 2.14 EAS emotionality score vs. covariates
(A) age (B) mother employment status (C) mother sexual orientation

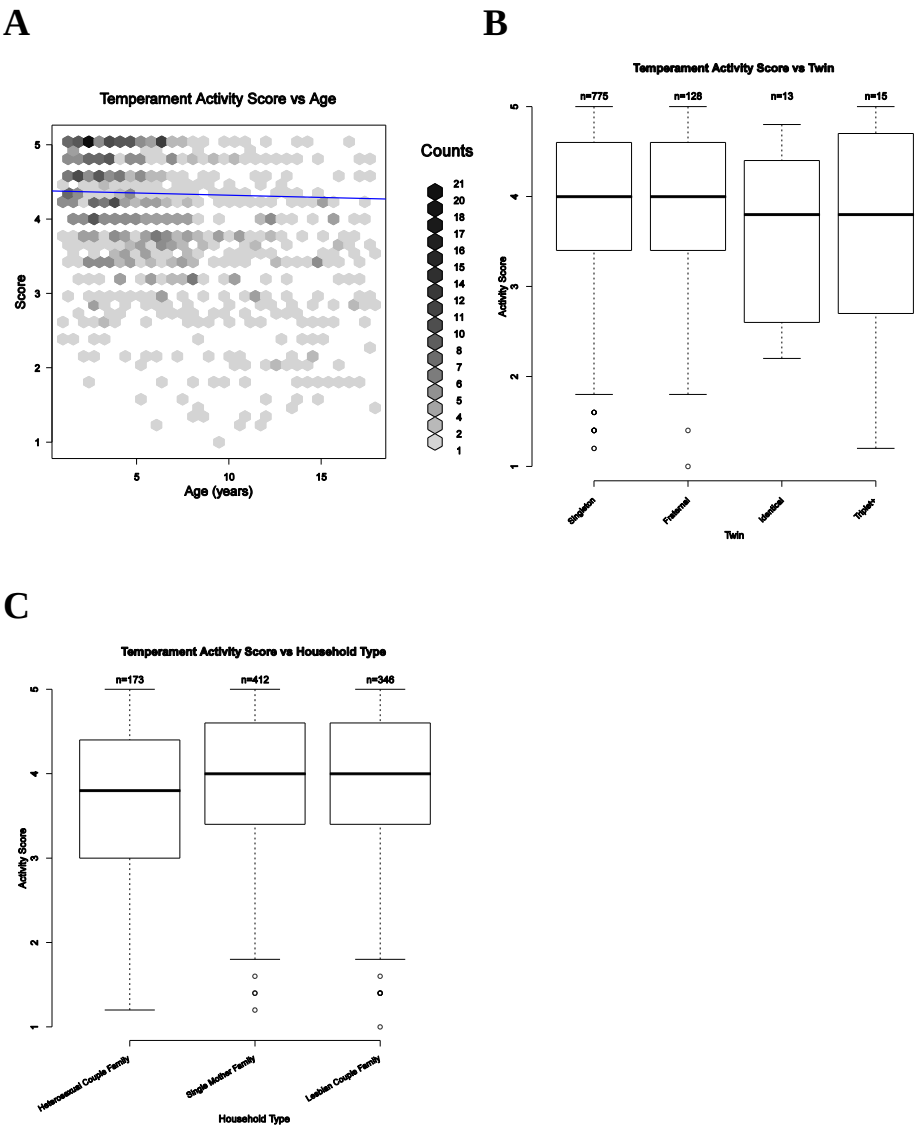

Figure 2.15 EAS activity score vs. covariates
(A) age (B) twin status (C) household type

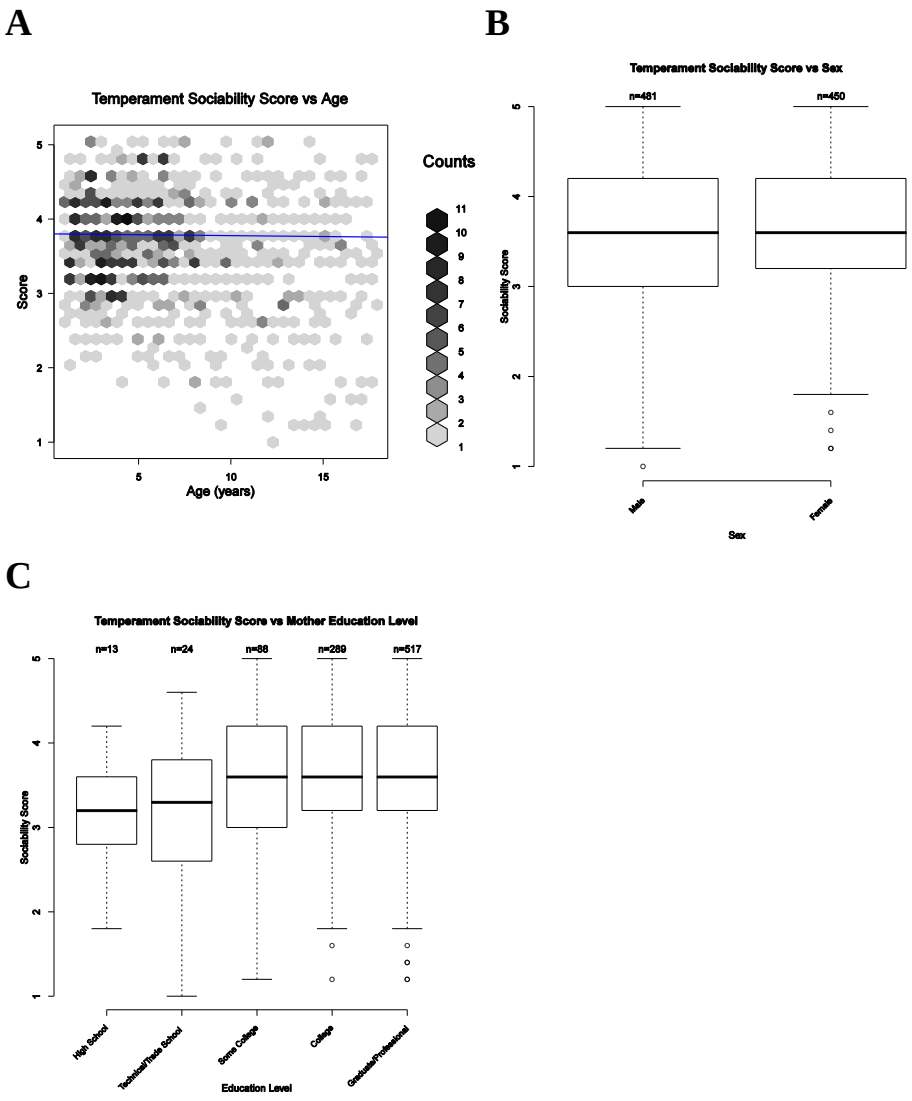

Figure 2.16 EAS sociability score vs. covariates
(A) age (B) sex (C) mother education level

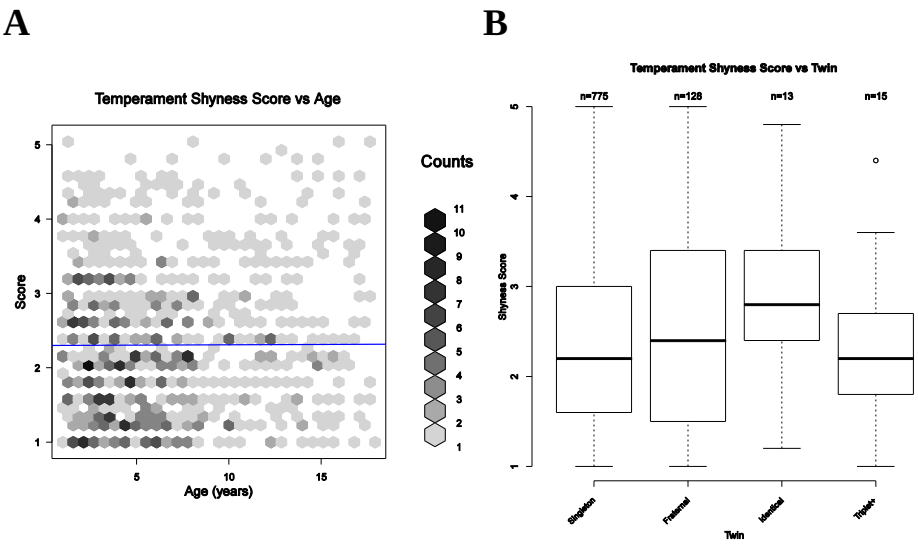

Figure 2.17 EAS shyness score vs. covariates
(A) age (B) twin status

2.4 Discussion

As of April 28, 2013, the DSR has grown to 39038 members and 10018 half-sibling matches. Donor families continue to expand in size and number as the use of assisted reproductive technology increases (*19*), making them a viable basis for quantitative genetic studies.

2.5 References

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3 Mate Choice Preferences, Phenotypic Assortment, and the Response to Selection in the Donor Sibling Registry

3.1 Introduction

Asymmetry in parental investment leads to females being the choosier sex in many species, including humans (*1*). Numerous surveys have been conducted to determine which traits women value when selecting a mate, but they all suffer from the same fault: women's stated preferences may not be reflected in their mate choices (*2-5*). Stated preferences disagree with actual choices for a number of reasons, including lack of available partners, unstable preferences, poor ability to verbalize internal thoughts, demand effects in which a person provides the response he thinks the questioner wants to hear, and masking true preferences to deceive competitors, potential mates, and ourselves (*3*). The only way to determine which traits undergo active selection is to examine real mating outcomes.

Assortative mating is the most common deviation from random mating in Western societies (*6-9*). This tendency to mate "like with like" is measured as a positive phenotypic correlation between partners. It is caused by phenotypic assortment (actively selecting a mate with similar observable characteristics) and/or social homogamy (mates passively coming from similar background environments). Assortative mating is easy to measure, yet it remains difficult to attribute its causes because pair formation is influenced by partner availability, intrasexual competition, mutual mate choice, and environmental factors (*10*).

Anonymous sperm donation eliminates these confounding processes to reveal a clear link between female mate choice preferences and mate selection. Mothers freely

choose a donor from a sperm bank, particularly single mothers who express their preferences without input from a partner. Thus, the single mother/donor correlation is the first direct measure of phenotypic assortment in humans, standing in contrast to previous indirect methods based on twins and their spouses (*5*, *11*-*13*). Any heterosexual mother/male partner or lesbian mother/female partner correlation in excess of the single mother/donor correlation is attributable to social homogamy (Table 2.2).

We used these parental relationships in the DSR to examine female mate choice preferences and determine which traits undergo active selection in humans. We then added donor-conceived children to our analysis and evaluated the response to selection as a realized heritability.

3.2 Materials and Methods

Assortative mating was measured using Cohen's Kappa for the categorical variables of race/ethnicity, education level, eye color, hair color, employment status and religion. Assortative mating was measured using Pearson's correlation coefficient for the continuous variables of height and BMI.

Pairwise associations between mother, donor, partner, and factor importance for eye color, religion, and race/ethnicity were evaluated using a log-linear regression model (*14*). Consider an $I \times J$ contingency table that cross-classifies n subjects with factor levels $i = 1,...,I$, $j = 1,...,J$, and cell counts u_{ij} , The log-linear regression model is given by

$$\log u_{ij} = \lambda + \lambda_i^X + \lambda_j^Y + \lambda_{ij}^{XY}$$

where λ_i^X are the row effects, λ_j^Y are the column effects, and λ_{ij}^{XY} are the pairwise association terms. The λ_{ij}^{XY} association terms (the log-linear regression coefficients for the interaction terms in Table 3.4, Table 3.5, and Table 3.6) can be interpreted as log odds ratios.

For example, the log-linear regression coefficient for the interaction between heterosexual couple donorBLU:partnerBLU eye color was 1.54 (Table 3.4). The marginal two-way contingency table between donor eye color and male partner eye color is shown in Table 3.1. In such an $I \times J$ table, one of λ_i^X variables and one of the λ_j^Y variables are redundant (analogous to needing one fewer indicator variable than the number of factor levels in a multiple regression). We specified the parameters so that "majority" variables were redundant. For race/ethnicity, since the majority of our sample was white and the majority of mothers said race/ethnicity was an important factor in donor choice, we made "white" and "factor important yes" the majority redundant variables. For eye color, the majority redundant variables were "brown" and "factor important yes". For religion, the majority redundant variables were "Christian" and "factor important no." Interaction terms compare the listed factor variables with the majority redundant variables.

Returning to our example, the donorBLU: partnerBLU interaction term compares donor blue eyes/partner blue eyes with majority redundant donor brown eyes/partner brown eyes. This reduces the contingency table to the table shown in Table 3.2. Calculating the log odds ratio from this table, $\ln(\frac{16*41}{10*14}) = 1.54$, which was the log-linear regression coefficient. Heterosexual couples were 4.66 times more likely to choose

a blue-eyed donor if the partner had blue eyes than if the partner had brown eyes. Log-odds ratios that were large in magnitude but not statistically significant indicate low counts for that particular combination in the contingency table.

It can be misleading to report main effects when interaction terms present, so we restricted our attention to interpreting the highest order terms. When interaction terms are not present, the main effect terms can be interpreted as the log odds of one variable compared to the majority redundant variable.

Table 3.1 Marginal two-way contingency table between donor eye color and male partner eye color

	Donor		
Partner	BRO	GR	BLU
BRO	16	8	14
GR	13	22	19
BLU	10	11	41

Table 3.2 Reduced marginal two-way contingency table between donor eye color and male partner eye color for brown and blue eyes only

	Donor	
Partner	BRO	BLU
BRO	16	14
BLU	10	41

3.3 Results

3.3.1 Female Mate Choice Preferences

We assessed female mate choice preferences by asking mothers to rate the importance of different factors in choosing their donor. The majority of mothers said race/ethnicity, education level, height, body mass index (BMI), eye color, and hair color were important, but employment status and religion were not (Table 3.3). Given the donor's wholly genetic contribution, these ratings can be interpreted as reflecting mothers' beliefs about heritability.

3.3.2 Phenotypic Assortment and Social Homogamy

3.3.2.1 Height and Eye Color

We used phenotypic assortment to determine which traits underwent active selection. For height and eye color, the single mother/donor correlations were greater than the heterosexual mother/male partner and lesbian mother/female partner correlations (Table 3.3). This suggests mutual mate choice limits phenotypic assortment in a monogamous mating system, as compared to unconstrained female choice of donor (*15*). A log-linear regression analysis of eye color shows single mothers preferentially selected donors with recessive blue eyes (Table 3.4, Figure 3.1). Thus, mothers actively selected for height and eye color in accordance with their stated preferences.

Examining the remaining parental correlations for height and eye color, the positive male partner/donor and female partner/donor correlations (Table 3.3) indicate biological mothers in heterosexual and lesbian couples chose a donor to match their partner in a transitive form of phenotypic assortment. Log-linear regression results show heterosexual and lesbian couples matched partner and donor eye colors (Table 3.4, Figure 3.2, Figure 3.3). The lesbian mother/donor correlations were significant, but the heterosexual mother/donor correlations were not. Lesbian couples could choose a donor to match either parent because they do not contend with the same paternity issues facing heterosexual couples (*16, 17*).

3.3.2.2 Education Level and BMI

For education level and BMI, the heterosexual mother/male partner (education level only) and lesbian mother/female partner correlations were significant, but the single mother/donor correlations were not (Table 3.3). Assortative mating for education level

and BMI was therefore driven by passive social homogamy, contrary to expectations from mothers' stated preferences. The single mother/donor correlations may have been influenced by a ceiling effect in which the majority of donors were college-educated and had healthy BMIs (Table 2.3).

3.3.2.3 Religion

For religion, the heterosexual mother/male partner and lesbian mother/female partner correlations were greater than the single mother/donor correlation (Table 3.3). All three correlations were significant, signaling the influence of both phenotypic assortment and social homogamy. Phenotypic assortment was driven by the association of atheist/atheist and Jewish/Jewish pairings between single mothers and donors (Table 3.5, Figure 3.4). Social homogamy was driven by atheist/atheist, Jewish/Jewish, and other/other pairings between mothers and their partners (Table 3.5, Figure 3.5, Figure 3.6). Judaism's dual role as a religion and an ethnicity could partially explain why there was phenotypic assortment for religion despite it not being an important factor in donor choice.

3.3.2.4 Race/Ethnicity

For race/ethnicity, our sample was approximately 90% white (Table 2.3). Heterosexual couples (Figure 3.7) and single mothers (Figure 3.9) were less diverse then lesbian couples (Figure 3.8). Lesbian couples demonstrated concordance for race/ethnicity via statistically significant correlations (Table 3.3) and associations (Table 3.6) between lesbian mother/female partner, lesbian mother/donor, and female partner/donor. The single mother/donor correlation was statistically significant (Table 3.3), but no log-linear regression associations were found between single mother and

donor due to small non-white sample size (Table 3.6). The heterosexual mother/male partner and heterosexual mother/donor correlations were not significant because the small number of non-white mothers in heterosexual couples almost exclusively had white male partners and they all chose white donors (Figure 3.7). This idiosyncratic pattern and lack of diversity precludes a general inference about selection for race/ethnicity.

3.3.2.5 Hair Color, and Employment Status

We did not observe any assortative mating for hair color or employment status between single mother/donor, heterosexual mother/male partner, or lesbian mother/female partner. Lesbian couples matched partner/donor hair color, while heterosexual couples did not (Table 3.3).

3.3.3 Response to Selection

Having established which traits underwent selection, we examined the effect of selection for height. The response to selection, R, is defined as the difference between the mean height of the offspring of the selected parents and the mean height of the population. Children in the DSR were taller than the median growth curve by $R = 1.23$ inches, averaged across all ages for both sexes (Figure 2.3B). The selection differential, S, measures the strength of selection and is defined as the difference between the mean height of the selected parents and the mean height of the population. Biological mothers were taller than the median Caucasian female by 0.7 inches and selected donors were taller than the median Caucasian male by 2 inches, resulting in a selection differential of $S = 1.35$ inches (Table 2.3) (*18*). The response to selection is related to the selection differential by the realized heritability $h^2 = R / S$. Assisted reproduction created a rare natural experiment to study artificial selection for height in humans; the effect of

selection as described by the realized heritability $h^2 = 0.91$ was consistent with the heritability of adult height calculated using traditional methods (*19*).

Table 3.3. Parent-parent relationship correlations for characteristics important in donor choice and partner selection.
Correlation for categorical variables was measured by Cohen's kappa (k). Correlation for continuous variables was measured by Pearson correlation coefficient (r).

	Mothers Rating Factor as Important (%)	Single Mother/Donor		Heterosexual Mother/Male Partner		Lesbian Mother/Female Partner		Heterosexual Mother/Donor		Lesbian Mother/Donor		Male Partner/Donor		Female Partner/Donor	
Physical Traits			n		n		n		n		n		n		n
Race/Ethnicity (k)	89.2	0.21 (0.01,0.41)	451	0.06 (-0.35,0.47)	163	0.26 (0.08,0.43)	307	-0.04 (-0.50,0.43)	163	0.22 (0.06,0.38)	322	0.29 (-0.08,0.66)	164	0.30 (0.13,0.46)	317
Height (r)	78.4	0.22 (0.11,0.32)	348	0.06 (-0.10,0.21)	160	0.14 (0.02,0.24)	303	0.02 (-0.15,0.19)	137	0.14 (0.02,0.26)	254	0.26 (0.09,0.41)	138	0.18 (0.05,0.29)	253
BMI (r)	60.8	0.07 (-0.04,0.18)	320	0.12 (-0.04,0.27)	157	0.33 (0.23,0.43)	298	0 (-0.17.0.17)	129	0.05 (-0.08,0.18)	231	0.13 (-0.04,0.30)	127	0.09 (-0.04,0.22)	228
Eye Color (k)	52.9	0.14 (0.07,0.20)	460	0.07 (-0.04,0.19)	161	-0.01 (-0.09,0.08)	302	0.05 (-0.06,0.17)	160	0.18 (0.10,0.26)	319	0.26 (0.14,0.38)	161	0.17 (0.08,0.25)	313
Hair Color (k)	52.7	0.07 (-0.03,0.17)	458	0.11 (-0.07.0.28)	160	-0.03 (-0.17,0.11)	297	0.04 (-0.17,0.24)	160	0.05 (-0.07,0.18)	317	0.07 (-0.11,0.25)	161	0.17 (0.06,0.29)	308
Non-Physical Traits															
Education (k)	80.9	0.04 (-0.03,0.12)	452	0.16 (0.05,0.26)	163	0.17 (0.09,0.26)	307	0.03 (-0.09,0.14)	156	0.10 (0.02,0.19)	317	0.05 (-0.06,0.15)	157	0.05 (-0.06,0.15)	312
Employment (k)	20	0.01 (-0.07,0.10)	383	-0.07 (-0.19,0.05)	163	-0.08 (-0.21,0.06)	306	0 (-0.09,0.10)	131	0 (-0.10,0.09)	258	0.03 (-0.12,0.18)	132	0.02 (-0.08,0.12)	254
Religion (k)	15.1	0.17 (0.07,0.26)	428	0.56 (0.43,0.70)	163	0.34 (0.24,0.44)	303	0.27 (0.10,0.44)	143	0.03 (-0.09,0.15)	283	0.27 (0.10,0.44)	144	0.15 (0.02,0.27)	280

Table 3.4 Log-linear regression coefficients for eye color.
Significant interaction associations are highlighted in gray. Terms not included in the regression model are blocked out in black. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. GR = green eyes, BLU = blue eyes, impY = eye color was an important factor in donor choice.

	Single Mother	Lesbian Couple	Heterosexual Couple
(Intercept)	3.56***	2.86***	1.19**
motherGR	-0.44	-0.84**	0.05
motherBLU	-0.86**	-0.95**	-1.1*
donorGR	-0.02	-0.96**	-2.09**
donorBLU	-0.67**	-1.38***	-0.66
impY	-0.95***	-1.03***	-0.28
donorGR:motherGR	0.31	0.82*	0.89
donorBLU:motherGR	0.85**	0.76	-0.56
donorGR:motherBLU	0.02	0.15	1.34*
donorBLU:motherBLU	1.22***	1**	0.23
donorGR:impY	0.37	0.83*	0.92
donorBLU:impY	1.05***	1.67***	1.04*
impY:motherGR	0.34	-0.22	0.32
impY:motherBLU	0.64*	0.5	0.99*
partnerGR		-1.08***	-0.21
partnerBLU		-0.65*	-0.47
donorGR:partnerGR		1.17**	1.22*
donorBLU:partnerGR		0.77*	0.51
donorGR:partnerBLU		0.51	0.79
donorBLU:partnerBLU		0.99**	1.54**

Table 3.5 Log-linear regression coefficients for religion.
Significant interaction associations are highlighted in gray. Terms not included in the regression model are blocked out in black. * p < 0.05, ** p < 0.01, *** p < 0.001. A = atheist, J = Jewish, O = Other, impY = religion was an important factor in donor choice.

	Single Mother	Lesbian Couple	Heterosexual Couple
(Intercept)	5.11***	4.62***	3.98***
motherA	-1.26***	-1.83***	-3.19***
motherJ	-1.73***	-2.56***	-3.22***
motherO	-2.81***	-2.32***	-3.87***
donorA	-2.36***	-2.9***	-2.5***
donorJ	-3.17***	-3.65***	-4.51***
donorO	-2.35***	-1.99***	-2.04***
impY	-1.41***	-2.51***	-1.3***
partnerA		-2.17***	-2.39***
partnerJ		-3.52***	-3.82***
partnerO		-2.59***	-2.8***
motherA:donorA	1.15**		-0.05
motherJ:donorA	0.14		0.38
motherO:donorA	0.05		-17.85
motherA:donorJ	0.44		1.67
motherJ:donorJ	1.73***		3.69***
motherO:donorJ	0.87		2.88*
motherA:donorO	-0.42		0.6
motherJ:donorO	1.08*		-19.27
motherO:donorO	0.05		1.7
motherA:impY	-1.05*	-0.47	
motherJ:impY	0.16	1.27*	
motherO:impY	-18.67	-0.4	
donorA:impY	-0.17	-0.17	-0.43
donorJ:impY	1.27**	2.08***	2.07**
donorO:impY	-1.17	0.75	-0.84
motherA:partnerA		2.14***	3.92***
motherJ:partnerA		0.25	1.88*
motherO:partnerA		0.27	-17.55
motherA:partnerJ		0.11	-17.43
motherJ:partnerJ		2.19***	4.33***
motherO:partnerJ		0.59	-17.33
motherA:partnerO		0.34	-17.61
motherJ:partnerO		-0.34	-17.68
motherO:partnerO		2.11***	3.14**
donorA:partnerA		0.83	

donorJ:partnerA		0.89	
donorO:partnerA		-0.86	
donorA:partnerJ		0.97	
donorJ:partnerJ		2.67***	
donorO:partnerJ		-0.09	
donorA:partnerO		0.77	
donorJ:partnerO		1.12	
donorO:partnerO		1.16*	
partnerA:impY			-20.64
partnerJ:impY			0.38
partnerO:impY			-19.41

Table 3.6 Log-linear regression coefficients for race/ethnicity.
Significant interaction associations are highlighted in gray. Terms not included in the regression model are blocked out in black. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. B = black, H = Hispanic, A = Asian, O = other, impN = race/ethnicity was not an important factor in donor choice.

	Single Mother	Lesbian Couple	Heterosexual Couple
(Intercept)	5.79***	5.23***	4.84***
motherB	-4.47***	-4.37***	-4.98***
motherH	-3.55***	-2.76***	-4.98***
motherA	-4.25***	-4.37***	-4.98***
motherO	-4.06***	-3.38***	-3.19***
donorB	-4.25***	-3.96***	-5.01***
donorH	-3.46***	-3.35***	-22.14
donorA	-5.86***	-5.06***	-4.32***
donorO	-4.07***	-2.95***	-4.32***
impN	-2.2***	-2.02***	-3.05***
donorB:impN	-16.85	-17.5	
donorH:impN	-0.27	0.98	
donorA:impN	2.82*	1.33	
donorO:impN	2.12***	-18.48	
motherB:impN	1.38		
motherH:impN	-17.81		
motherA:impN	-17.12		
motherO:impN	1.89**		
partnerB		-24.96	-3.88***
partnerH		-3.96***	-4.98***
partnerA		-3.97***	-4.29***
partnerO		-3.82***	-3.88***
donorB:partnerB		23.28	
donorH:partnerB		22.36	
donorA:partnerB		4.39	
donorO:partnerB		22.27	
donorB:partnerH		2.83**	
donorH:partnerH		3.42***	
donorA:partnerH		-16.23	
donorO:partnerH		1.13	
donorB:partnerA		-16.38	
donorH:partnerA		-17.58	
donorA:partnerA		-16.03	
donorO:partnerA		-17.31	
donorB:partnerO		-16.82	
donorH:partnerO		2.32**	

donorA:partnerO		2.83*	
donorO:partnerO		1.13	
partnerB:motherB		3.67**	
partnerH:motherB		-17.43	
partnerA:motherB		-16.15	
partnerO:motherB		-17.18	
partnerB:motherH		-17.45	
partnerH:motherH		2.44***	
partnerA:motherH		-17.76	
partnerO:motherH		0.68	
partnerB:motherA		-15.84	
partnerH:motherA		-17.43	
partnerA:motherA		-16.15	
partnerO:motherA		-17.18	
partnerB:motherO		-16.82	
partnerH:motherO		-18.41	
partnerA:motherO		-17.13	
partnerO:motherO		2.4**	

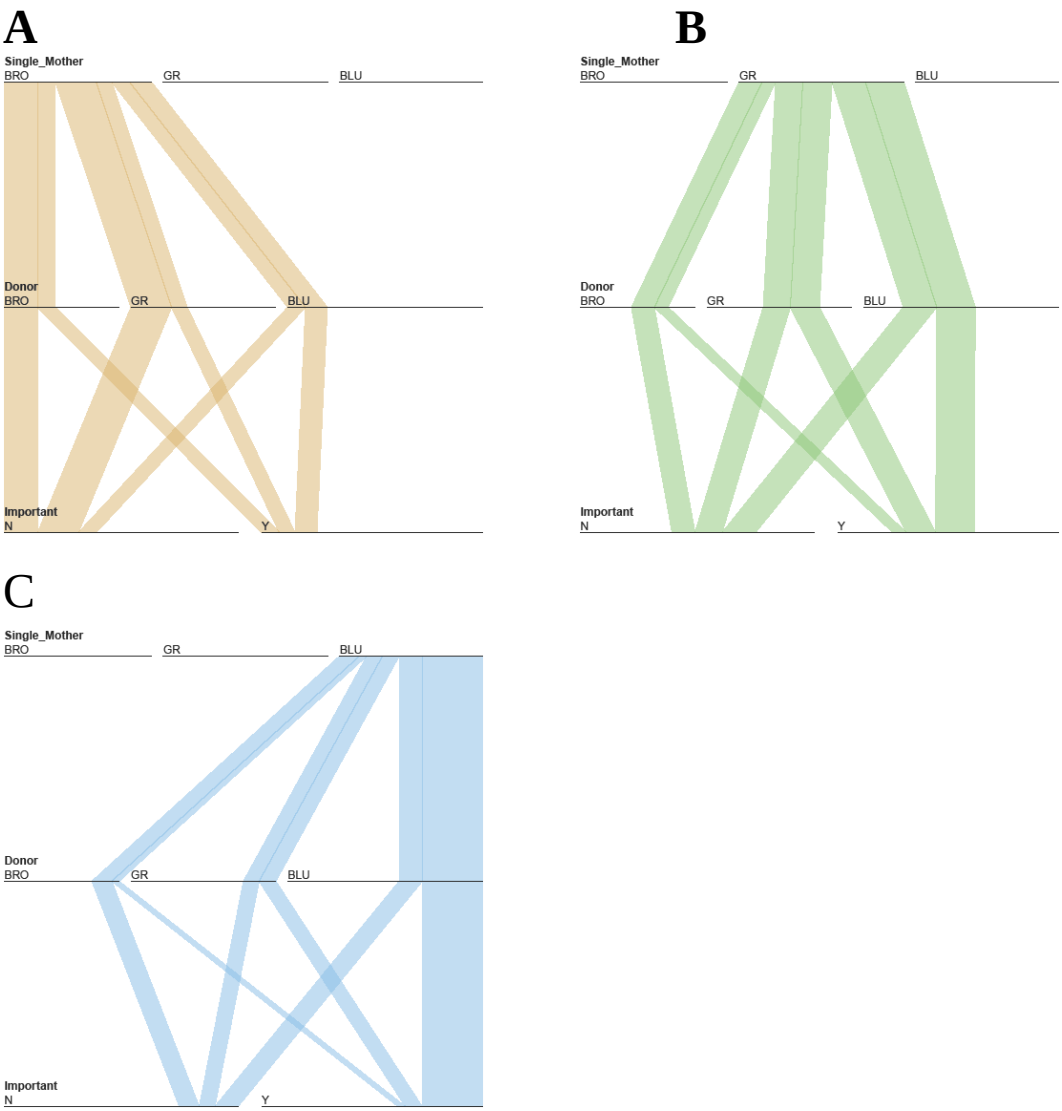

Figure 3.1 Parallel set visualization of cross-tabulated eye color data for single mothers.
Eye colors for single mothers are distributed across the top; the length of the bar is proportional to the frequency in our sample. The bars branch according to the chosen donor's eye color and whether eye color was an important factor in donor choice for (A) Brown-eyed mothers (B) Green-eyed mothers (C) Blue-eyed mothers

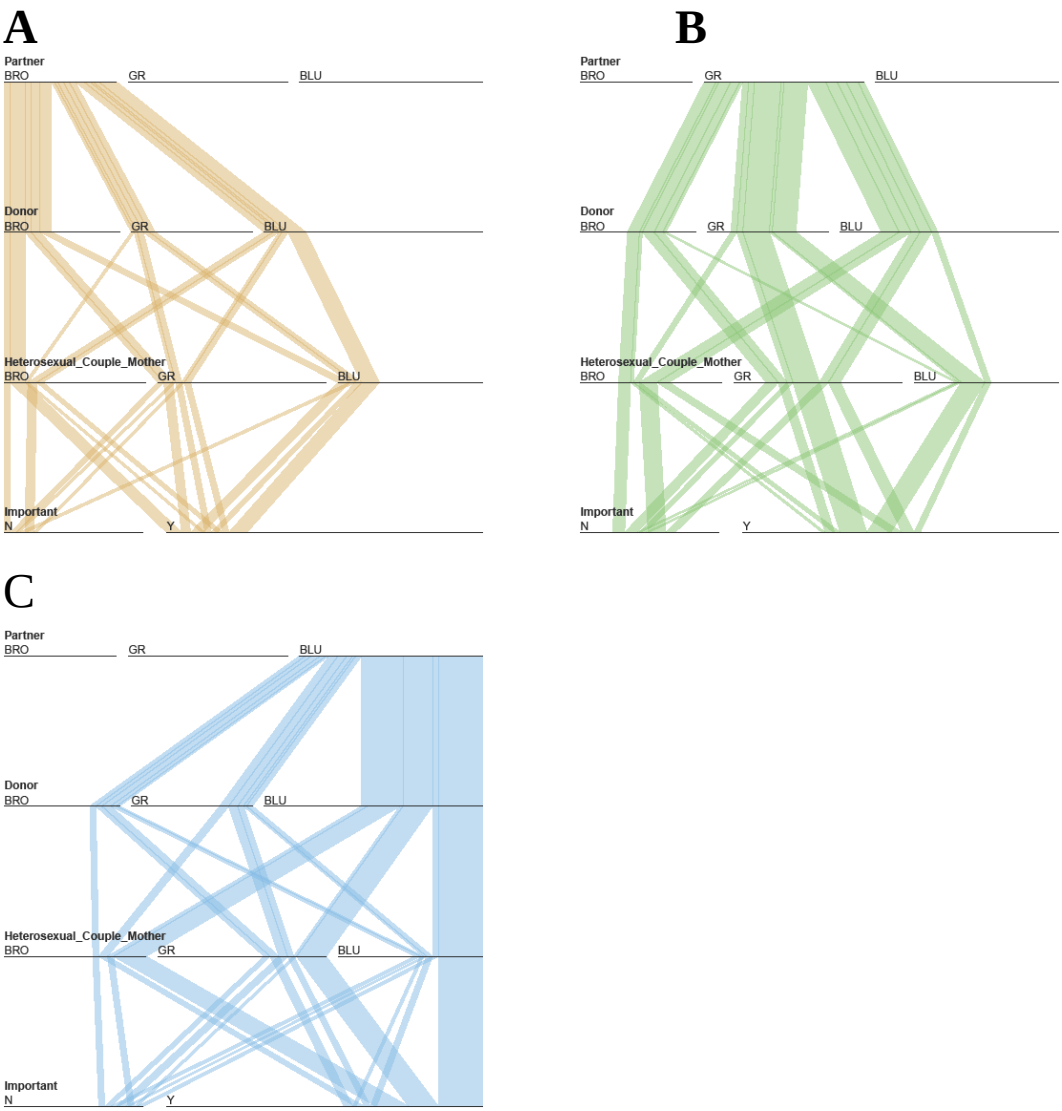

Figure 3.2 Parallel set visualization of cross-tabulated eye color data for heterosexual couples. Eye colors for male partners are distributed across the top; the length of the bar is proportional to the frequency in our sample. The bars branch according to the chosen donor's eye color, heterosexual mother's eye color, and whether eye color was an important factor in donor choice for (A) Brown-eyed male partners (B) Green-eyed male partners (C) Blue-eyed male partners.

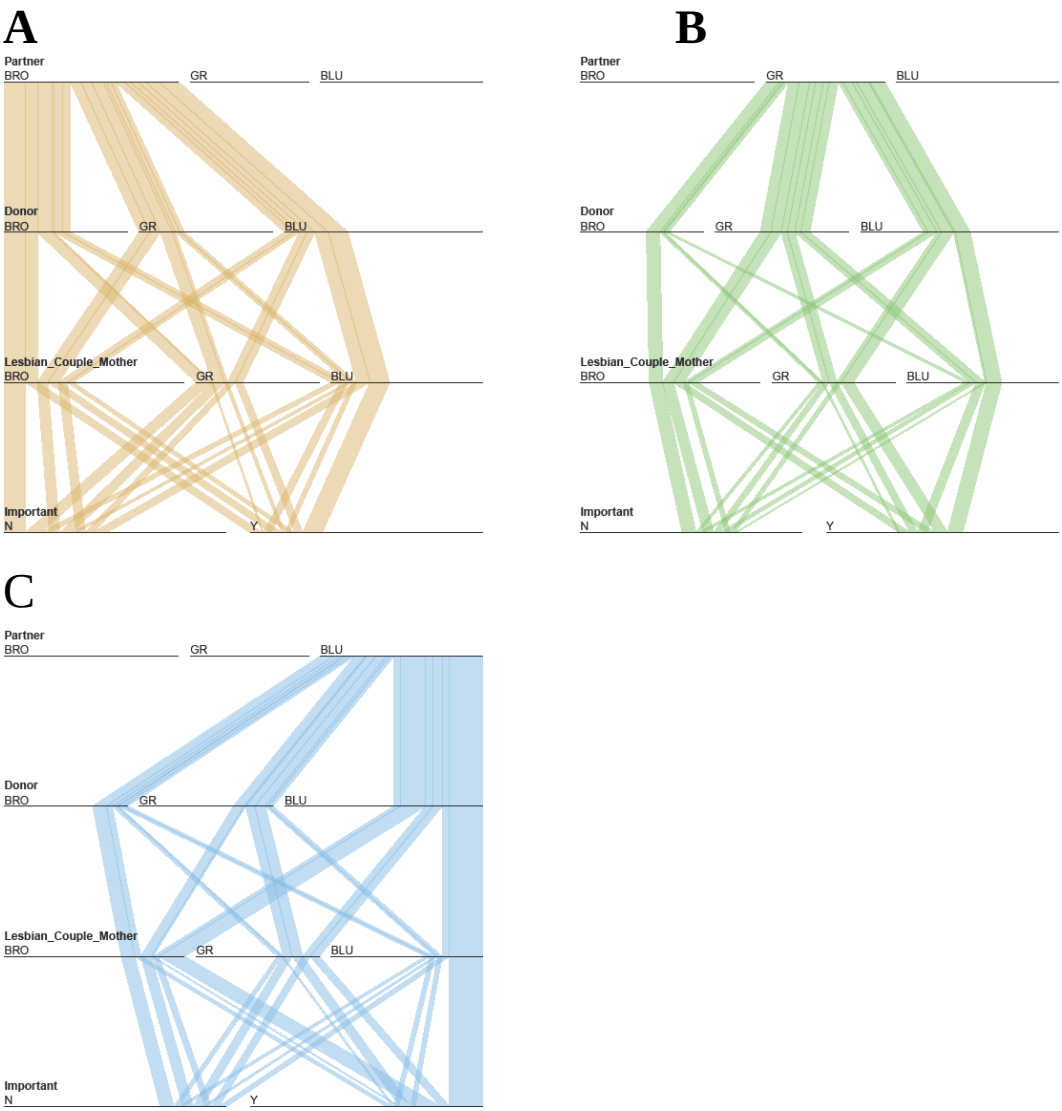

Figure 3.3 Parallel set visualization of cross-tabulated eye color data for lesbian couples.
Eye colors for female partners are distributed across the top; the length of the bar is proportional to the frequency in our sample. The bars branch according to the chosen donor's eye color, lesbian mother's eye color, and whether eye color was an important factor in donor choice for (A) Brown-eyed female partners (B) Green-eyed female partners (C) Blue-eyed female partners.

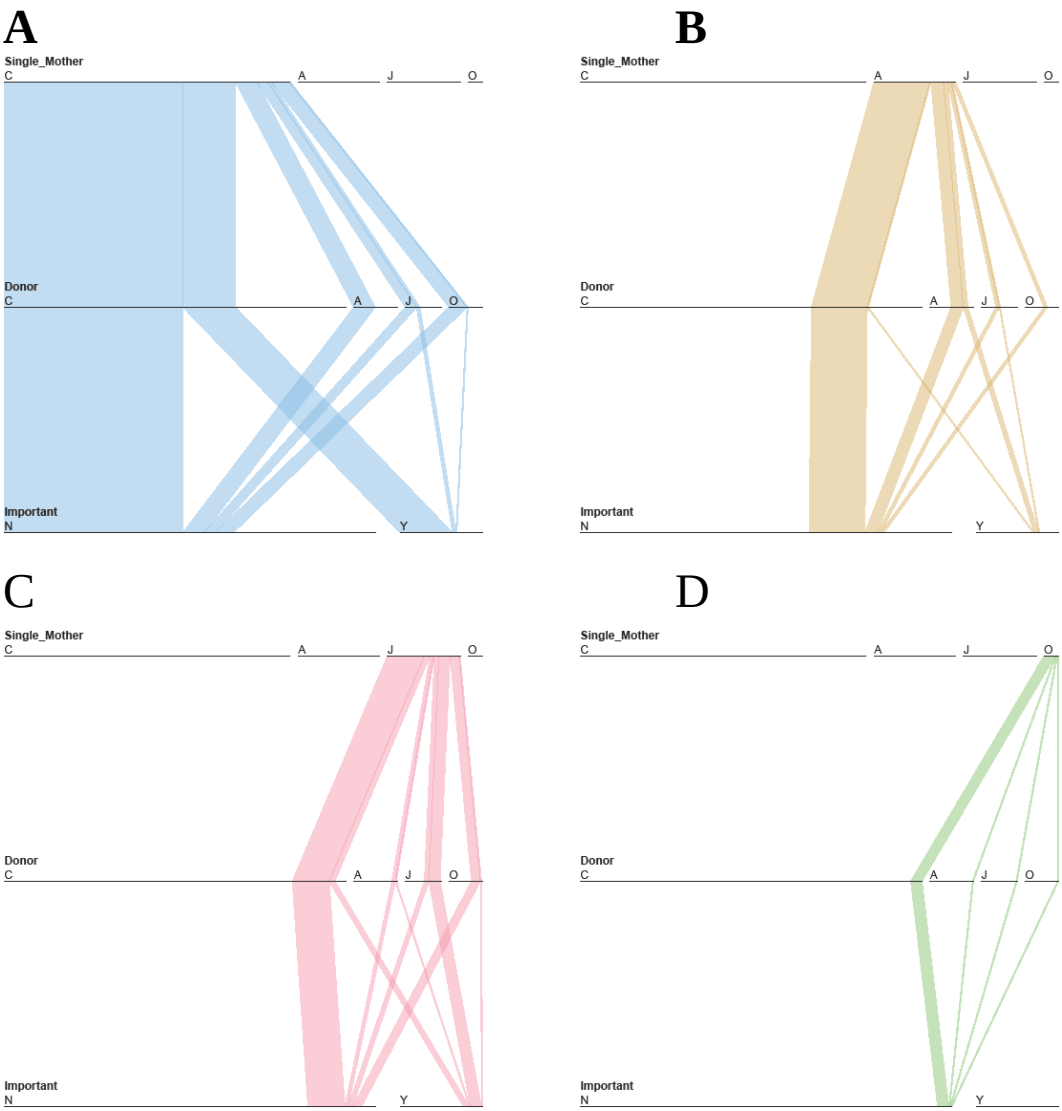

Figure 3.4 Parallel set visualization of cross-tabulated religion data for single mothers. Religions for single mothers are distributed across the top; the length of the bar is proportional to the frequency in our sample. The bars branch according to the chosen donor's religion and whether religion was an important factor in donor choice for (A) Christian mothers (B) Atheist mothers (C) Jewish mothers and (D) Other mothers.

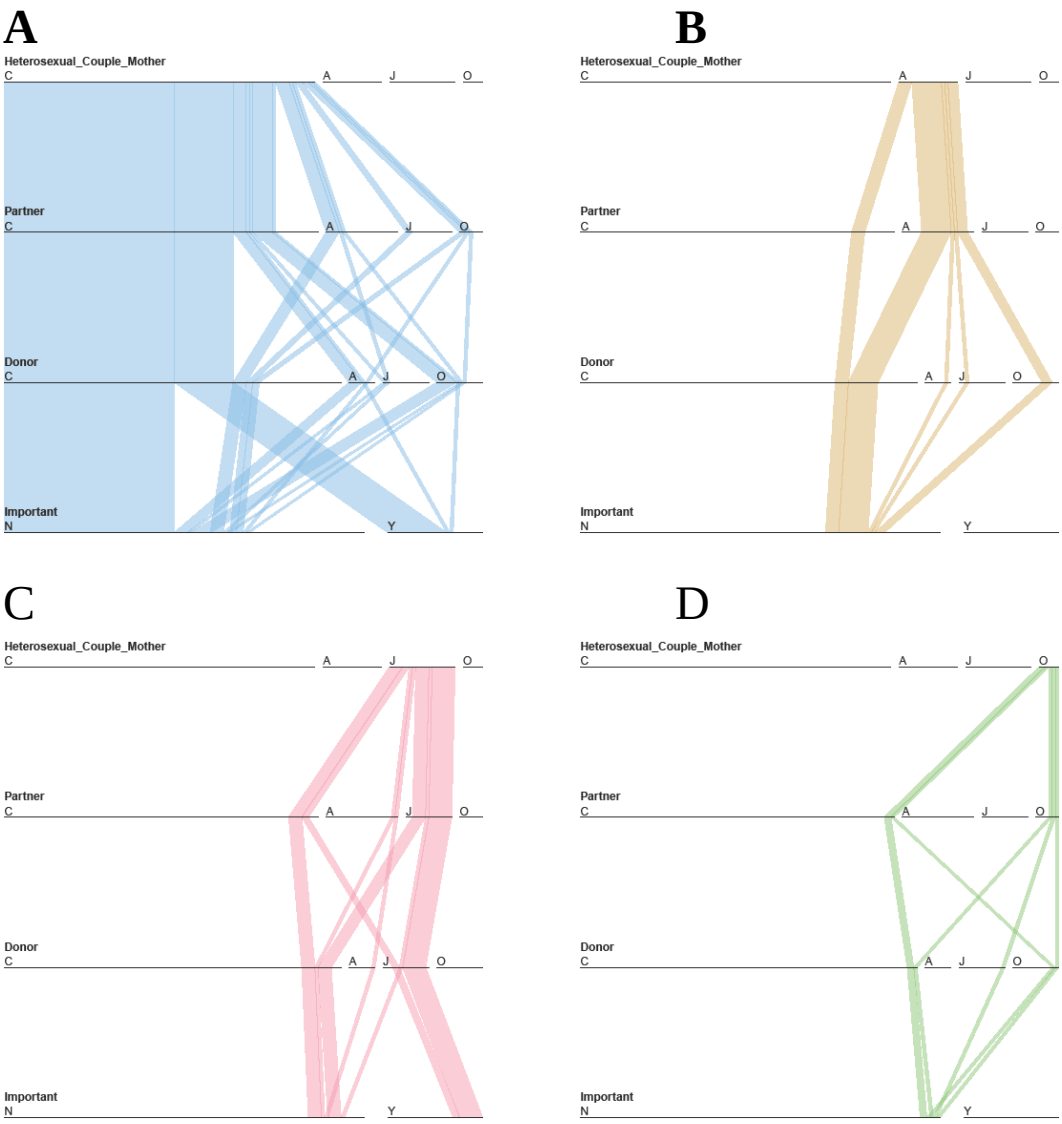

Figure 3.5 Parallel set visualization of cross-tabulated religion data for heterosexual mothers. Religions for heterosexual mothers are distributed across the top; the length of the bar is proportional to the frequency in our sample. The bars branch according to the partner's religion, donor's religion, and whether religion was an important factor in donor choice for (A) Christian mothers (B) Atheist mothers (C) Jewish mothers and (D) Other mothers.

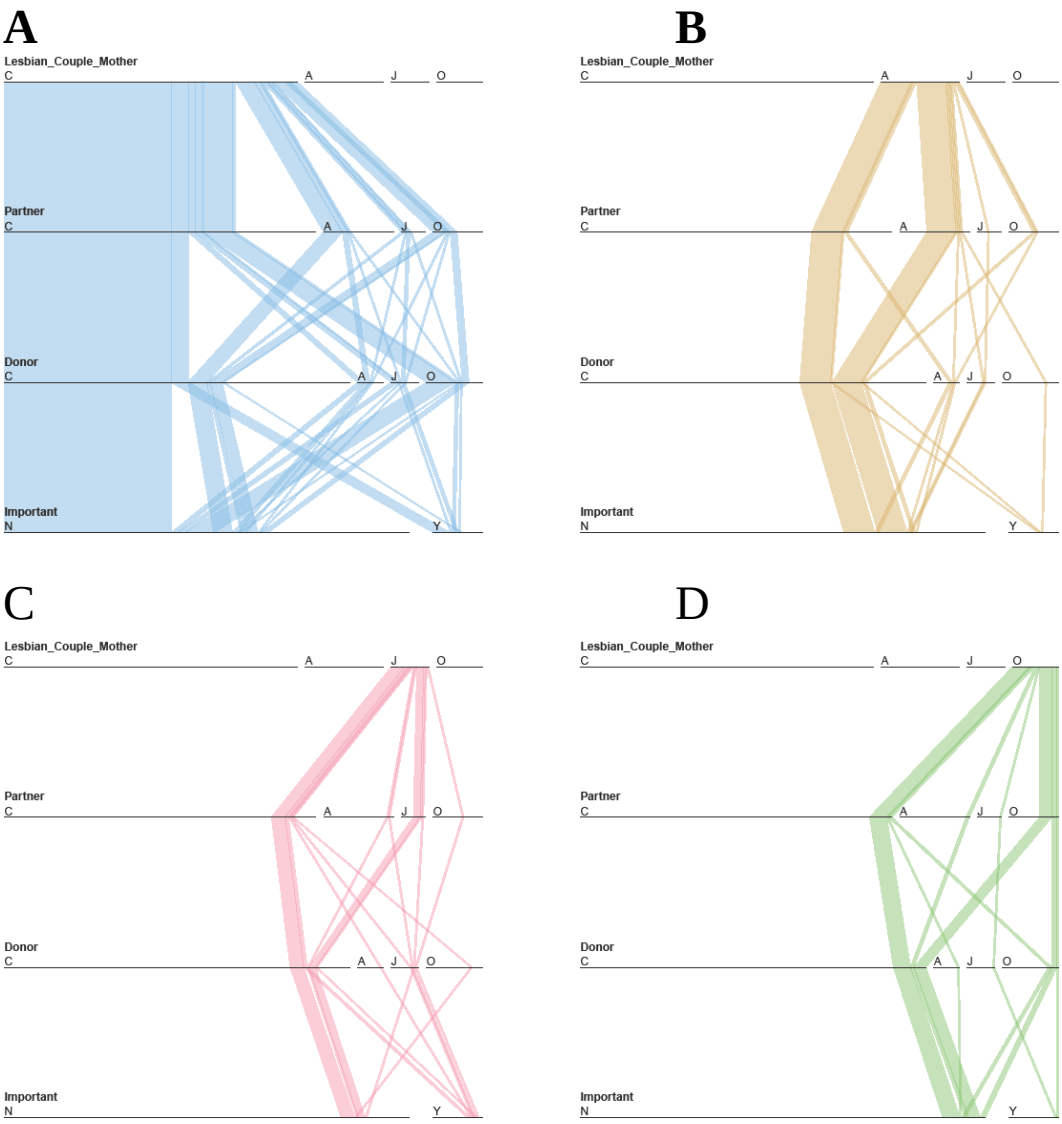

Figure 3.6 Parallel set visualization of cross-tabulated religion data for lesbian mothers.
Religions for lesbian mothers are distributed across the top; the length of the bar is proportional to the frequency in our sample. The bars branch according to the partner's religion, donor's religion, and whether religion was an important factor in donor choice for (A) Christian mothers (B) Atheist mothers (C) Jewish mothers and (D) Other mothers.

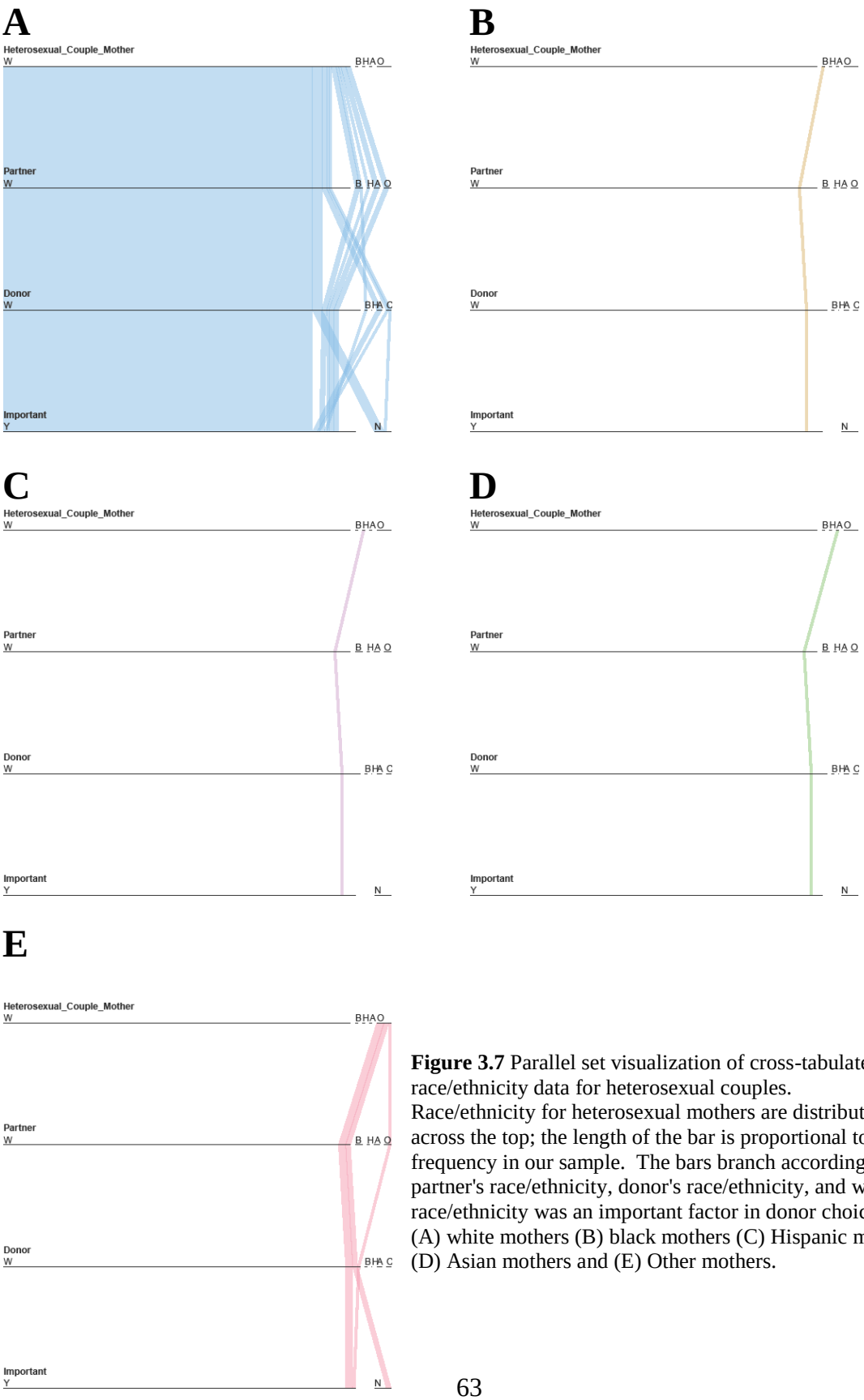

Figure 3.7 Parallel set visualization of cross-tabulated race/ethnicity data for heterosexual couples. Race/ethnicity for heterosexual mothers are distributed across the top; the length of the bar is proportional to the frequency in our sample. The bars branch according to the partner's race/ethnicity, donor's race/ethnicity, and whether race/ethnicity was an important factor in donor choice for (A) white mothers (B) black mothers (C) Hispanic mothers (D) Asian mothers and (E) Other mothers.

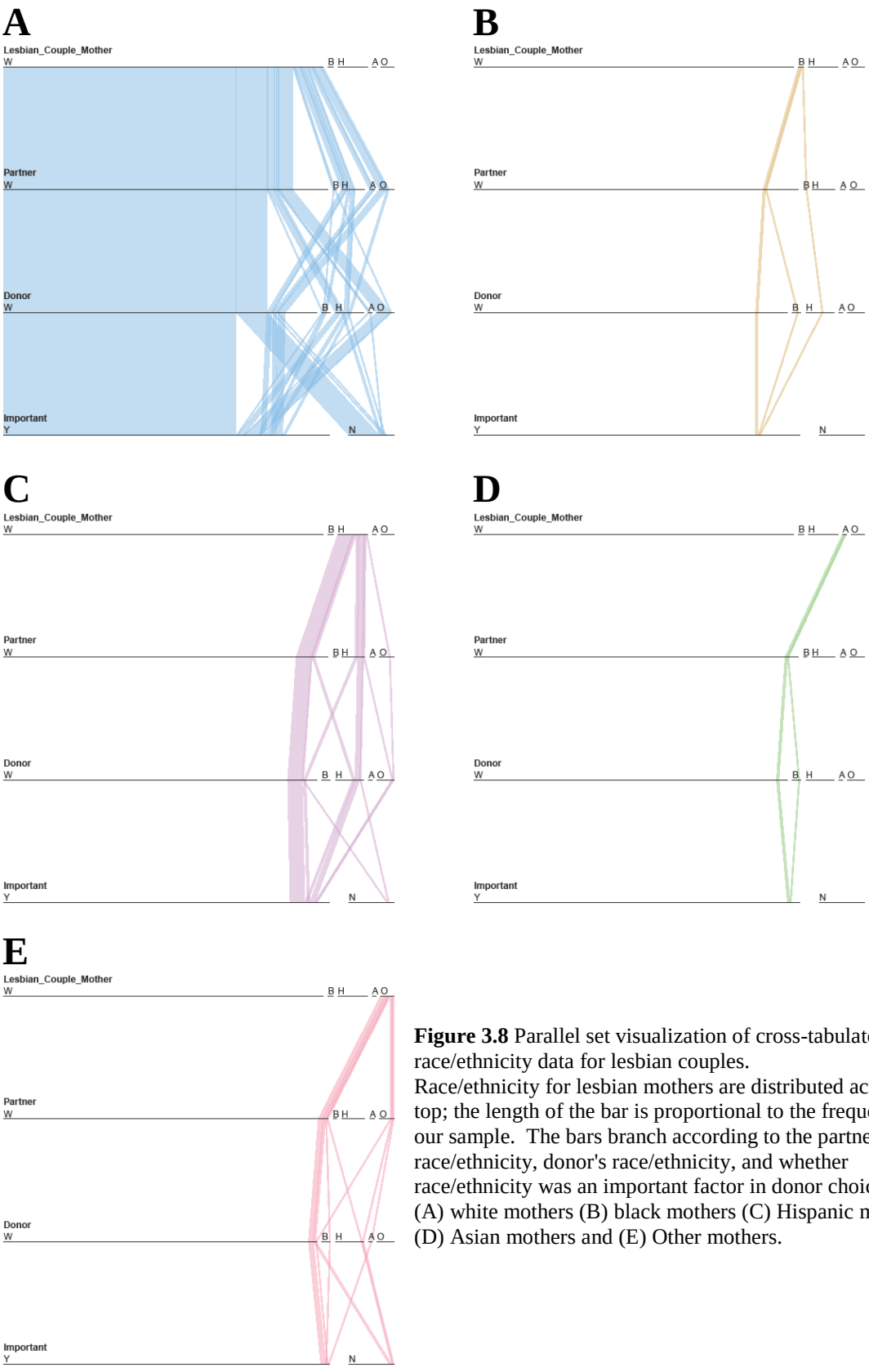

Figure 3.8 Parallel set visualization of cross-tabulated race/ethnicity data for lesbian couples.
Race/ethnicity for lesbian mothers are distributed across the top; the length of the bar is proportional to the frequency in our sample. The bars branch according to the partner's race/ethnicity, donor's race/ethnicity, and whether race/ethnicity was an important factor in donor choice for (A) white mothers (B) black mothers (C) Hispanic mothers (D) Asian mothers and (E) Other mothers.

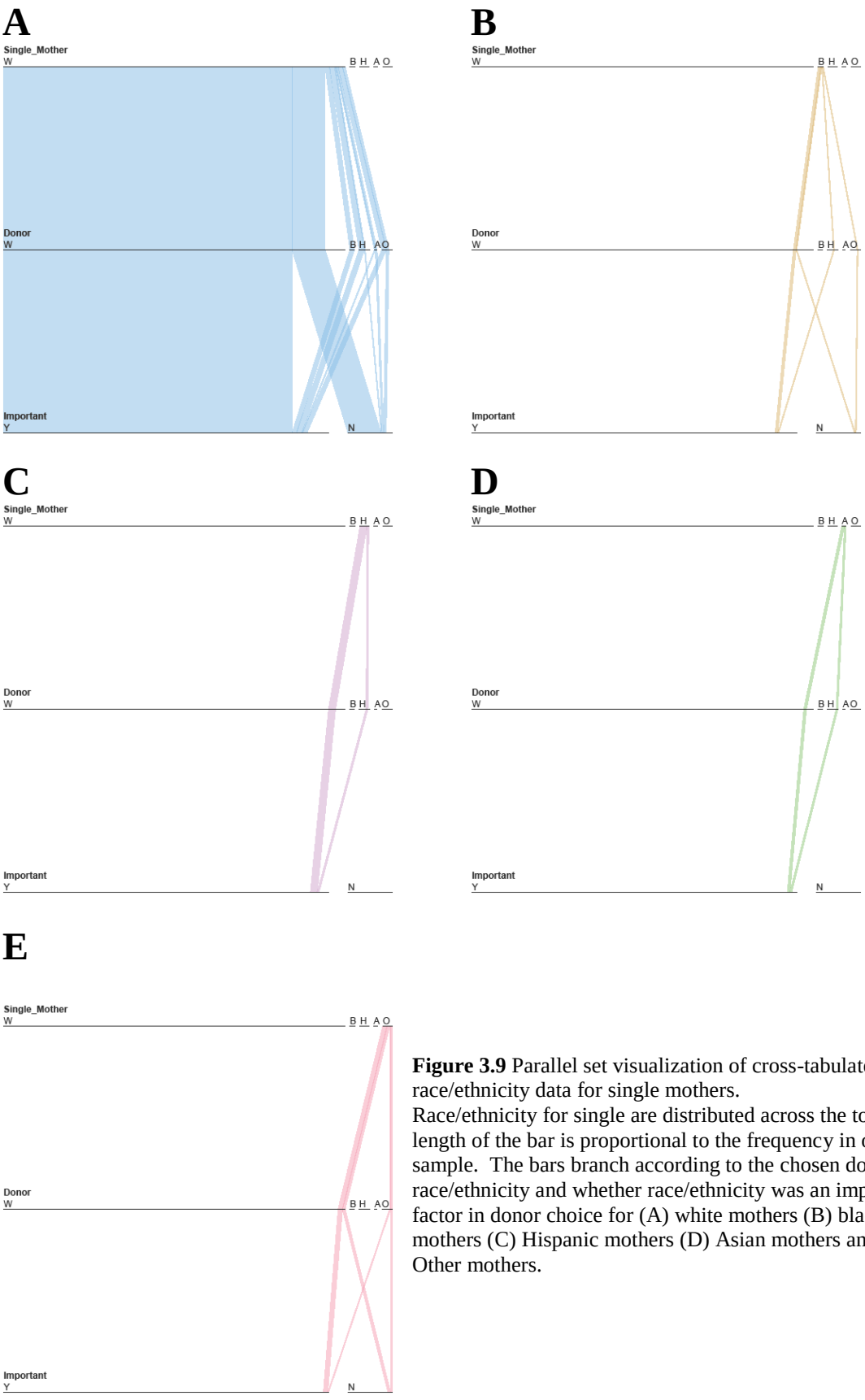

Figure 3.9 Parallel set visualization of cross-tabulated race/ethnicity data for single mothers.
Race/ethnicity for single are distributed across the top; the length of the bar is proportional to the frequency in our sample. The bars branch according to the chosen donor's race/ethnicity and whether race/ethnicity was an important factor in donor choice for (A) white mothers (B) black mothers (C) Hispanic mothers (D) Asian mothers and (E) Other mothers.

3.4 Discussion

The donor pedigree enables the first direct measure of phenotypic assortment in humans. We compared mother/donor with mother/partner correlations and found mothers actively selected for height, eye color, and religion. The response to selection for height matched theoretical predictions; taller donors begat taller children in a manner consistent with previous heritability estimates. Our results represent a unique experimental validation of ethical artificial selection in humans. Mothers who selected for height endowed their children with an economic advantage because height is positively associated with social status and labor market outcomes (*20*).

Although we used assortative mating to determine which traits underwent active selection, it is not the only non-random mating system in humans. Polyandry (women taking multiple husbands), polygyny (men taking multiple wives), and hypergamy (women marrying upwards in the socioeconomic hierarchy) all exist to varying degrees. Mate choice preferences under these other mating systems may be orthogonal to those expressed when selecting an anonymous sperm donor for genetic reasons. Thus, the major caveat of our study is assortative mating only provides one specific view of mate choice preferences.

Future work could expand the scope of phenotypes studied to include those found in expanded donor profiles, such as personality. Additionally, an overarching analysis could be conducted to integrate assortative mating with other non-random mating theories and show natural selection is still acting on modern humans.

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4 Childhood Heritability of Physical and Behavioral Traits in the Donor Sibling Registry

4.1 Introduction

Paternal half-siblings conceived using anonymous sperm donation are an intriguing experiment of modern reproductive medicine. They combine the individual strengths of disparate heritability study designs into a single, powerful method to estimate the genetic and environmental components of human traits.

Historically, studies of twins reared apart have reigned supreme in their ability to generate heritability estimates unconfounded by shared environmental factors (*1, 2*). Donor-conceived paternal half-siblings challenge this supremacy with a new ideal. Reared apart by different mothers, they generate a direct estimate of the narrow-sense heritability of a trait (Table 2.2), as opposed to the broad-sense heritability found using MZ twins reared apart. Donor-conceived paternal half-siblings can also be used to analyze traits influenced by maternal or contrast effects that are intractable to other study designs.

4.2 Materials and Methods

We stratified our analysis of physical traits by child age. We separated children in the DSR into two age groups, using an age cutoff of eight years for two reasons. First, eight years is past the age of adiposity rebound for BMI (Figure 2.3D-E) (*3*). Second, eight years was an empirical division in which half-siblings switch from a broad age range to being more closely matched in age (Figure 4.1A). We attempted to isolate the effect of age differences between sibling comparisons because siblings close in age exhibit higher correlations than siblings farther apart for BMI (*4*). Age differences are an

important consideration because intra-person correlations for a person compared with themselves at different ages during childhood is approximately 0.8 for height and 0.6 for BMI (*5*). Figure 4.1B shows a violin plot of the age distribution for children included in the height and BMI analyses. The median age of children eligible for the parent-offspring regression was 6.8 years, while children who matched with a half-sibling skewed younger with a median age of 5.8 years.

The parent-offspring regressions for height and BMI were weighted by family size (*6*). Offspring values were the mean of the children from each mother/donor pair.

We calculated reared-apart paternal half-sibling intraclass correlations for each phenotype using a half-sibling/full-sibling nested ANOVA method (*6*), excluding all children who were part of multiple births. We calculated full-sibling and DZ twin intraclass correlations using a standard ANOVA. Each ANOVA was adjusted for unequal numbers of offspring per mother and mothers per donor pedigree according to Turner (*7*). Standard errors were also calculated according to Turner. Since eye color is a categorical trait, we treated eye color as three binary traits when running the ANOVA: blue vs. non-blue, green vs. non-green, and brown vs. non-brown.

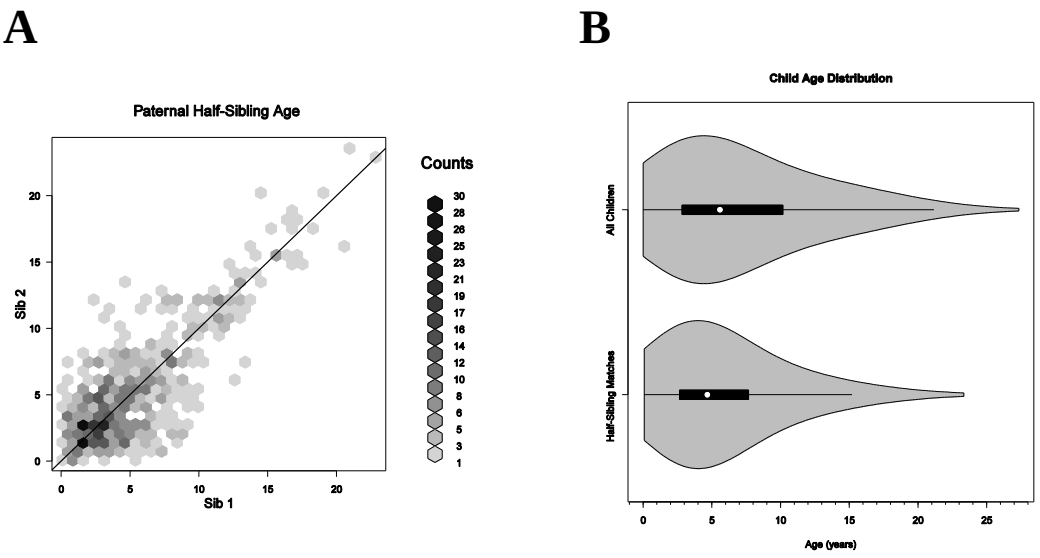

Figure 4.1 Child ages in the DSR
(A) A plot of the ages of paternal half-sibling pairs shows a transition at eight years old, where the older donor-conceived half-sibling matches tend to be closer in age. (B) Violin plot of child age distributions for all children and children who matched with a paternal half-sibling in our sample.

4.3 Results

4.3.1 Physical Traits

4.3.1.1 Height, BMI, and Eye Color

We first estimated the heritability of height, BMI, and eye color to verify the half-sibling matching process. The biological mother/child and donor/child regression coefficients for height and BMI were significant and increased as a function of child age, while the non-biological parent/child regression coefficients were not significant (Table 4.1). These results match expectations for parent-offspring estimates of heritability (*8-10*). The paternal half-sibling correlations for height and BMI showed the same pattern of increasing heritability with child age (Table 4.2) and were consistent with previous child-child studies (*10, 11*). A simple weighted average of heritability from all relationships involving children greater than eight years old yielded $h^2 = 0.65$ for height and $h^2 = 0.41$ for BMI; the decreasing DZ twin and full-sibling correlations with age

indicate the presence of childhood environmental effects (Table 4.2). Paternal half-sibling correlations for eye color show blue and brown eyes were nearly completely heritable (Table 4.2) (*12*). Indeed, donor-conceived paternal half-siblings shared paternity.

4.3.1.2 Birth Weight

Paternal half-siblings cleanly measure fetal genetic effects for traits influenced by maternal effects, such as birth weight, because they do not share an in utero environment (*13*). The paternal half-sibling correlation for birth weight in our sample was not statistically significant (Table 4.3). A small number of mothers conceived multiple children by different sperm donors; the correlation for birth weight among these maternal half-siblings was 0.54 (95% confidence interval 0.04,1.05, n=41 children). The non-significant paternal half-sibling correlation and significant full-sibling and maternal half-sibling correlations imply maternal effects are more important than fetal genetics in determining the variance of birth weight (*13, 14*).

4.3.2 Behavioral Traits

Childhood behavioral traits measured by parent report are often biased by sibling contrast effects in which parents artificially magnify the differences between their children (*15*). This inflates heritability estimates in behavioral genetic studies of twins and adoptees. External evaluations performed by teachers or researchers in laboratory settings can reduce sibling contrast effects, but are harder to conduct (*3*). In the donor family study design, each mother rates her child independent of the half-siblings in other households, producing the first parent-report free from contrast effects. We used this

property to examine the heritability of temperament (*16*) and traits from the strengths and difficulties questionnaire (SDQ) (*17*).

4.3.2.1 Temperament

For temperament, the negative full-sibling and dizygotic twin correlations (Table 4.3) illustrate the presence of contrast effects when mothers rate siblings within the same household. By comparison, the reared-apart paternal half-sibling correlations for activity, sociability, and shyness were positive, showing how contrast effects disappear when using independent mother ratings. We found significant heritability for sociability, corroborating observations from the Colorado Adoption Project where adoptee temperament was evaluated by an independent tester in a laboratory setting (*18*).

4.3.2.2 Strengths and Difficulties Questionnaire (SDQ)

For the SDQ, none of the paternal half-sibling correlations were statistically significant (Table 4.3). Our results stand in contrast to high heritabilities reported in twin studies, ranging from 0.35 to 0.83 for all SDQ scales (*19, 20*). Contrast effects do not explain this difference because the twin studies used independent teacher ratings. Additional non-twin studies of the genetic influence on childhood behavioral problems are necessary to resolve this discrepancy.

Table 4.1. Parent-child regression coefficients (b) for height and BMI, stratified by child age. The heritability is equal to twice the donor/child regression coefficient. The proportion of phenotypic variance attributable to shared environment is equal to the non-biological parent/child regression coefficient. The biological mother/child regression is equal to half the additive genetic variance plus the shared environmental variance (Table 2.2).

	Height					
	Child < 8 years old		Child >= 8 years old		All Ages	
Biological Mother	b	n	b	n	b	n
Male Child	0.17 (0.06,0.27)	301	0.31 (0.17,0.45)	235	0.22 (0.14,0.31)	536
Female Child	0.22 (0.11,0.34)	265	0.40 (0.27,0.53)	214	0.31 (0.22,0.39)	479
All	0.20 (0.13,0.28)	566	0.35 (0.26,0.45)	449	0.27 (0.21,0.34)	1015
Donor						
Male Child	0.23 (0.09,0.38)	286	0.21 (0.04,0.38)	201	0.21 (0.10,0.32)	487
Female Child	0.21 (0.05,0.38)	245	0.36 (0.18,0.54)	171	0.29 (0.17,0.41)	416
All	0.24 (0.12,0.35)	531	0.30 (0.17,0.43)	372	0.26 (0.18,0.35)	903
Non-Biological Parent						
Male Child	0.07 (-0.08,0.21)	150	-0.03 (-0.25,0.19)	107	0.02 (-0.11,0.14)	257
Female Child	0.23 (0.05,0.42)	145	-0.12 (-0.35,0.12)	76	0.09 (-0.06,0.23)	221
All	0.15 (0.03,0.27)	295	-0.07 (-0.23,0.10)	183	0.05 (-0.04,0.15)	478
	BMI					
	Child < 8 years old		Child >= 8 years old		All Ages	
Biological Mother	b	n	b	n	b	n
Male Child	0.03 (-0.02,0.08)	287	0.13 (0.05,0.21)	220	0.07 (0.03,0.11)	507
Female Child	0.04 (-0.01,0.10)	253	0.14 (0.05,0.22)	206	0.08 (0.03,0.13)	459
All	0.04 (0.00,0.08)	540	0.13 (0.07,0.19)	426	0.07 (0.04,0.11)	966
Donor						
Male Child	-0.04 (-0.18,0.08)	264	0.17 (-0.05,0.40)	181	0.03 (-0.09,0.15)	445
Female Child	-0.07 (-0.22,0.08)	223	0.24 (0.02,0.45)	151	0.05 (-0.07,0.19)	374
All	-0.07 (-0.17,0.04)	487	0.19 (0.04,0.35)	332	0.04 (-0.05,0.13)	819
Non-Biological Parent						
Male Child	0.15 (0.03,0.27)	143	0.01 (-0.18,0.19)	96	0.07 (-0.03,0.18)	239
Female Child	0.00 (-0.14,0.13)	136	0.04 (-0.19,0.27)	64	0.01 (-0.10,0.13)	200
All	0.04 (-0.05,0.13)	279	0.04 (-0.09,0.18)	160	0.05 (-0.03,0.12)	439

Table 4.2 Paternal half-sibling, full-sibling and dizygotic twin correlations for height, BMI and eye color.

	Paternal Half-Siblings		**Full-Siblings**		**DZ Twins**	
	t	n (children)	t	n (children)	t	n (children)
Height						
< 8 years	-0.06 (-0.22,0.10)	196	0.39 (0.10,0.68)	68	0.81 (0.68,0.93)	62
>= 8 years	0.16 (-0.14,0.46)	76	0.26 (-0.16,0.69)	37	0.19 (-0.27,0.65)	36
All	-0.03 (-0.17,0.10)	293	0.40 (0.20,0.60)	133	0.65 (0.49,0.81)	98
BMI						
< 8 years	0.10 (-0.07,0.26)	193	0.23 (-0.10,0.55)	68	0.89 (0.82,0.97)	60
>= 8 years	0.27 (-0.05,0.58)	77	0.08 (-0.39,0.55)	35	0.51 (0.15,0.87)	34
All	0.18 (0.03,0.32)	290	0.26 (0.04,0.49)	129	0.68 (0.53,0.84)	94
Eye Color						
Brown	0.24 (0.11,0.37)	408	0.38 (0.21,0.54)	205	0.45 (0.26,0.64)	134
Green	0.14 (0.02,0.25)	408	0.07 (-0.12,0.26)	205	0.06 (-0.18,0.30)	134
Blue	0.23 (0.10,0.36)	408	0.33 (0.16,0.50)	205	0.44 (0.25,0.64)	134

Table 4.3. Child-child intraclass correlation coefficients (t) for traits affected by maternal or contrast effects.

	Paternal Half-Siblings		**Full-Siblings**		**DZ Twins**	
	t	n (children)	t	n (children)	t	n (children)
Birth Weight	0.09 (-0.03,0.22)	380	0.46 (0.31,0.61)	209	0.33 (0.11,0.55)	128
EAS Temperament						
Emotionality	-0.02 (-0.12,0.08)	339	-0.27 (-0.48,-0.07)	140	-0.15 (-0.42,0.12)	102
Activity	0.09 (-0.03,0.20)	339	-0.21 (-0.43,0.00)	140	-0.17 (-0.44,0.10)	102
Sociability	0.15 (0.03,0.28)	339	-0.06 (-0.29,0.17)	140	-0.26 (-0.52,0.00)	102
Shyness	0.09 (-0.03,0.21)	339	0.03 (-0.20,0.26)	140	-0.24 (-0.50,0.03)	102
SDQ						
Emotional Problems	0.11 (-0.08,0.30)	175	-0.05 (-0.38,0.29)	67	-0.15 (-0.51,0.21)	58
Conduct Problems	-0.03 (-0.19,0.14)	175	-0.05 (-0.29,0.28)	67	0.05 (-0.32,0.42)	58
Hyperactivity/ Inattention	-0.07 (-0.24,0.10)	175	-0.02 (-0.36,0.32)	67	-0.05 (-0.42,0.32)	58
Peer Problems	0.00 (-0.18,0.17)	175	0.01 (-0.33,0.35)	67	0.04 (-0.33,0.41)	58
Total Problems	-0.08 (-0.26,0.09)	175	0.17 (-0.16,0.50)	67	0.11 (-0.25,0.48)	58
Prosocial Behavior	-0.01 (-0.18,0.17)	175	-0.09 (-0.42,0.25)	67	-0.11 (-0.48,0.26)	58

4.4 Discussion

Donor-conceived paternal half-siblings offer a universal study design to disentangle the genetic and environmental components of human traits. Here, we confirmed the results from parent-offspring, twin, adoption, half-sibling, and cousin study designs for physical and behavioral traits affected by maternal and contrast effects.

One caveat to our study is donor-conceived children may grow up in non-representative environments biased by demographic factors. Our study also had a limited sample size. We only sampled 8.1% of the children in the DSR who matched with a half-sibling. Our largest donor pedigree contained 10 children, but some donors in the DSR have greater than 100 donor-conceived children. Although DSR members value their privacy, improving our sampling yield would translate into more precise statistical estimates.

Reports of medical conditions traced to anonymous sperm donation have recently surfaced (*21*). As the use of artificial reproduction becomes more widespread and DSR children reach the age of onset for common medical conditions, large pedigrees of donor-conceived half-siblings will provide a unique resource for understanding the genetic components of disease.

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5 Conclusion

The donor pedigree is a remarkable unintended consequence of assisted reproductive technology. It raises a number of interesting questions, including: How should anonymous sperm donation be regulated? What is the ethical limit for designing babies? What do the economics of sperm donation say about mate choice preferences? Are there differences in parenting between heterosexual and lesbian couples? Thus, the donor pedigree is an important research topic that sits at the intersection of genetics, sociology, ethics, economics, and government regulation.

The donor pedigree differs from traditional paternal half-sibling study designs in two key ways. First, a traditional paternal half-sibling study design does not guarantee a lack of shared environment. Unlike half-siblings in a donor pedigree, traditional paternal half-siblings may be in extended contact with one another and feel the same paternal influence because their father is present in their lives. Second, a traditional paternal half-sibling study design scales by recruiting large numbers of small half-sibships that have formed as a result of divorce or death. In contrast, the donor pedigree study design scales by recruiting fewer numbers of exceedingly large half-sibships. Increasing the number of half-sibships increases the statistical power of heritability study designs, while increasing the size of the half-sibships enables new types of quantitative genetic studies in humans. For instance, a large half-sibship can be used to determine a donor's expected breeding value. Thus, a traditional paternal half-sibling study design is suited to traditional heritability questions, while a donor pedigree design is suited to previously intractable questions regarding selection in humans.

The present study could be improved on in a number of ways. The first major improvement would be to increase the sample size. Survey response rate could be improved by reducing its length – we were not able to use the long and tedious working memory and personality constructs due to a lack of participation among the children. Recruitment efforts should be focused solely on adults in the DSR.

The second major improvement would be to focus on recruiting only the largest pedigrees rather than recruiting from the entire DSR. As discussed above, the donor pedigree is unique for its size, not its numbers. Recruiting many small pedigrees is less helpful than recruiting fewer large pedigrees. A more focused recruiting approach would concentrate the compensation pool to further encourage participation.

The third major improvement would be to collect DNA to verify paternity. Although we are confident in the donor ID/sperm bank matching process, mistakes are inevitably made that reduce the study's power. Additionally, DNA from large pedigrees could be used to examine other issues such as paternal chromosome recombination and set the stage for future molecular genetic studies.

The ideal DSR study would longitudinally collect data on a wide variety of physiological and behavioral variables. As children in the DSR mature and reach the age of onset for adult conditions, having DNA on large donor pedigree structures would be invaluable for understanding the genetics of complex diseases.

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