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Consanguineous Marriage and the Psychopathology of Progeny
A Population-wide Data Linkage Study

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IMPORTANCE Approximately 1 in 10 children worldwide are born to consanguineous parents. The literature on consanguinity and mental health of progeny is scarce despite the fact that many of the factors associated with consanguineous unions are also associated with mental health.

OBJECTIVE To investigate if children of consanguineous parents are at increased risk of common mood disorders or psychoses.

DESIGN, SETTING, AND PARTICIPANTS This investigation was a retrospective population-wide cohort study of all individuals born in Northern Ireland between January 1, 1971, and December 31, 1986, derived from the Child Health System data set and linked to nationwide administrative data sources on prescription medication and death records. Data from the Child Health System data set identified all 447 452 births delivered to mothers residing in Northern Ireland between 1971 and 1986. The final data set comprised 363 960 individuals, alive and residing in Northern Ireland in 2014, with full data on all variables. The dates of analysis were June 1 to October 31, 2017.

MAIN OUTCOMES AND MEASURES Degree of parental consanguinity was assessed from questions asked of the parents during routine health visitor house calls within 2 weeks of the child's birth. Potential mental ill health was estimated by receipt of psychotropic medication in 2010 to 2014. Ever or never use was used for the main analysis, with sensitivity analyses using a cutoff of at least 3 months' prescriptions. Receipt of antidepressant or anxiolytic medications was used as a proxy for common mood disorders, whereas receipt of antipsychotic medications was used as a proxy indicator of psychoses.

RESULTS Of the 363 960 individuals (52.5% [191 102] male), 609 (0.2%) were born to consanguineous parents. After full adjustment for factors known to be associated with poor mental health, multilevel logistic regression models found that children of first-cousin consanguineous parents were more than 3 times as likely to be in receipt of antidepressant or anxiolytic medications (odds ratio, 3.01; 95% CI, 1.24-7.31) and more than twice as likely to be in receipt of antipsychotic medication (odds ratio, 2.13; 95% CI, 1.29-3.51) compared with children of nonrelated parents.

CONCLUSIONS AND RELEVANCE A child of consanguineous parents is at increased risk of common mood disorders and psychoses.

Editorial

Supplemental content

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Across the world, approximately 1 in 10 children are the progeny of consanguineous parents despite concerns about the genetic safety of such a partnership.[1] Consanguinity is defined as the union between 2 individuals related as second cousins or closer. The most commonly reported form of consanguineous partnership worldwide is between first cousins, who on average have coinherited one-eighth of their genes from one or more common ancestors. Therefore, first-cousin offspring will be homozygous at one-sixteenth of all loci (ie, they will receive identical gene copies from each parent at these sites in their genome).[2,3] It is this shared genetic profile that is thought to lead to a higher prevalence of autosomal recessive disorders in children of consanguineous unions. The risk of abnormality or death in early childhood is approximately 5% in children of consanguineous couples compared with 2% to 2.5% for children of nonconsanguineous couples.[4] Unsurprisingly, rates of miscarriage and stillbirth are higher among children of consanguineous parents.[5,6] However, the results of some studies[4,7] also suggest that consanguinity deleteriously affects late pregnancy and postpregnancy outcomes, including preeclampsia, prematurity, and low birth weight.[4,7] A recent report from the United Kingdom stated that, in 1 London borough, 1 in 5 of all neonatal deaths were owing to their parents being related.[8] Consanguinity has also been associated with increased risk of later-life effects such as cardiovascular disease, cancer, and Alzheimer disease.[9]

However, the validity of these associations and the magnitude of the risk have often been contested.[10] Researchers in Australia found the risk of congenital defects in infants born to first-cousin marriages to be comparable to the risk to infants born to women older than 40 years.[11] A narrative review[12] on the effect of consanguinity on neonatal outcomes concluded that the findings were inconsistent, citing poor study design and inadequate adjustment for confounding factors as the reasons for the observed variability. In addition, the National Society of Genetic Counselors[13] in North America concluded that risks quoted from studies based on non-Western populations may not be applicable to all consanguineous unions owing to underlying societal differences and ethnicity-related risk factors, suggesting that well-controlled studies evaluating the effect of consanguinity have not yet been conducted.

The literature on consanguinity and the mental health of progeny is scarce despite the fact that many of the factors associated with consanguineous unions are also associated with mental health outcomes.[14-16] It is widely known that early-life factors such as parental deprivation and low birth weight are associated with poor mental health outcomes in adulthood.[17,18] Furthermore, these factors are associated with consanguinity.[19,20] Consanguineous pregnancies are also associated with younger maternal age, which is a risk factor for poor mental health in children.[5,21] Children of consanguineous parents also face a certain degree of stigma, especially in communities where consanguinity is not the norm, and this stigma could negatively affect their mental well-being.[13] Extant studies[15,16,22-24] exploring the association between consanguinity and mental health have been limited by study cohort size, a lack of adequate controls, and inconsistent measurement of mental health. One recent study[22] in Iran found no association between consanguinity and mental ill health in students aged 18 to 39 years as measured by the General Health Questionnaire 28; however, that study was based on a small sample of medical sciences students in 1 university and excluded anyone with a prediagnosed psychiatric disorder. There is a recognized need for further studies of the effect of consanguinity on late-onset disorders such as psychoses and common mood disorders that rigorously control for potential confounding variables like socioeconomic status, birth weight, maternal age, and rural dwelling.[1]

It is difficult to carry out a population-wide study on the effects of consanguinity in children owing to the lack of routine records on consanguineous marriage. First-cousin marriages are legal throughout the world with the exception of the United States, North Korea, and the People's Republic of China.[2] However, actual rates of consanguinity within populations are impossible to determine. It is estimated that consanguineous unions are increasing across Western Europe owing to migration from areas where consanguinity is commonplace.[25,26]

Data from church records are available on Roman Catholic consanguineous unions because special dispensation is required from the Catholic Church for such individuals to marry. Roman Catholics constitute the largest majority religion in Northern Ireland (NI), and recent data suggest that 1 in 625 (0.2%) of all Roman Catholic marriages in Ireland are consanguineous,[26] with an estimated 0.1% to 0.2% of Roman Catholic marriages in Canada also being consanguineous.[27] A random survey of 630 presentations to emergency departments in NI in 1955 found 0.3% of the population to be in consanguineous unions.[28]

This article presents the findings of a retrospective population-wide cohort study of data from the Child Health System (CHS) data set, which recorded information on all births in NI between January 1, 1971, and December 31, 1986, along with parental information, including degree of consanguinity. This cohort allows for the first population-wide data linkage study to date linking data from the CHS data set to primary care records, prescription medication data, and death records to investigate the association between consanguinity and the long-term mental health outcomes of progeny.

Key Points

Question Are children of consanguineous parents at increased risk of common mood disorders or psychoses?

Findings In this population-wide cohort study of 363 960 participants, being a child of consanguineous parents was associated with having an increased likelihood of psychotropic medication use in adulthood. Children of first-cousin consanguineous parents are more than 3 times as likely to receive medications for common mood disorders and more than twice as likely to receive medications for psychoses compared with children of nonrelated parents.

Meaning A child of first-cousin consanguineous parents is at increased risk of common mood disorders and psychoses.

Methods

Study Population and Design

We used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting. Data from the CHS data set were used to form a historical cohort of all 447 452 births delivered to mothers residing in NI during a 15-year period (between 1971 and 1986).[29,30] Details were collated on the child (including gestational age, birth weight, and delivery method) from obstetric records at the time of delivery and on the mother (including mother's age, parity, and area of residence) and the father (including father's age and degree of consanguinity to the mother) by health visitors in the home, typically within 1 to 2 weeks of the birth.[30] Health visitors are public health practitioners that provide support to all families in NI as part of the free-at-the-point-of-service National Health Service.[31] After the introduction of the unique individual Health and Care Number (HCN) in 1998 (which replaced the previously used Community Health Index [CHI] identifier), the CHS data set was updated, allowing for direct one-to-one linkage to other contemporary health care–related data sets. However, not all individuals were successfully assigned a new HCN owing to name changes, marriages, and duplication errors. All CHS data with an HCN were linked to current population-wide data on prescription medication from the Enhanced Prescribing Database (EPD) and death records to investigate the mental health profile of our cohort. The final study data set comprised 363 960 individuals born between 1971 and 1986, alive and residing in NI in 2014, with full data on all variables (447 452 minus 74 738 with missing HCN, 3328 deaths, and 5426 with missing data) (eFigure in the Supplement). The dates of analysis were June 1 to October 31, 2017.

The EPD contains information on all prescriptions dispensed in community pharmacies in NI from 2010 onward.[32] Northern Ireland's health system includes free prescription medication, and every individual is registered with a general practitioner (GP) at birth. For this study, prescribed medication was collated for the calendar years 2010 to 2014 inclusive.

Individual-level informed consent was not required because only nonidentifiable data were made available to the research team. Ethical approval was obtained from the Office for Research Ethics Committees Northern Ireland.

Child Characteristics

Child sex was identified from the CHS data set. Age was calculated as of the study midpoint (June 15, 2012) and grouped as 26 to 29, 30 to 33, 34 to 37, or 38 to 41 years. Birth weight and gestational age were used to calculate a small for gestational age (SGA) variable as per the global reference for fetal weight and birth weight percentiles.[33] An infant was considered SGA if he or she weighed below the 10th percentile of the sex-specific, population-based birth weight reference curve for gestational age. Being SGA has been linked to increased risk of long-term health and social consequences such as neurocognitive impairment, hyperactivity, and lower educational attainment.[34-36] Delivery method was categorized as natural, natural assisted, or cesarean delivery. Births were identified as singleton (n = 357 351) or multiple (n = 6609) to allow for sensitivity analyses limited to singleton births only. Ethnicity information was not available; however, less than 0.8% of the NI population at the time of the CHS were nonwhite.[37]

Parental Characteristics

Maternal and paternal ages were obtained from the CHS data set. Each sex contained a large age range, so only ages within 3 SDs of the mean were accepted, with all others deemed at high risk of error and placed in the "unknown" age group category. Parental age was defined as younger than 18 years, 18 to 35 years, and older than 35 years because parents younger than 18 years and older than 35 years have been identified as having a high risk of psychiatric morbidity in offspring.[38-40] Maternal parity was also identified and categorized as firstborn, parity 1, parity 2, or parity 3 or more. The mother's address at the time of the child's birth was used to assign area-level deprivation.[41] Areas are ranked from most affluent to most deprived based on the number of households in receipt of income-related state benefits and tax credits. Degree of consanguinity between the parents was based on response to questions from the health visitor and was identified as nonrelated parents, first-cousin pairing, second-cousin pairing, or not known.

Prescribed Medication

Receipt of psychotropic medication was used as a proxy indicator of psychopathology. Individuals were classified as being in receipt of antipsychotic medication if they received at least 1 prescription for antipsychotics (British National Formulary [BNF] category 4.3.6) and were classified as being in receipt of medications for common mood disorders if they received at least 1 prescription for antidepressant medication (BNF category 4.3.4) or anxiolytic medication (BNF category 4.3.1) over the 5-year study period (2010-2014). The BNF is the standard reference digest for medications in the United Kingdom.[42] Ever or never use was used for the main analysis, and sensitivity analyses were carried out using a cutoff of at least 3 months' prescriptions, yielding similar results (eTable 1 in the Supplement).

Data Linkage

The prescribing data were linked to the CHS data set using the unique individual HCN. Linkages were undertaken by the data custodians, and the resultant research data set containing only fully anonymized data was made available to the research team within a secure analysis environment.

Analytic Approach

Analysis was divided into 3 stages. First, descriptive analysis of the cohort aimed to investigate the demographic profile of children born to consanguineous partnerships. Second, multilevel multivariable regression models were constructed to assess the likelihood of medication use for common mood disorders given the degree of consanguinity between the parents, adjusting for factors known to be associated with mental ill health and multilevel adjustment for the natural clustering of individuals within GP practices. Receipt of antidepressant or anxiolytic medications was used as a proxy indicator of common mood disorders. This method has been

validated in previous studies.[43,44] Owing to small numbers in each of the consanguinity categories, measures of area deprivation and area rurality were added to the multilevel models separately to ensure convergence. Third, as per the method above, multilevel multivariable regression models were constructed to estimate the likelihood of psychotropic medication use given the degree of parental consanguinity. Receipt of psychotropic medication was used as a proxy measure of psychoses.[32] Sensitivity analyses were carried out repeating each of the multilevel regression analyses limited to singleton births only (n = 357 351), yielding similar results.

Missing HCN

A total of 74 738 individuals (16.7%) were not included in the cohort because they were unable to be assigned an HCN when the unique identifier was updated from CHI to HCN. A CHI-to-HCN lookup was created matching individuals on name, address, and date of birth and allowing a present HCN to be assigned to the historical CHS data set. Individuals with incomplete data in these fields may not have been successfully assigned an HCN. The HCN indicator was used to link the CHS with the EPD data set. This proportion of the population was further explored to assess whether it varied significantly from the study cohort. Female sex (odds ratio [OR], 1.35; 95% CI, 1.33-1.37) was associated with missing HCN, likely owing to marital name changes or migration since assignment of the original CHI. Older age (OR, 3.09; 95% CI, 3.01-3.17 for 38-41 years compared with 26-29 years), SGA (OR, 1.88; 95% CI, 1.83-1.93), and first-cousin consanguineous parents (OR, 1.74; 95% CI, 1.35-2.25) were also associated with missing HCN, likely owing to the higher mortality risk in this group (eTable 2 in the Supplement).

Results

Of the 363 960 individuals born between 1971 and 1986 in our cohort (52.5% [191 102] male), 609 (0.2%) were born to consanguineous parents, including 349 to second-cousin consanguineous parents and 260 to first-cousin consanguineous parents. These results are listed in **Table 1**.

There was no significant difference in the sex distribution of offspring of consanguineous parents. However, a larger proportion of consanguineous offspring were younger, with 43.1% (112 of 260) of the first-cousin group aged 26 to 29 years compared with just 27.1% (93 105 of 344 183) of the nonrelated group. There was no significant difference in SGA or delivery method between consanguineous offspring vs nonconsanguineous offspring, but consanguineous offspring tended to come from larger families, with almost half (46.2% [120 of 260]) of children of first cousins being third born or greater (ie, parity ≥2). Father's age was also older in first-cousin consanguineous unions (mean age, 37.4 years) compared with nonrelated parents (mean age, 30.1 years). A greater proportion of consanguineous offspring were from deprived and rural areas.

There was a clear stepwise increase in the proportion of consanguineous offspring in receipt of psychotropic medication with degree of consanguinity. More than one-third (35.8% [93 of 260]) of children of first-cousin consanguineous unions were in receipt of antidepressant or anxiolytic medications compared with just over one-quarter (26.0% [89 412 of 344 183]) of nonrelated offspring. Furthermore, 8.5% (22 of 260) of first-cousin consanguineous parent offspring were in receipt of antipsychotic medication compared with 4.3% (15 of 349) of second-cousin consanguineous parent offspring and 2.7% (9167 of 344 183) of nonrelated offspring.

In the multilevel regression models, female sex (OR, 1.79; 95% CI, 1.72-1.88), middle age (OR, 1.11; 95% CI, 1.04-1.19 for those aged 38-41 years compared with those aged 26-29 years), and residence in a deprived area at birth (OR, 1.10; 95% CI, 1.04-1.15 for deprived compared with nondeprived areas) were associated with increased likelihood of being in receipt of medications for common mood disorders, while residence in a rural area at birth was associated with decreased likelihood of medication use (OR, 0.91; 95% CI, 0.85-0.97) (**Table 2**). These values reflect well-established associations between sociodemographic factors and mental ill health and affirm the robustness of prescribed antidepressant or anxiolytic medications as a measure of common mood disorders. There was a clear stepwise increase in the ORs for antidepressant or anxiolytic medication use given the degree of consanguinity of parents. After full adjustment for factors known to be associated with poor mental health, children of first-cousin consanguineous parents were more than 3 times as likely to be in receipt of medications for common mood disorders compared with children of nonrelated parents (OR, 3.01; 95% CI, 1.24-7.31). The association between being a child of second-cousin consanguineous parents and receiving medications for common mood disorders was elevated but not statistically significant at the conventional 5% level (OR, 1.31; 95% CI, 0.63-2.71). Restricting analysis to singleton births did not affect these associations (OR, 3.01; 95% CI, 1.23-7.41 for first cousin and OR, 1.31; 95% CI, 0.63-2.71 for second cousin) (full sensitivity results are available in eTable 3 in the Supplement).

Table 3 lists the results of the multilevel models investigating the association between antipsychotic medication use and consanguinity of parents. Being older (OR, 1.15; 95% CI, 1.08-1.23 for those aged 38-41 years compared with those aged 26-29 years), greater than fourth born (OR, 1.15; 95% CI, 1.07-1.23 for parity ≥3 compared with firstborn), and from a deprived area (OR, 1.34; 95% CI, 1.28-1.41 for deprived compared with nondeprived) were associated with increased likelihood of receiving antipsychotic medication, while being female (OR, 0.57; 95% CI, 0.55-0.60) and from a rural area (OR, 0.92; 95% CI, 0.85-0.99 for rural compared with urban) were associated with decreased likelihood of receiving antipsychotic medication. After full adjustment for factors known to be associated with poor mental health, children of first-cousin consanguineous parents were more than twice as likely to be in receipt of antipsychotic medication compared with children of nonrelated parents (OR, 2.13; 95% CI, 1.29-3.51). Restricting analysis to singleton births did not affect these associations (OR, 2.19; 95% CI, 1.32-3.61 for first cousin and OR, 1.37; 95% CI, 0.78-2.40 for second cousin) (full sensitivity results are available in eTable4 in the Supplement).

Risk of psychotropic medication use was also elevated in children of second-cousin consanguineous parents but was not sta-

Table 1. Proportion of the Population With Consanguineous Parents by Level of Consanguinity and Demographic Characteristics

Variable	All, No. (%) (N = 363 960)	%				*P* Value[a]
		Not Related (n = 344 183)	First Cousins (n = 260)	Second Cousins (n = 349)	Not Known (n = 19 168)	
Sex						
Male	191 102 (52.5)	52.5	53.9	51.3	51.7	.82
Female	172 858 (47.5)	47.5	46.1	48.7	48.3	
Age, y						
26-29	97 399 (26.8)	27.1	43.1	39.8	21.1	<.01
30-33	95 663 (26.3)	26.4	18.1	21.2	24.3	
34-37	87 065 (23.9)	23.0	22.3	17.5	40.5	
38-41	83 833 (23.0)	23.5	16.5	21.5	14.1	
SGA						
No	342 412 (94.1)	94.1	92.3	93.7	93.8	.45
Yes	21 548 (5.9)	5.9	7.7	6.3	6.2	
Delivery method[b]						
Vaginal	290 841 (79.9)	80.0	82.3	78.2	79.0	.46
Vaginal assisted (ie, forceps, vacuum) and cesarean delivery	73 119 (20.1)	20.0	17.7	21.8	21.0	
Parity						
Firstborn	96 685 (26.6)	26.5	20.0	27.8	27.9	<.01
1	105 750 (29.1)	29.3	23.5	22.6	25.8	
2	64 794 (17.8)	17.9	12.7	16.1	16.0	
≥3	70 968 (19.5)	19.5	33.5	22.4	19.7	
Unknown	25 763 (7.1)	6.9	10.4	11.2	10.6	
Mother's age, mean, y	27.7	27.7	27.0	27.0	27.3	.08
Father's age, mean, y	30.2	30.1	37.4	35.2	31.6	<.01
Deprivation at birth						
Not deprived	200 238 (55.0)	55.4	41.9	58.7	48.0	<.01
Deprived	156 797 (43.1)	42.7	53.1	38.4	49.8	
Not known	6925 (1.9)	1.9	5.0	2.9	2.2	
Urbanicity at birth						
Urban	144 647 (39.7)	39.8	31.2	22.4	39.2	<.01
Rural	212 369 (58.3)	58.3	63.9	74.8	58.6	
Not known	6944 (1.9)	1.9	5.0	2.9	2.2	
Common mood medication use						
No	269 201 (74.0)	74.0	64.2	68.8	73.2	<.01
Yes	94 759 (26.0)	26.0	35.8	31.2	26.8	
Antipsychotic medication use						
No	354 156 (97.3)	97.3	91.5	95.7	96.9	<.01
Yes	9804 (2.7)	2.7	8.5	4.3	3.1	

Abbreviation: SGA, small for gestational age.

[a] *P* values represent χ^2 test for difference between not related and related populations only (excluding the "Not Known" column).

[b] Delivery method summarized as "Natural" or "Other" owing to small cell counts.

tistically significant at the conventional 5% level (OR, 1.37; 95% CI, 0.79-2.40). Likelihood ratio tests for interactions found no interaction between rurality and consanguinity (χ^2 = 6.37, *P* = .38) or between deprivation and consanguinity (χ^2 = 7.99, *P* = .63).

Discussion

This study shows that a child of first-cousin consanguineous parents is at increased risk of common mood disorders and psychoses. In the study population, 0.2% of children were born to consanguineous parents, which is consistent with previous estimates of population consanguinity in Ireland and among Roman Catholic populations.[26-28] Female sex, middle age, and deprivation were associated with receipt of antidepressant or anxiolytic medications, validating this measure because these factors are known in the literature to be associated with risk of depression and anxiety disorders.[45,46] Children of first-cousin consanguineous parents were more than 3 times as likely to be in receipt of medications for common mood disorders compared with children of nonrelated parents. In addition, children of first-cousin consanguineous parents were more than twice as likely to be in receipt of antipsychotic medication compared with children of nonrelated parents. Male sex, older age, birth weight (SGA), parity, and deprivation also were significantly associated with antipsychotic risk, validating this measure further because these factors are known to be associated with risk of psychoses.[18,47,48]

Table 2. Multilevel Regression Models to Investigate the Likelihood of Antidepressant or Anxiolytic Medication Use Given Parental Consanguinity, Adjusting for the Clustering of Individuals Within GP Practices

	OR (95% CI)		
Variable	Unadjusted	Model 1	Model 2
Consanguineous parents			
Not related	1 [Reference]	1 [Reference]	1 [Reference]
First cousins	3.01 (1.24-7.31)	2.99 (1.23-7.27)	3.01 (1.24-7.31)
Second cousins	1.32 (0.64-2.72)	1.30 (0.63-2.70)	1.31 (0.63-2.71)
Not known	1.03 (0.94-1.14)	1.00 (0.90-1.10)	1.00 (0.90-1.10)
Sex			
Male	NA	1 [Reference]	1 [Reference]
Female	NA	1.79 (1.72-1.88)	1.79 (1.71-1.87)
Age, y			
26-29	NA	1 [Reference]	1 [Reference]
30-33	NA	1.05 (0.99-1.12)	1.05 (0.99-1.12)
34-37	NA	1.10 (1.03-1.17)	1.09 (1.02-1.17)
38-41	NA	1.11 (1.04-1.19)	1.11 (1.04-1.19)
SGA			
No	NA	1 [Reference]	1 [Reference]
Yes	NA	1.06 (0.97-1.16)	1.06 (0.97-1.17)
Delivery method			
Vaginal	NA	1 [Reference]	1 [Reference]
Vaginal assisted (ie, forceps, vacuum)	NA	1.03 (0.95-1.10)	1.02 (0.95-1.10)
Cesarean delivery	NA	0.97 (0.89-1.06)	0.97 (0.89-1.05)
Parity			
Firstborn	NA	1 [Reference]	1 [Reference]
1	NA	0.97 (0.91-1.04)	0.97 (0.92-1.04)
2	NA	0.93 (0.87-1.00)	0.93 (0.87-1.00)
≥3	NA	1.00 (0.93-1.07)	1.01 (0.94-1.09)
Unknown	NA	0.93 (0.84-1.03)	0.93 (0.84-1.04)
Mother's age, y			
<18	NA	1.06 (0.85-1.33)	1.04 (0.86-1.34)
18-35	NA	1 [Reference]	1 [Reference]
>35	NA	1.01 (0.92-1.10)	1.00 (0.92-1.10)
Not known	NA	1.05 (0.67-1.64)	1.04 (0.67-1.63)
Father's age, y			
<18	NA	1.90 (0.86-4.21)	1.91 (0.87-4.23)
18-35	NA	1 [Reference]	1 [Reference]
>35	NA	0.93 (0.86-1.00)	0.93 (0.86-1.00)
Not known	NA	1.11 (1.02-1.20)	1.12 (1.03-1.22)
Deprivation at birth			
Not deprived	NA	1 [Reference]	NA
Deprived	NA	1.10 (1.04-1.15)	NA
Not known	NA	0.88 (0.73-1.04)	NA
Urbanicity at birth			
Urban	NA	NA	1 [Reference]
Rural	NA	NA	0.91 (0.85-0.97)
Not known	NA	NA	0.79 (0.65-0.94)
Variance	0.352759	0.351842	0.352919
P value	<.001	<.001	<.001
Variance partition coefficient	0.097	0.097	0.097

Abbreviations: GP, general practitioner; NA, not applicable; OR, odds ratio; SGA, small for gestational age.

There are several theories as to why consanguinity may result in mental ill health in progeny. First, high heritability points to a major role for inherited genetic variants in the etiology of psychiatric disorders.[49] In recent years, genome-wide association studies[50,51] of schizophrenia, bipolar disorder, and major depression have provided strong support for a substantial polygenic contribution of a large number of small genetic effects. An alternative view is that most of the variance for certain complex diseases is owing to moderately highly penetrant rare variants.[52] As a form of assortative mating, consanguinity increases polygenic loading and thus is likely associated with a higher risk of mental disorder in progeny.[53] However, this is only true if each of the parents carries common susceptibility loci.

Table 3. Multilevel Regression Models to Investigate the Likelihood of Antipsychotic Medication Use Given Parental Consanguinity, Adjusting for the Clustering of Individuals Within GP Practices

	OR (95% CI)		
Variable	Unadjusted	Model 1	Model 2
Consanguineous parents			
Not related	1 [Reference]	1 [Reference]	1 [Reference]
First cousins	2.30 (1.40-3.77)	2.09 (1.26-3.44)	2.13 (1.29-3.51)
Second cousins	1.39 (0.80-2.42)	1.39 (0.79-2.43)	1.37 (0.79-2.40)
Not known	0.97 (0.89-1.06)	0.92 (0.84-1.01)	0.92 (0.84-1.01)
Sex			
Male	NA	1 [Reference]	1 [Reference]
Female	NA	0.57 (0.55-0.60)	0.57 (0.55-0.60)
Age, y			
26-29	NA	1 [Reference]	1 [Reference]
30-33	NA	1.04 (0.98-1.11)	1.04 (0.98-1.11)
34-37	NA	1.10 (1.03-1.17)	1.10 (1.03-1.17)
38-41	NA	1.15 (1.08-1.23)	1.15 (1.08-1.22)
SGA			
No	NA	1 [Reference]	1 [Reference]
Yes	NA	1.16 (1.07-1.26)	1.18 (1.09-1.28)
Delivery method			
Vaginal	NA	1 [Reference]	1 [Reference]
Vaginal assisted (ie, forceps, vacuum)	NA	1.04 (0.97-1.11)	1.03 (0.96-1.10)
Cesarean delivery	NA	1.09 (1.01-1.18)	1.08 (1.00-1.17)
Parity			
Firstborn	NA	1 [Reference]	1 [Reference]
1	NA	1.04 (0.98-1.11)	1.05 (0.98-1.11)
2	NA	1.08 (1.00-1.15)	1.08 (1.01-1.16)
≥3	NA	1.15 (1.07-1.23)	1.18 (1.10-1.26)
Unknown	NA	1.03 (0.93-1.13)	1.03 (0.93-1.14)
Mother's age, y			
<18	NA	1.12 (0.93-1.35)	1.15 (0.96-1.39)
18-35	NA	1 [Reference]	1 [Reference]
>35	NA	0.98 (0.90-1.06)	0.97 (0.90-1.05)
Not known	NA	0.90 (0.60-1.35)	0.88 (0.59-1.33)
Father's age, y			
<18	NA	1.43 (0.84-2.42)	1.45 (0.85-2.47)
18-35	NA	1 [Reference]	1 [Reference]
>35	NA	1.02 (0.95-1.10)	1.01 (0.94-1.09)
Not known	NA	1.32 (1.23-1.42)	1.35 (1.26-1.45)
Deprivation at birth			
Not deprived	NA	1 [Reference]	NA
Deprived	NA	1.34 (1.28-1.41)	NA
Not known	NA	1.13 (0.94-1.35)	NA
Urbanicity at birth			
Urban	NA	NA	1 [Reference]
Rural	NA	NA	0.92 (0.85-0.99)
Not known	NA	NA	0.89 (0.74-1.07)
Variance	0.354988	0.318330	0.348805
P value	<.001	<.001	<.001
Variance partition coefficient	0.097	0.088	0.096

Abbreviations: GP, general practitioner; NA, not applicable; OR, odds ratio; SGA, small for gestational age.

A second theory suggests that having consanguineous parents is associated with "social stigma," especially in Western societies where consanguineous partnerships are considered taboo.[13] Being a member of a minority population and having even perceived discrimination are known to be associated with poor mental health outcomes.[54,55] However, it is not known how many of the children in our cohort were aware of the genetic relationship of their parents.

Third, the observed association may be owing to some unmeasured confounding associated with the likelihood of consanguinity and to decreased mental health. However, the study design allowed for a robust examination of the mental health risk associated with consanguineous parents: the data were population wide, capturing an entire cohort born over 15 years, and contained detailed neonatal information on the individual and detailed sociodemographic information on the

parents. The prevalence of consanguineous parents recorded in this study is in keeping with other estimates,[26-28] and the associations between mental health and a range of sociodemographic factors reflect those found in other studies worldwide.[17,46-48] The analysis included regression modeling, adjusting for a range of confounders known to be associated with mental health, and multilevel modeling allowed for excellent adjustment of the potential unknown confounding associated with the natural clustering of individuals within GP practices. The results illustrate a clear increasing, stepwise association between level of consanguinity and mental ill health, suggesting a quasi-dose-response association, supporting a causal association between consanguineous parents and mental health of progeny.

Strengths and Limitations

Our study has significant strengths and limitations. Regarding its strengths, this study is the first population-wide study to date of consanguinity and mental health of progeny, and it uses an objective measure of mental ill health in the form of prescribed medication data.

Its caveats concern the information limitations of the data, including prescription data without accompanying diagnosis codes or indication for use. However, prescription medication receipt as an indicator of mental ill health has been used effectively in previous studies[44,56-58] worldwide. Consanguinity was identified by parents' response to a question asked by a health visitor in their home, but some individuals may not have identified themselves as consanguineous parents owing to fears of stigma, discrimination, and even legal prosecution.[13] However, there is no legal impairment to consanguinity in NI, so fear of legal prosecution is unlikely to be a factor herein. There is no information on the mental health of the parents of our cohort. Parental mental health is known to be related to the mental health of the children; however, almost all consanguineous parents would have had to have poor mental health themselves to produce the associations observed in this study, and there is no evidence to suggest poorer mental health among consanguineous couples. Last, to experience the outcome of interest, participants must have been alive in 2010 to 2014. However, psychopathology is known to be associated with mortality risk, meaning there is mortality bias in our results. This factor likely excludes those with the most severe mental disorders, biasing the results toward the null, but does not affect the robustness of the observed associations.

Conclusions

Despite the recent debate around the physical genetic risk of consanguineous parents, more research is required on the psychological effects of consanguineous parents on progeny. The results of this study suggest a significant association of consanguinity with mental health independent of birth weight, mother's parity, parental age, deprivation, and rurality. However, to effectively analyze the effect of consanguinity on physical and mental ill health, there is a need to implement accurate record keeping of marriage between cousins. This study demonstrates the ability of population-wide data linkage to explore hard-to-reach populations, and we call on other countries with similar large-scale administrative data sources to use their data to explore the effects of consanguinity on offspring. We suggest that these findings will be of value to health promotion and public health professionals and to those commissioning antenatal, pediatric, and clinical genetic services. Sensitive advice about the risks should be provided to communities that favor consanguineous unions to assist in reproductive decision making.

ARTICLE INFORMATION

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Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Maguire, O'Reilly.
Critical revision of the manuscript for important intellectual content: All authors.
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EDITORIAL

Consanguineous Marriage and the Psychopathology of the Progeny of First-Cousin Couples

Alison Shaw, MA, DPhil

In the late 19th century, George Darwin, a child of first-cousin parents, investigated the parental consanguinity of inmates of lunatic asylums in England. He found the prevalence of cousin marriage among the parents of inmates to be no higher than among the general population, and so could "only draw the negative conclusion that as far as insanity and idiocy go, no evil *has been shown* to accrue from consanguineous marriages"[1(p1434)] [italics in original]. But, he added, "it might still be shown, by more accurate methods of research, that it is so."[1(p1436)]

Related article

A higher risk of recessively inherited single-gene disorders in the progeny of consanguineous couples compared with nonconsanguineous couples has since been established.[2,3] The elevated risk is for a wide range of medical problems: thousands of mostly very rare dysmorphic syndromes, metabolic conditions, neurologic conditions, skeletal problems, renal problems, and hematologic conditions such as thalassemias.[2,4] We also understand that the principles of Mendelian inheritance underpin this risk: the child of first-cousin parents can inherit from each parent an identical recessive mutation that originated with 1 of the 2 grandparents that the parents have in common.

What has not until now been demonstrated is that parental consanguinity also elevates the risk for serious common psychiatric disorders. In their population-wide data-linkage study from Northern Ireland, Maguire et al[5] used pharmacy prescriptions for antipsychotic medications and antidepressant drugs as proxies for psychoses and severe depression, respectively, to investigate this risk. Adult offspring of first-cousin parents were more than 3 times more likely than individuals with nonconsanguineous parents to be receiving mood-disorder medication and more than twice as likely to be receiving antipsychotic medication, after controlling for other factors known to be associated with these conditions. The authors suggest that the outcome is step-wise, the risk being higher for the progeny of first cousins than for people with second-cousin parents (whose risk was elevated but not statistically significant). The authors call for sensitive counseling for consanguineous couples and for the systematic collection of consanguinity data to enable further research.

What might be entailed in counseling consanguineous couples about these risks? Risk information can be put to work in different ways. A risk that is double or triple the risk to children of unrelated parents sounds scary, but in absolute terms, disease incidence depends on the initial background risk. Background risk to nonconsanguineous couples of having a child with a medical congenital or genetic problem is approximately 2.5%.[4] For first cousins, this risk is usually described as approximately doubled.[3] Another way of putting this is to say that there is a roughly 95% chance that a first-cousin couple will have a child unaffected by a genetic medical problem, which sounds much less scary.

For psychosis, let us assume for simplicity that prescriptions for antipsychotic medications are an indication of schizophrenia diagnosis, even though antipsychotic drugs are also prescribed for other indications. Since the lifetime prevalence of schizophrenia is between 0.30% and 0.66%,[6] a doubled risk for first cousins gives them about a 0.60% to 1.32% chance of having a child who, as an adult, will be prescribed antipsychotic medications for this condition. For depression, background risk is much higher, although harder to pinpoint[7]; if we estimate it at approximately 10%, then there is a 30% chance of an adult child of a first-cousin couple being prescribed antidepressant medications. In a more positive spin, this yields a 99% chance that the grown child of first-cousin parents will not need to take antipsychotic medications and a 70% chance that they will not be prescribed antidepressant drugs.

Risk information is also only as good as the data on which it is based. One of the reasons why the elevated medical risks associated with consanguineous marriage are (as Maguire et al[5] note) hotly debated is that establishing accurate levels of consanguinity is difficult. Particular recessive mutations may be more prevalent within endogamous subpopulations even where marriages are not consanguineous, and first cousins with a family history of consanguineous marriage across generations may have a higher risk than first cousins without any additional consanguinity.[3,4] The definition of *cousin* is not universal: it may denote a social category rather than a person in a particular genealogical position, and, in terms of shared blood, a father's-side cousin may be viewed as closer than a cousin on the mother's side of the family.[8] This calls for caution in using risk data from the study from Northern Ireland by Maguire et al[5] for counseling couples elsewhere in the world.

What can be done to manage the risk? Again, the contrast with recessive medical conditions is instructive. Parents in receipt of a firm recessive diagnosis in a child have, as obligate carriers, a recurrence risk of 25% with each conception. If the mutation has been identified, a prenatal genetic test or preimplantation genetic diagnosis may be available to refine the risk to show that a child will be affected or not. Genetic counseling and premarital or preconception carrier testing may also be offered beyond the carrier couple to other members of the family

(such as the siblings of the carrier couple) in communities in which consanguineous marriages are usual. In this context, what matters clinically is establishing the carrier status of specific conditions in specific people, rather than parental consanguinity as such. By contrast, there is currently no means of managing the elevated risk for psychosis or severe depression in progeny, except by cousin couples refraining from reproduction.

A further challenge in conveying genetic risk information is that laypeople have prior understandings of biological inheritance and/or the causes of illness that do not necessarily match medical models.[9] People often understand medical and psychiatric illnesses as having environmental causes—unintentional injuries, infections, a traumatic life event, migration, drug use, the will of God, or the intervention of malicious spirits—and thus to be potentially treatable by altering these external forces. Moreover, for someone without knowledge of Mendelian genetics, it is counterintuitive that we all carry genetic mutations for conditions that do not affect us. Conveying risk information for complex conditions may be trickier still because straightforward Mendelian principles do not apply. Complex risks may map more easily onto lay models in which psychiatric illness is viewed as the result of both external and internal factors, such as trauma and a family predisposition. On the other hand, evidence of an elevated risk of psychoses and depression with parental consanguinity might also be misleadingly interpreted to indicate that psychiatric conditions are entirely genetically determined.

Like any marriage, a consanguineous one can be viewed as a balance of socioeconomic, political, medical, psychological, and emotional risks and benefits.[10] Any attempt to weigh all these factors objectively to make a case for or against cousin marriage would be difficult, if not futile. Collecting nationwide data on parental consanguinity for health research will require sensitivity to the stigma currently associated with cousin marriage on grounds of genetic risk, and this is true beyond Western Europe.[8]

Despite these caveats, the paper by Maguire et al[5] is important and should be a major stimulus to future efforts to understand the genetic contribution to common complex psychiatric conditions. Given the impetus toward whole-genome sequencing in many parts of the world, including among the rapidly modernizing Gulf states,[8,11] we may have entire genomes at our disposal to guide genetic counseling for medical and psychiatric conditions.

ARTICLE INFORMATION

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Supplementary Online Content

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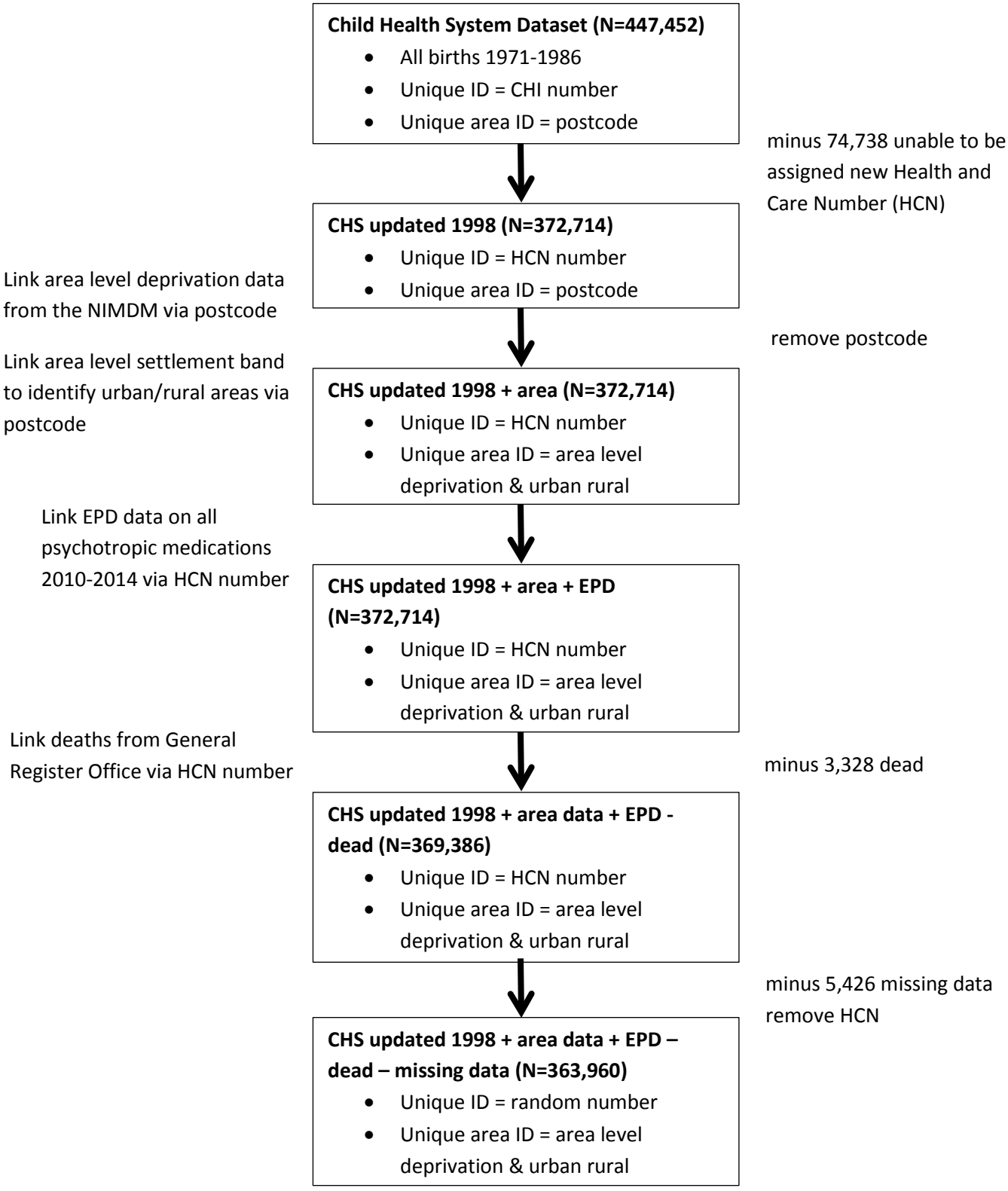
This supplementary material has been provided by the authors to give readers additional information about their work.



eFigure. Flowchart Illustrating the Generation of the Study Data Set

eTable 1. Multilevel Regression Models to Investigate the Likelihood of ≥3 Months' Antidepressant and/or Anxiolytic or ≥3 Months' Antipsychotic Medication Prescriptions Given Parental Consanguinity, Adjusting for the Clustering of Individuals Within GP Practices. Figures represent Odds Ratios (95% Confidence Intervals)

		CMD ≥3		AP≥3	
		Model 1	**Model 2**	**Model 1**	**Model 2**
Parents Related	**Not related**	1.00	1.00	1.00	1.00
	First cousins	1.99 (1.27,3.12)	2.01 (1.28,3.15)	1.98 (1.04,3.77)	2.03 (1.07,3.85)
	Second cousins	1.06 (0.73,1.54)	1.06 (0.73,1.54)	1.83 (0.94,3.55)	1.82 (0.94,3.52)
	Not known	0.98 (0.92,1.03)	0.98 (0.92,1.03)	0.95 (0.84,1.07)	0.95 (0.84,1.08)
Gender	**Male**	1.00	1.00	1.00	1.00
	Female	1.47 (1.43,1.50)	1.46 (1.42,1.50)	0.49 (0.46,0.52)	0.49 (0.46,0.52)
Age (years)	**26-29**	1.00	1.00	1.00	1.00
	30-33	1.16 (1.12,1.21)	1.16 (1.12,1.21)	1.12 (1.03,1.22)	1.12 (1.03,1.22)
	34-37	1.34 (1.29,1.39)	1.34 (1.29,1.39)	1.22 (1.12,1.33)	1.22 (1.12,1.33)
	38-41	1.44 (1.39,1.50)	1.44 (1.39,1.49)	1.45 (1.33,1.58)	1.45 (1.33,1.57)
SGA	**No**	1.00	1.00	1.00	1.00
	Yes	1.11 (1.06,1.16)	1.12 (1.06,1.17)	1.25 (1.13,1.39)	1.27 (1.15,1.41)
Delivery Method	**Natural**	1.00	1.00	1.00	1.00
	Assisted	1.02 (0.98,1.06)	1.02 (0.97,1.06)	1.03 (0.94,1.13)	1.02 (0.93,1.11)
Parity	**First Born**	1.00	1.00	1.00	1.00
	1	0.97 (0.94,1.01)	0.97 (0.94,1.01)	1.06 (0.97,1.14)	1.06 (0.98,1.15)
	2	0.97 (0.93,1.01)	0.97 (0.94,1.01)	1.08 (0.99,1.18)	1.09 (1.00,1.19)
	>3	1.02 (0.97,1.06)	1.03 (0.99,1.07)	1.18 (1.08,1.29)	1.22 (1.11,1.33)
	Unknown	0.92 (0.87,0.98)	0.92 (0.87,0.98)	1.04 (0.90,1.19)	1.04 (0.91,1.19)
Mother's Age	**<18**	1.09 (0.97,1.22)	1.10 (0.98,1.24)	1.26 (1.00,1.60)	1.30 (1.02,1.64)
	18-35	1.00	1.00	1.00	1.00
	>35	0.99 (0.94,1.04)	0.98 (0.93,1.04)	1.02 (0.91,1.13)	1.01 (0.90,1.13)
	Not known	0.88 (0.69,1.13)	0.88 (0.69,1.13)	1.03 (0.62,1.70)	1.01 (0.61,1.67)
Father's Age	**<18**	1.22 (0.85,1.77)	1.24 (0.86,1.79)	1.19 (0.57,2.46)	1.21 (0.58,2.51)
	18-35	1.00	1.00	1.00	1.00
	>35	0.97 (0.93,1.01)	0.97 (0.93,1.01)	1.08 (0.99,1.19)	1.07 (0.97,1.17)
	Not known	1.10 (1.05,1.15)	1.12 (1.07,1.17)	1.28 (1.17,1.40)	1.31 (1.19,1.44)
Deprivation at Birth	**Not Deprived**	1.00	-	1.00	-
	Deprived	1.14 (1.11,1.18)	-	1.35 (1.27,1.44))	-
Urbanicity at Birth	**Urban**	-	1.00	-	1.00
	Rural	-	0.91 (0.87,0.95)	-	0.93 (0.85,1.01)
Variance		0.159565	0.1584288	0.2210672	0.2385557
p		<0.001	<0.001	<0.001	<0.001
VPC*		0.046	0.046	0.063	0.068

*VPC = Variance Partition Co-efficient

eTable 2. Regression Analysis to Investigate the Likelihood of Missing HCN Given Neonatal Factors and Consanguinity of Parents

		Model 1
Consanguineous Parents	**No**	1.00
	First Cousins	1.74 (1.35,2.25)
	Second Cousins	1.18 (0.92,1.52)
	Not Known	1.72 (1.67,1.77)
Gender	**Male**	1.00
	Female	1.35 (1.33,1.37)
Age (years)	**26-29**	1.00
	30-33	1.27 (1.23,1.31)
	34-37	1.53 (1.50,1.58)
	38-41	3.09 (3.02,3.17)
SGA	**No**	1.00
	Yes	1.89 (1.83,1.93)
Delivery Method	**Natural**	1.00
	Other	1.06 (1.04,1.08)
Parity	**First Born**	1.00
	1	0.85 (0.83,0.87)
	2	0.78 (0.76,0.80)
	>3	0.75 (0.73,0.76)
	Unknown	1.26 (1.22,1.31)

eTable 3. Multilevel Regression Models to Investigate the Likelihood of Antidepressant and/or Anxiolytic Medication Given Parental Consanguinity for Singleton Births Only, Adjusting for the Clustering of Individuals Within GP Practices. Figures represent Odds Ratios (95% Confidence Intervals)

		Unadjusted	Model 1	Model 2
Consanguineous Parents	**No**	1.00	1.00	1.00
	First Cousins	3.00 (1.22,7.36)	3.00 (1.22,7.38)	3.01 (1.23,7.41)
	Second Cousins	1.32 (0.64,2.72)	1.30 (0.63,2.70)	1.31 (0.63,2.71)
	Not Known	1.02 (0.92,1.13)	0.98 (0.89,1.09)	0.98 (0.89,1.09)
Gender	**Male**		1.00	1.00
	Female		1.79 (1.71,1.87)	1.78 (1.70,1.86)
Age (years)	**26-29**		1.00	1.00
	30-33		1.06 (0.99,1.13)	1.06 (0.99,1.13)
	34-37		1.10 (1.03,1.18)	1.10 (1.03,1.17)
	38-41		1.12 (1.05,1.19)	1.11 (1.04,1.19)
SGA	**No**		1.00	1.00
	Yes		1.07 (0.98,1.18)	1.08 (0.98,1.19)
Delivery Method	**Natural**		1.00	1.00
	Natural Assisted		1.04 (0.97,1.12)	1.04 (0.96,1.12)
	C-section		0.98 (0.90,1.07)	0.98 (0.90,1.07)
Parity	**First Born**		1.00	1.00
	1		0.98 (0.92,1.05)	0.98 (0.92,1.05)
	2		0.94 (0.88,1.01)	0.95 (0.88,1.02)
	>3		1.00 (0.93,1.08)	1.02 (0.94,1.10)
	Unknown		0.94 (0.84,1.04)	0.94 (0.85,1.04)
Mother's Age	**<18**		1.06 (0.85,1.33)	1.07 (0.86,1.34)
	18-35		1.00	1.00
	>35		0.99 (0.91,1.09)	0.99 (0.90,1.09)
	Not known		1.05 (0.67,1.65)	1.04 (0.67,1.64)
Father's Age	**<18**		1.90 (0.86,4.21)	1.92 (0.87,4.24)
	18-35		1.00	1.00
	>35		0.93 (0.87,1.01)	0.93 (0.86,1.01)
	Not known		1.11 (1.02,1.20)	1.12 (1.03,1.22)
Deprivation at Birth	**Not Deprived**		1.00	-
	Deprived		1.10 (1.04,1.15)	-
	Not known		0.87 (0.73,1.05)	-
Urbanicity at Birth	**Urban**		-	1.00
	Rural		-	0.91 (0.86,0.97)
	Not known		-	0.79 (0.65,0.94)
Variance		0.3550799	0.3542844	0.3554447
p		<0.001	<0.001	<0.001
VPC*		0.100	0.097	0.098

*VPC = Variance Partition Co-efficient

eTable 4. Multilevel Regression Models to Investigate the Likelihood of Antipsychotic Medication Given Parental Consanguinity for Singleton Births Only, Adjusting for the Clustering of Individuals Within GP Practices. Figures represent Odds Ratios (95% Confidence Intervals)

		Unadjusted	Model 1	Model 2
Consanguineous Parents	**No**	1.00	1.00	1.00
	First Cousins	2.37 (1.44,3.89)	2.13 (1.29,3.53)	2.19 (1.32,3.61)
	Second Cousins	1.39 (0.80,2.41)	1.38 (0.79,2.42)	1.37 (0.78,2.40)
	Not Known	0.97 (0.89,1.07)	0.92 (0.84,1.01)	0.92 (0.84,1.01)
Gender	**Male**		1.00	1.00
	Female		0.57 (0.55,0.60)	0.57 (0.55,0.60)
Age (years)	**26-29**		1.00	1.00
	30-33		1.04 (0.98,1.11)	1.04 (0.98,1.11)
	34-37		1.10 (1.03,1.17)	1.10 (1.03,1.17)
	38-41		1.15 (1.08,1.22)	1.14 (1.07,1.22)
SGA	**No**		1.00	1.00
	Yes		1.18 (1.09,1.28)	1.20 (1.11,1.30)
Delivery Method	**Natural**		1.00	1.00
	Natural Assisted		1.04 (0.97,1.12)	1.03 (0.96,1.11)
	C-section		1.09 (1.00,1.18)	1.08 (1.00,1.17)
Parity	**First Born**		1.00	1.00
	1		1.05 (0.99,1.12)	1.05 (0.99,1.12)
	2		1.08 (1.01,1.16)	1.09 (1.02,1.17)
	>3		1.16 (1.08,1.24)	1.18 (1.10,1.27)
	Unknown		1.03 (0.93,1.14)	1.03 (0.94,1.14)
Mother's Age	**<18**		1.12 (0.93,1.35)	1.14 (0.95,1.38)
	18-35		1.00	1.00
	>35		0.97 (0.89,1.06)	0.97 (0.89,1.05)
	Not known		0.90 (0.60,1.36)	0.89 (0.59,1.34)
Father's Age	**<18**		1.44 (0.85,2.45)	1.47 (0.86,2.50)
	18-35		1.00	1.00
	>35		1.02 (0.94,1.09)	1.01 (0.93,1.08)
	Not known		1.32 (1.23,1.42)	1.35 (1.25,1.44)
Deprivation at Birth	**Not Deprived**		1.00	-
	Deprived		1.34 (1.28,1.41)	-
	Not known		1.10 (0.92,1.33)	-
Urbanicity at Birth	**Urban**		-	1.00
	Rural		-	0.92 (0.86,0.99)
	Not known		-	0.88 (0.72,1.06)
Variance		0.3562542	0.3519837	0.350317
p		<0.001	<0.001	<0.001
VPC*		0.098	0.097	0.096

*VPC = Variance Partition Co-efficient