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Consanguinity Associated With Increased Risk for Bipolar I Disorder in Egypt

Hader Mansour^{1,2}, Lambertus Klei¹, Joel Wood¹, Michael Talkowski^{1,3}, Kodavali Chowdari¹, Warda Fathi², Ahmed Eissa², Amal Yassin², Hala Salah², Salwa Tobar², Hala El-Boraie², Hanan Gaafar², Mai Elassy², Nahed E. Ibrahim¹, Wafaa El-Bahaei², Mohamed Elsayed², Mohamed Shahda², Eman El Sheshtawy², Osama El-Boraie², Farha El-Chennawi⁴, Bernie Devlin^{1,3}, and Vishwajit L. Nimgaonkar^{1,3,*}

¹Department of Psychiatry, University of Pittsburgh School of Medicine, Western Psychiatric Institute and Clinic, Pittsburgh, Pennsylvania

²Department of Psychiatry, Mansoura University School of Medicine, Mansoura, Egypt

³Department of Human Genetics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania

⁴Department of Clinical Pathology, Mansoura University School of Medicine, Mansoura, Egypt

Abstract

We aimed to contrast rates of consanguinity among patients with bipolar I disorder (BP1) and controls in a population with customary consanguineous marriages (i.e., marriage between related individuals). Consanguinity increases risk for numerous monogenic and polygenic diseases. Whether the risk for BP1 increases with consanguinity has not been investigated systematically. Two independent studies were conducted in Egypt: (1) Case-control study 93 patients with BP1, 90 screened adult control individuals, and available parents. The inbreeding coefficient/consanguinity rate was estimated in two ways: using 64 DNA polymorphisms (“DNA-based” rate); and from family history data (“self report”); (2) Epidemiological survey: total of 1,584 individuals were screened, from whom self-reported consanguinity data were obtained for identified BP1 cases (n=35) and 150 randomly selected, unaffected control individuals. DNA-based consanguinity rates showed significant case-control differences ($P=0.0039$). Self-reported consanguinity rates were also elevated among BP1 patients in both samples (Study #1 OR=2.66, 95% confidence intervals, CI: 1.34, 5.29; Study #2: OR=4.64, 95% CI: 2.01, 10.34). In conclusion, two independent, systematic studies indicate increased consanguinity among Egyptian BP1 patients in the Nile delta region. Self-reported estimates of consanguinity are bolstered by DNA-based estimates, and both show significant case-control differences for BP1.

Keywords

bipolar disorder; consanguinity; DNA; genetic; association; inbreeding

*Correspondence to: Vishwajit L. Nimgaonkar, WPIC, Room. 441, 3811 O'Hara Street, Pittsburgh, PA 15213. nimga+@pitt.edu. Additional Supporting Information may be found in the online version of this article.

INTRODUCTION

The etiology of bipolar I disorder (BP1) remains a mystery. A familial tie to an affected individual, however, is a well-known risk factor. Adoption and twin studies suggest that the familial aggregation is likely to be due to genetic factors [Bertelsen et al., 1977; McGuffin et al., 2003], with the heritability of BP1 estimated at 60–80% [Tsuang and Faraone, 2000; McGuffin et al., 2003]. Yet even the mode of inheritance is unknown, beyond the observation that it has a complex inheritance pattern, implying that the interplay of many genes and environmental factors probably determines risk [McGuffin et al., 1994].

For simple Mendelian inheritance, consanguineous offspring, resulting from parents who share a common ancestor no more remote than a great-great grandparent, are at increased risk when the risk alleles show recessive inheritance [Teebi and Farag, 1997; Charlesworth and Charlesworth, 1999; Bittles, 2002; Al-Gazali et al., 2006]. For convenience offspring of consanguineous parents are referred to as being consanguineous here, though the term inbreeding is also used. Consanguinity increases the risk for childhood mortality as well [Bittles and Neel, 1994; Stoltenberg et al., 1999; Jorde, 2001]. What is perhaps more remarkable is that consanguinity also appears to impact the risk for disorders of complex inheritance. Recent evidence suggests that the risk for hypertension, coronary artery disease and certain types of cancer [Charlesworth and Hughes, 1996; Rudan et al., 2003a,b] also increases with the degree of consanguinity. The increased risk cannot be attributed solely to socio-economic factors and is consistent with deleterious effects of consanguinity on fitness [Shami et al., 1989; Bittles et al., 1991]. The risks could have considerable public health impact, as it is estimated that consanguineous marriages are being practiced among approximately one billion people worldwide [Rudan et al., 2003a].

Since the turn of the 20th century, it has been claimed that the familial distribution of certain psychiatric disorders is consistent with recessive inheritance or complex inheritance involving recessive loci [Hurst, 1972; Stewart et al., 1980; Craddock et al., 1994; Lerer et al., 2003]. Indeed, some family based studies and anecdotal reports have reported increased consanguinity among relatives of patients with psychoses and mood disorders [Gomaa, 1985; Chaleby and Tuma, 1987; Gindilis et al., 1989; Bulaeva et al., 2003; Ewald et al., 2003]. However, few studies have systematically examined this hypothesis at the population level. Two case-control studies reported increased frequency of parental consanguinity among patients with schizophrenia (SZ) [Abaskuliev and Skoblo, 1975; Dobrusin et al., 2008]. Island communities in Croatia demonstrate a gradient of increased risk for SZ with degree of inbreeding [Rudan et al., 2003a], estimated indirectly from pedigree data among 480 individuals. Importantly, in this study elevated consanguinity increased risk for SZ, unipolar or bipolar depression (treated as a single group), Alzheimer's disease, coronary artery disease, stroke, cancer, asthma, and peptic ulcer, but not type 2 diabetes mellitus. Thus, for this sample, consanguinity resulted in a general increase in risk for a host of diseases. This observation leads to an intriguing question for psychiatry: could inbreeding be a risk factor for psychiatric disorders more generally?

Middle Eastern populations offer a unique opportunity to measure the impact of consanguinity, as consanguinity rates are relatively high (20–60%) [Bittles, 1995; Hoodfar

and Teebi, 1996; Teebi and Farag, 1997; Rudan et al., 2006]. In Egypt, consanguineous marriages are practiced by Muslims, as well as the minority Christians, for economic and social reasons. The public health impact of consanguinity has come to the fore recently in the Middle East [Al-Gazali et al., 2006] due to a relatively high frequency of recessively inherited disorders, [Barakat et al., 1986; Bittles, 1995; Hoodfar and Teebi, 1996; Alwan and Modell, 1997; Teebi and Farag, 1997; Zlotogora, 1997]. Some investigators have also reported increased rates of consanguinity among patients with psychoses [Gomaa, 1985; Chaleby and Tuma, 1987].

We report on the relationship of consanguinity and risk for BP1 in Dakahlia governorate, a province in the Nile delta. Prior regional pilot studies supported an association between parental consanguinity and risk for BP1. Two independent surveys, one a medical record study and another outpatient study, produced consanguinity rates of roughly 36–42% for SZ and BP1 patients (n=228) [Yassin, 2003], substantially higher than published rates of consanguinity for this population (24%) [Settin and Algelani, 1997]. With these suggestive but preliminary results, we launched a study of two independent samples at Mansoura, Egypt and the surrounding villages. Similar to other studies, we estimated consanguinity rate on the basis of self-reported family history data. Because there could be unforeseen and unknown biases in these reports, we also estimated consanguinity rate on the basis of polymorphic genetic markers. Such markers are highly informative and thus are very useful when estimating consanguinity. This dual approach distinguishes our study from most other published studies.

METHODS

The studies were conducted in Dakahlia governorate (province) in the North eastern part of the Nile delta region of Egypt. Its population is approximately 6 million; 60% of the people live in villages. Dakahlia has been populated since recorded times. Dakahlia is not geographically or genetically isolated and marriages across village lines are common. Individuals in Dakahlia also frequently marry outside the region and vice versa. Consanguinity is not taboo in this region. Marriages between first cousins are the most common form of consanguineous marriages in Egypt, and uncle niece marriages are rare.

Mansoura, the capital city of Dakahlia is located 70 miles north of Cairo and 40 miles from the Mediterranean Sea. Mansoura University Hospital (MUH) is a Government funded facility that serves as the primary psychiatric care facility for a population of over 7 million from Mansoura and the surrounding villages.

Care was taken to ensure that there was no overlap between participants in each of the following studies. All the data were gathered by local interviewers who were known to the participants.

Study #1: Case–Control Study

Clinical

Cases: Consenting, unrelated outpatients attending the MUH Psychiatry outpatient clinics who received a clinical diagnosis of BP1 (DSM IV criteria) were ascertained without knowledge of their family structure.

Controls: The controls were consenting adults who resided in the same geographic areas as the patients. The sample included pregnant women admitted for normal delivery to MUH or their spouses (n=30) and donors at the MUH blood bank (n=60). The control individuals were recruited without knowledge of family structure and were balanced with regard to age and area of residence to the cases. They were recruited from the same residential area and over the same period as the cases.

Interview schedules: Participants were interviewed by trained psychiatrists using the Arabic version of the Schedule for Clinical Assessment in Neuropsychiatry (SCAN), a structured diagnostic interview schedule [Wing et al., 2001]. Additional clinical information was obtained as needed from available clinical records and from relatives. All available clinical information was synthesized and consensus diagnoses assigned by two or more faculty members of the MUH Psychiatry Department who had participated in inter-rater diagnostic reliability exercises (details below).

Family history of parental consanguinity, as well as family history of BP1 and psychoses was obtained using the Arabic version of the Family Interview for Genetic Studies (FIGS). The FIGS is a semi-structured interview schedule for collection of familial psychiatric and non-psychiatric data [Maxwell, 1992]. Bilingual Egyptian psychiatrists translated the English version of the FIGS into Arabic and validated the translation for use in the Egyptian setting. All participants completed the FIGS. In addition, parents of cases and controls were also interviewed with regard to consanguinity when available, but diagnostic interviews were not conducted among the parents.

Inter-rater reliability: Five psychiatrists (H.M., W.F., A.Y., A.E., and S.T.) reviewed blinded printouts of 13 English DIGS interview schedules conducted by the Pittsburgh investigators. Their diagnoses correlated significantly with the US consensus diagnoses ($\kappa=0.88$ or better).

Laboratory—Short tandem repeat polymorphisms (STRPs, n=64) were assayed among cases, controls and available parents from Study #1. The STRPs were selected from the Human Linkage Mapping Set v2.5 (Applied Biosystems, Inc., Foster City, CA, ABI). We randomly selected sets of markers that spanned chromosomes 1, 2, 3, 4, 17, 18, 19, 20, 21, and 22 (supplementary Table I). The STRPs were used to estimate consanguinity among cases and controls. They were also used to evaluate paternity using parental DNA samples. Parental DNA samples were not used to estimate consanguinity as parental DNA samples were not available for all cases and controls.

Genomic DNA samples were amplified using polymerase chain reactions (PCR), with fluorescently labeled PCR primer pairs and True Allele PCR Premix. The latter includes AmpliTaq Gold DNA polymerase, dNTP's, MgCl₂, and buffer. It is intended for use with the ABI PRISM Linkage Mapping Set (www.appliedbiosystems.com). PCR conditions were 10 min at 95°C for initial denaturation followed by 34 cycles of 45 sec at 94°C for denaturation, 45 sec at 60°C for annealing, 1 min at 72°C for extension, and 10 min at 72°C for final extension. The amplified products were electrophoresed using an ABI PRISM 3130 Genetic Analyzer (Applied Biosystems) and the identified products were analyzed using GeneScan software. Data were imported into the Genemapper 4.0 program for allele calls. One CEPH individual, NA10859 (#1347-02), was used as a reference for all assays (www.appliedbiosystems.com).

All allele calls were initially made blind to clinical status. They were re-checked by an independent rater, also blind to the clinical status. Markers with discordant genotyping calls exceeding 1.0% were discarded. Parental genotypes were used to evaluate for Mendelian consistency using PedCheck software [O'Connell and Weeks, 1998]. In case of discrepancy, samples were re-typed. Out of the 73 STRP markers selected initially, nine were dropped due to unacceptably high genotype failures, discordant calls between raters or because called genotypes were discordant from known relationships among CEPH samples. All clinical and genetic data were double-checked to guard against data entry errors. All genotype distributions were in Hardy–Weinberg equilibrium. Three families were excluded from the analysis due to uncertain paternity (one case family and two controls). The overall missing genotype rate was 2.76% (2.98% for cases and 2.36% for controls). There was 100% concordance rate between our calls and reference genotypes for the CEPH sample 1347-02.

Study #2: Community-Based Survey of Psychiatric Morbidity

A separate team of psychiatrists conducted an epidemiological study. Using a multi-stage, random selection process, defined geographical areas in Dakahlia governorate were surveyed, so as to sample households in the rural and the urban population. One consenting adult over 18 years of age was interviewed from each household selected for the study. The rural sample consisted of every 15th household in two villages that were selected randomly (total number of households, n=1,200; the populations of the villages were 7,645 and 6,103, respectively). The urban sample comprised of households in two randomly selected neighborhoods of Mansoura (populations 40,493 and 39,493, respectively). The streets were selected randomly and every 15th household on these streets was approached for participation (n=800 households,). All consenting participants completed the Mini International Neuropsychiatric Interview (Arabic version) [Sheehan et al., 1998]. Consensus diagnoses were assigned by two psychiatrists using DSM IV criteria. Detailed family histories were also obtained from all BP1 cases identified during the survey, with semi-structured questions regarding parental consanguinity. Among the unaffected individuals, 150 participants were selected randomly as controls. The distribution of the control individuals was consistent with the sizes of the rural and the urban samples. Parental history of consanguinity was obtained from the control individuals in the same way as the cases.

Estimates for rates of consanguinity

DNA-based rates: We estimated the parental consanguinity, $\hat{f}$, quantitatively for individual i by using maximum likelihood on the 64 STRP marker genotypes from their offspring. Technically this is the same as the estimated inbreeding coefficient for the offspring. This coefficient ranges from 0, or no consanguinity, to 1, with first cousin marriage corresponding to a value of 0.0625. DNA-based rates were estimated for Study #1 only as DNA samples were not available from Study #2.

Self-reported rates: Parental consanguinity was estimated as a dichotomous variable, based on family history data, consistent with prior published studies [Hafez et al., 1983; Helgason et al., 2008]. Participants were considered to be consanguineous, if their parents shared a common ancestor no more remote than a great-great grandparent.

Both studies were approved by the Mansoura University Ethics Committee and the University of Pittsburgh Institutional Review Board (IRB). Verbal consent was obtained in Study #2. All participants in Study #1 provided written informed consent.

Statistical Analysis

The DNA-based estimates of $\hat{f}$ for 92 cases and 88 control individuals in Study #1 were tested for a mean difference, assuming these data were distributed exponential with a common mean and variance of the difference estimated from the data (see Fig. 1). This is a test for equality of the exponential parameter for the two distributions, based on maximum likelihood estimation. Other data were compared using SPSS version 14.0.

RESULTS

There was no overlap among participants in the two surveys. All participants reported themselves as Muslims.

Study #1: Case–Control Survey

The sample was composed of 93 BP1 patients, 90 community based control individuals and their available parents (total 462 participants). There were no significant differences in age among the cases and controls (Table I). While there were approximately equal numbers of men and women among the cases, there were significantly more men among the controls ($\chi^2=7.225$, 1 df, P -value=0.007).

DNA-based estimates of consanguinity—The rates of homozygosity for markers varied from 10.53% to 63.16% among cases and 4.71% to 54.39% among controls (see supplementary Table I). The estimated genetic rates of consanguinity tend toward higher levels in cases relative to controls (Fig. 1). Assuming rates of consanguinity are distributed exponential, which is consistent with the data (Fig. 1), the mean estimated genetic consanguinity rates for the cases versus control individuals were tested, resulting in a test statistic of -2.6594 , which is significant ($P=0.0039$).

Self-reported rates of consanguinity—The BP1 patients had significantly elevated rates of self-reported consanguinity compared with the controls (n=34 cases with consanguineous parents, 36.5% of all cases; n=16 controls with consanguineous parents, 17.7% of all controls, $P=0.004$; see Table I). The prevalence of parental consanguinity did not vary by proband gender among the cases or controls (data not shown).

Types of self-reported parental consanguineous relationships—Among 34 cases with parental consanguinity, there were 15 first cousin parental marriages, with more remote relationships among the rest (n=19). Among 16 controls with consanguineous parents, 6 had parents, who were first cousins, the rest being related more remotely prior to marriage (n=10). There was a significant difference between cases and controls overall ($\chi^2=8.295$, 2 df, $P\text{-value}=0.016$).

Consanguinity by area of residence—Individuals who lived in towns with a population of 10,000 or greater were considered to have urban residences. The remainders, drawn mainly from villages surrounding Mansoura were classified as rural. Over three quarters of the participants were drawn from the rural areas. The rates of parental consanguinity were similar among controls from both groups (17.14% among rural and 20% among urban groups). Parental consanguinity rates were elevated among cases in both groups (36.11% among rural and 38.10% among urban), but attained statistical significance only in the larger, rural groups ($\chi^2=6.516$, 1 df, $P=0.011$). Given the similarity of rates, it is reasonable to assume the population (rural vs. urban) is homogenous.

Study #2: Community-Based Case Control Survey

A total of 1,584 individuals agreed to participate in the survey out of 2,000 individuals approached (overall participation rate: 79.2%; rural, n=921, 76.8%; urban, n=663, 82.9%). Thirty-five patients with BP1 were identified (24 patients from rural and 11 from urban areas). The patients were compared with randomly selected individuals without any psychiatric symptoms (total n=150; rural sample, n=100, urban sample, n=50). The mean ages and the gender distributions of the cases and controls were not significantly different (Table I).

Self-reported estimates of consanguinity—Consanguinity, as defined in Study #1 was significantly higher among the BP1 patients compared with the controls (cases: 45.7%, controls: 15.3%, $P<0.0001$; Table I).

Consanguinity by area of residence—The rates of parental consanguinity were similar among controls from both groups (17% among rural and 12% among urban groups). Parental consanguinity rates were elevated among cases in both groups (54.17% among rural and 27.27% among urban). Like Study 1, these differences were statistically significant only in the rural group ($\chi^2=14.578$, 1 df, $P=0.0001$).

DISCUSSION

Our study demonstrates replicably that consanguinity is a substantial risk factor for BP1 in Dakahlia. Over the two samples, consanguinity results in 3.30-fold increased risk of BP1,

based on self-reported or declared family history. Moreover, differences among cases and controls for consanguinity are confirmed by DNA-based genetic data, a feature that distinguishes this study from most other studies evaluating the relationship between risk for disease and consanguinity.

Self-reported consanguinity rates among the controls from our community based survey (15.3%) were similar to the estimates for controls from our second case-control study (17.7%), and both compared adequately with contemporaneous rates elsewhere (10–19%) [Consang.net., 2007]. Our studies were conducted in a region of Egypt that is not geographically or genetically isolated, nor are participants drawn from isolated tribes or clans. Two other surveys have been reported from Mansoura and its surrounding regions. One reported a consanguinity rate of 29% [Hafez et al., 1983]. Another study, conducted a decade later reported a lower rate of 24% [Settin and Algelani, 1997]. The difference in rates between these studies conducted over a decade apart could indicate that consanguinity is in decline in this region of Egypt, an observation consistent with other reports [Settin and Algelani, 1997]. The early community surveys did not differentiate between individuals with and without disease burden [Hafez et al., 1983; Settin and Algelani, 1997], yet both yielded substantially lower than our estimates for the BP1 patients (36.5–45.7%).

Consanguineous individuals often belong to lower socio-economic groups compared with non-consanguineous persons in the same population [Bittles and Neel, 1994]. It was difficult to quantify socio-economic status precisely in our predominantly agrarian samples. Hence we analyzed our rural and urban cohorts separately, with the expectation that consanguinity rates would be lower among urban dwellers and that risk would accrue mainly in the rural samples. Unexpectedly, the self-reported consanguinity rates were similar among controls from both areas. Consistent with the overall results, consanguinity rates were elevated among patients in both groups, though they attained statistical significance only in the rural groups in both Studies 1 and 2. Another explanation that we cannot presently discount is the possibility that controls individuals from consanguineous families were more likely to decline participation, but the replicated evidence from two independent samples suggests other explanations.

At least three etiological mechanisms can explain the increased risk for BP1 due to consanguinity. It is possible that one or more risk alleles for BP1 act recessively, and consanguineous matings increase the chance that the alleles will be homozygous in offspring. This mechanism then directly increases the risk for BP1. Alternatively, from studies of other organisms, inbreeding is well known to produce a general homeostatic decline [Falconer, 1981; Charlesworth and Hughes, 1996; Charlesworth and Charlesworth, 1999; Crnokrak and Roff, 1999], at least in organisms without a mating system of regular inbreeding [Jinks and Mather, 1955]. These observations are consistent with studies that suggest that consanguinity in humans produces impairment of physiological processes. For example, it has been known for some time that the probability of survival in children rises and falls with the level of consanguinity [Bittles and Neel, 1994] as do physiological traits such as blood pressure and serum cholesterol (and its components) [Rudan et al., 2003a; Weiss et al., 2006; Campbell et al., 2007] and the risk for a span of human diseases [Rudan et al., 2003a]. A general decline in physiological processes and wellness in turn could

generate greater stress and risk for specific diseases, including BP1. An exception to these observations is a recent study from Iceland, which suggested a *positive* association between kinship and fertility [Helgason et al., 2008]. Finally, while we know of no supporting evidence for it, it is possible that the relationship between BP1 and consanguinity is due to a kind of “assortative mating” which results from stigmatization of families containing BP1 patients that limits mate choice. Instead of stigmatization, the more likely source of consanguineous matings is the desire to maintain property within the same family, as has been reported among agricultural communities in Egypt, Lebanon, Palestine, and Jordan [Klat and Khudr, 1984], as well as other endogamous nomadic groups such as the Bedouins [Teebi, 1994].

Distinguishing among these three possibilities will require further research but the distinction is more than academic. For instance, if consanguinity has a direct effect on risk for BP1 by bringing together recessive risk alleles of major effect, then genetic studies of inbred population samples could prove to be a very effective way to finding risk alleles. Indeed, homozygosity mapping is being considered for genetically complex disorders such as SZ [Lencz et al., 2007], but success will likely be determined by a number of factors [Miyazawa et al., 2007]. On the other hand, if the impact of consanguinity is more diffuse, elevating risk for a broad range of diseases by altering general physiological processes and inducing physiological stress, then inbred populations samples will prove no more effective at risk genes discovery than are outbred populations.

It is intriguing to consider the physiological scenario further. One hypothesis about the origins of SZ and BP1 is that they are due to physiological diseases that impact on general metabolism and disrupt brain function [Lewis and Mirnics, 2006; Huang et al., 2007]. This observation comports with the suggested general effect of consanguinity. Could it be that as we understand more about the relationships of physiological and psychiatric diseases, and more about the impact of consanguinity on physiology, we could well see a clear connection from consanguinity to brain dysfunction? Results from studies such as ours, along with in-depth studies on consanguineous populations, could cast light on the critical factors underlying risk to BP1.

From a public health perspective in Egypt, BP1 accounts for 1.732 million Disability Adjusted Life Years (DALYs) in this region [Murray and Lopez, 1996]. The estimates are comparable to DALYs for common diseases such as tuberculosis (1.82 million), HIV (0.34 million), and diabetes mellitus (1.49 million). Consanguinity thus appears to pose a significant psychiatric health burden by increasing risk for BP1 in Egypt. Awareness of the burden, and the impact of consanguinity more generally on both common and rare diseases, could have far-reaching impact on health world-wide.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIG. 1.
Distribution of DNA-based consanguinity rates for controls (gray bars) and cases (black bars).

TABLE I

Self-Reported Consanguinity Among Participants in Studies 1 and 2

Study	Group	N	Age (in years)			Gender		Parental consanguinity present	OR (95% CI)
			Mean	Standard deviation		Male	Female		
Study 1 (case-control study)	BP1	93	25.10	6.08		47	46	34 (36.5%) *	2.66 (1.34, 5.29)
	Controls	90	27	6.0		63	27	16 (17.7%)	
Study 2 (community-based case control survey)	BP1	35	27.57	8.58		20	15	16 (45.7%) **	4.64 (2.01, 10.34)
	Controls	150	35.28	10.82		68	82	23 (15.3%)	

BP1, bipolar I disorder; OR, odds ratio; CI, confidence interval, Parental consanguinity significantly different from controls:

* $\chi^2=8.125$, $P=0.004$, 1 df,

** $\chi^2=15.744$, $P<0.0001$, 1 df; There were significantly more men among the controls in Study 1 ($\chi^2=7.225$, 1 df, $P\text{-value}=0.007$).