Psychological Medicine, 2005, **35**, 1611–1621. © 2005 Cambridge University Press
doi:10.1017/S0033291705005441 Printed in the United Kingdom

A direct interview family study of obsessive–compulsive disorder. I

ABBY J. FYER[1]*, JOSHUA D. LIPSITZ, SALVATORE MANNUZZA, BONNIE ARONOWITZ AND TIMOTHY F. CHAPMAN

Anxiety Genetics Unit, New York State Psychiatric Institute, NY, USA and Department of Psychiatry, College of Physicians and Surgeons, Columbia University, NY, USA

ABSTRACT

Background. This and the companion paper present two sequential family studies of obsessive–compulsive disorder (OCD) conducted by the same research group, but with different sampling and best-estimate procedures. In addition to providing further data on familial transmission of OCD, we used comparison of disparate findings (moderate, specific familial aggregation in this first study *versus* a stronger effect for other anxiety disorders than for OCD alone in the second) to examine possible effects of proband characteristics and informant data on outcome.

Method. In this initial study we interviewed 179 first-degree relatives of 72 OCD probands and 112 relatives of 32 never mentally ill (NMI) controls. Informant data were obtained on an additional 126 relatives (total 'combined' samples of 263 and 154 respectively). Analyses used best-estimate diagnoses made by consensus of two 'blinded' senior clinicians who reviewed all diagnostic materials including proband informant data about relatives.

Results. Significantly higher risk for OCD but not other anxiety disorders was found in relatives of OCD probands compared to relatives of controls in both the directly interviewed and combined samples. There was no relationship between proband age at onset of OCD and strength of familial aggregation.

Conclusions. These data indicate moderate familial aggregation of OCD, but do not support increased transmission by early onset probands, or a familial relationship between OCD and other anxiety disorders with the possible exception of generalized anxiety disorder.

INTRODUCTION

Obsessive–compulsive disorder (OCD) is a disabling, chronic illness that occurs in 1–3% of the population (Weissman *et al*. 1994). As many as half of patients are treatment refractory and most suffer ongoing difficulties (Rosenberg & Hanna, 2000; Grados *et al*. 2001). While OCD can occur as part of certain neurological syndromes (Childers *et al*. 1998; Berthier *et al*. 2001; Cavallaro *et al*. 2002), the pathophysiology of most cases is unknown. Heritability of OCD has been studied since the 1940s with mixed results. Recently, hope of jump starting etiological research through application of new molecular genetic techniques has led to renewed interest in this area.

Results of early family and twin studies of OCD were both contradictory, and difficult to interpret due to methodologic limitations (for review see Carey & Gottesman, 1981; Black *et al*. 1992). Twin studies were small and subjects were not systematically sampled. Diagnostic criteria were often unspecified and the family studies were conducted without blind assessments and/or appropriate controls. Some investigators reported familial aggregation of OCD,

* Address for correspondence: Abby J. Fyer, M.D., New York State Psychiatric Institute, Unit 82, 1051 Riverside Drive, New York, NY 10032, USA.
(Email: ajfyer@pi.cpmc.columbia.edu)

https://doi.org/10.1017/S0033291705005441 Published online by Cambridge University Press

Table 1. *Comparison of aspects of methodology/outcome in blind, controlled family studies of obsessive–compulsive disorder (OCD)*

	McKeon & Murray (1987)	Black *et al.* (1992)	Pauls *et al.* (1995)	Nestadt *et al.* (2000)
OCD probands, *n*	50	32	100	80
Onset ⩽17 years (%)	Not reported	50	82[a]	90
Co-morbidity	No exclusion	Exclude all but post-OCD depression	Exclude psychotic disorders	Exclude schizophrenia, dementia, retardation and Tourette's
Relatives of OCD probands				
No. directly interviewed/ total (% *n*)	59/160 (37%)	120/166 (72%)	?/466 (39%)[b]	221/343 (64%)
Best-estimate sample (direct and/or informant)	149	120	466	343
Controls	Matched attendees of general-practice surgeries	NMI volunteers	NMI volunteers	Random digit dial, exclude same disorders as in OCD probands
Criteria	RDC	DSM-III	DSM-III-R	DSM-IV
Diagnosis				
Interviewer blind to proband diagnosis	No	Yes	Yes	Yes
Best estimate includes proband informant data about relatives	Yes	No	Yes	Yes
Outcome				
% OCD in relatives of:				
OCD *v.* Control probands	1 *v.* 1% (N.S.)	2·8 *v.* 2·3 (N.S.)	10·3 *v.* 1·9% ($p<0·005$)[d]	11·7 *v.* 2·7 ($p=0·001$)
Early *v.* late onset OCD probands		Rates not given (N.S.)	10·7 *v.* 8·7 (N.S.)[d]	13·8 *v.* 0 ($p=0·006$)
Other disorders increased in relatives of OCD probands	Any mental disorder 36 *v.* 17% ($p<0·001$)	Any anxiety disorder 30 *v.* 17 ($p=0·008$) GAD 27 *v.* 12 ($p<0·03$)	Not reported	Agoraphobia OR[c] 5·3 ($p<0·05$) GAD OR[c] 3·4 ($p<0·001$) Separate Anxiety OR[c] 2·5 ($p<0·05$)

RDC, Research diagnostic criteria; OR, odds ratio; GAD, generalized anxiety disorder; NMI, never mentally ill.
[a] Age ⩽18 years.
[b] Separate figures not given for OCD and comparison relatives, for combined group 223/579 were interviewed directly.
[c] Compared to rates in relatives of controls.
[d] Morbid risk, age corrected.

others found an increase in familial anxiety, but no specific transmission of OCD, and still others no pattern at all. In an effort to resolve these differences, several more methodologically rigorous family studies of OCD were undertaken during the late 1980s to 1990s (Table 1) (McKeon & Murray, 1987; Black *et al.* 1992; Pauls *et al.* 1995; Nestadt *et al.* 2000). Surprisingly, results of these new efforts are similarly inconsistent. Two studies (Pauls *et al.* 1995; Nestadt *et al.* 2000) found strong familial aggregation of OCD, one (Black *et al.* 1992) found increased rates of anxiety but not of OCD and the fourth (McKeon & Murray, 1987) found increased rates of familial psychopathology but no specific effects for OCD or anxiety disorders.

This persistent variability could reflect etiologic heterogeneity. If the DSM-IV category covers a substantial number of non-familial OCD cases, then chance fluctuation in the proportion of these in each proband sample could account for positive *versus* negative outcomes. For example, both late onset and the absence of symmetry/ordering rituals in probands have been associated with decreased familial risk for OCD (Pauls & Alsobrook, 1999; Alsobrook *et al.* 1999). Methodologic differences may also contribute. Inclusion of larger samples and more detailed OCD symptom probes, as in the two most recent studies (Pauls *et al.* 1995; Nestadt *et al.* 2000) reduces the possibility of Type II error. On the other hand, methods for interpretation of informant data may bias in the other direction. In some studies individuals who have no evidence of symptoms on direct interview are sometimes diagnosed

https://doi.org/10.1017/S0033291705005441 Published online by Cambridge University Press

with OCD because of information provided by relatives. In this case, the absence of symptoms during direct interview may reflect a subject's embarrassment or lack of insight, while the informant report may reflect the 'true' situation (Lenane *et al*. 1990; Pauls *et al*. 1995). However, there is also evidence that informants sometimes report illness in individuals who have none. Ill individuals are more likely to do this than well ones particularly in the case of their own illness (Kendler *et al*. 1991; Chapman *et al*. 1994; Roy *et al*. 1994, 1996). From the first perspective, failure to use informant data could result in under-diagnosis of 'true' OCD cases in relatives of OCD probands, contributing to negative studies. From the second, inclusion of informant data in the best-estimate procedure may create a bias toward finding specific familial aggregation, contributing to positive studies.

In this and the companion paper (Lipsitz *et al*. 2005) we present two sequential family studies of OCD conducted by the same research group using similarly trained interviewers and instruments, but different procedures for proband sampling and handling of proband informant data within the best-estimate procedure. We present these data together because, to some extent our findings parallel the mixed picture in the literature: one study indicates moderate, specific familial aggregation; the other a stronger effect for other anxiety disorders than for OCD alone. These studies contribute to available data about familial aggregation of OCD. In addition, the juxtaposition provides the opportunity to further investigate the effects of proband characteristics and informant data on outcome.

This first report presents results of our initial OCD family study using traditional best-estimate procedure that includes proband informant data and sampling sequential subjects from a pharmacologically based research clinic. Our second study combined sequential samples from several diverse settings (non-research as well as cognitive behavioral and pharmacologic research clinics) and also included a prospective assessment of effects of proband informant data on best-estimate diagnosis. The companion paper presents these second study results and examines the effects of the methodologic variation on outcome.

The specific questions addressed in this first paper are: (1) is there familial aggregation of obsessive–compulsive disorder or symptoms?; (2) is the strength of aggregation greater in families of early onset ($\leqslant$18 years) probands?; and (3) is there an increased risk for either other anxiety disorders or depression in families of OCD probands?

METHOD

Subjects

OCD probands were adult patients participating in out-patient or in-patient research programs at the New York State Psychiatric Institute/Columbia Anxiety Disorders Clinic from 1990 to 1993. All individuals who met DSM-III-R criteria for current OCD (by both our study interview and independent research psychiatrist evaluation) and had at least one available living first-degree relative were invited to participate in the family study. The only exception to this was that by study convention we did not exclude subjects who felt there might be some rational basis for their obsessions or compulsions. This exclusion was dropped in the DSM-IV. Never mentally ill (NMI) probands were recruited using a previously described modification of the acquaintance method (Katz *et al*. 1979; Fyer *et al*. 1995). Briefly, all interviewed relatives were asked to give the names of five individuals of the same age, gender and socio-economic status as themselves. A randomly chosen acquaintance from each the list was screened over the telephone. Those who had no evidence of psychiatric illness were asked to undergo a lifetime psychiatric evaluation interview identical to that of patient probands. Raters were blind to subject's potential status as a NMI proband. Interview materials were reviewed by one of the senior investigators (S.M.) and subjects who had no evidence of DSM-III-R disorder or panic attacks and at least one available relative were asked to participate as NMI probands. All patient and NMI probands signed informed consent for both their own evaluation and to allow our staff to contact their first-degree relatives. All consented for English-speaking relatives aged 18 years and over were contacted and asked to participate.

Interview procedures and assessments

Interviews were conducted by specially trained clinicians who had demonstrated test–retest

https://doi.org/10.1017/S0033291705005441 Published online by Cambridge University Press

reliability with senior raters (S.M. or J.L.) prior to going into the field. Relative and control interviewers were blind to subject group membership. Patient proband interviewers were not blind to clinic diagnosis. Directly interviewed subjects were assessed with the SADS – Lifetime Anxiety Version (SADS-LA) (Fyer *et al.* 1985; Mannuzza *et al.* 1986). The SADS-LA is a modification of the SADS – Lifetime version (Spitzer & Endicott, 1979) that in addition to lifetime diagnosis provides detailed information on subdisorder anxiety symptoms. For this study the SADS-LA was additionally modified (SADS-LA-Revised or SADS-LA-R) (Schleyer *et al.* 1991) to include DSM-III-R tic, Tourette's and affective and anxiety diagnoses. Several items based on the anxiety disorders section of the DSM-IV Options Book (APA, 1991) were also included to facilitate transition to DSM-IV. The OCD section of the SADS-LA-R includes items covering onset, duration, severity, interference, and 'rationality' of 54 specific types of obsessions and compulsions subdivided into nine categories (disgust/contamination; aggressive/impulsive; sexual; checking, ordering, grooming; memory/doubting/decision making; hoarding, and other). The section on Tourette's and tic disorders was adapted from assessments developed by Pauls *et al.* (1995) and proband interviewers received training in its use from the author's group. An overall global assessment of functioning (GAF) rating and a clinical global impression of impairment due to OCD (1 = slight, 5 = extreme) are also included.

After completion of the interview raters wrote a detailed narrative history that included a description of onset, symptoms and course of psychiatric disorders within the social context of the subject's life as well as discussion of any diagnostic uncertainties (Mannuzza *et al.* 1993). All interviewed individuals were administered the Family Informant Schedule and Criteria (FISC; Mannuzza *et al.* 1985) to obtain information about psychiatric symptoms and disorder in their first-degree relatives. Probands were interviewed at the Anxiety Disorders Clinic. Relatives who lived within 1 hour's travel of the clinic were interviewed at their homes. Those who lived further away were interviewed by telephone.

Best-estimate procedure and role of informant data

All data on relatives are 'best-estimate' diagnoses derived from a consensus meeting between two senior clinicians who had independently rated a 'blinded' packet containing all available information on each individual (interviews, narratives, informant data including data provided by OCD probands, etc.). Diagnosticians were specially trained, experienced Ph.D.-level psychologists. Best-estimate ratings were made for occurrence, onset, offset of DSM-IV disorders, and a variety of subdisorder symptoms. Although the direct interview instrument (SADS-LA-R) was based on DSM-III-R we were able to make DSM-IV best-estimate diagnoses due to inclusion of DSM-III-R Options Book (1991) items and our convention of not excluding individuals from the OCD category on the basis of the 'rationality' criterion.

After arriving at a diagnosis, raters were also asked to indicate the role of informant data in their decision (essential, corroborative, non-contributory). This was a retrospective summary assessment. We did not collect data on whether the informant reports led to a change in diagnosis or whether diagnosis was influenced by information from specific types of informants (e.g. ill *versus* non-ill informants, probands *versus* other relatives, etc). Best estimate was not done on probands.

OCD diagnoses and symptoms

Subjects were given a best-estimate diagnosis of *definite* DSM-IV OCD if the two best estimators agreed they met all of the DSM-IV criteria. A *probable* OCD diagnosis was given if: (1) a subject had definite DSM-IV obsessions or compulsions and at least some impairment; but (2) either the impairment or duration of symptoms was not sufficiently well documented to be certain they met definite OCD criteria; and (3) there were no data indicating that the subject did not meet definite criteria. Subjects were given a diagnosis of obsessive–compulsive (OC) symptoms or *possible* OCD if they had definite obsessions or compulsions but did not meet probable OCD criteria (e.g. duration of symptoms <1 hour; explicit statement of no significant impairment or distress). As the criteria for OC symptoms and possible OCD

https://doi.org/10.1017/S0033291705005441 Published online by Cambridge University Press

were indistinguishable, for the purpose of simplicity, these individuals are combined under the OC symptom category. Age at onset was ascertained separately for each type of OC symptom (e.g. checking, hand washing, etc.). For each individual, the earliest symptom onset was considered as their age at onset of OC symptoms.

Data analysis

Best-estimate diagnoses were used in all analyses of relative data. Best estimate was not conducted for probands so that proband characteristics (e.g. age at onset, co-morbidity) are from direct interview data. For each question data analysis was done two ways: (1) using only directly interviewed relatives; and (2) using a '*combined*' sample that includes all relatives (interviewed and uninterviewed) for whom we had diagnostic information from at least one informant. Differences in categorical demographic variables and proportions of affected individuals and families were tested with the χ^2 or Fisher's exact test (FET) (cell sizes <5). A Student's t test was used for dimensional variables. Proportional hazards analyses (SAS PHGLM procedure) (SAS Institute Inc., 1986) were used to calculate the hazard ratio and 95% confidence limits (CI) for disorder in the relatives of the two proband groups. This method was used to take into account possible confounding effects of between-group demographic differences. However, given the low rates of OCD/OC symptoms, models that included several independent covariates were unstable with very large confidence intervals. To provide a more conservative estimate we tested the effect of each demographic variable separately and used in our final model only those that had a significant independent effect on familial rates. To examine whether familial effects were dependent on family size we also compared the proportion of families with at least one member affected with OCD or OC symptoms in the OCD *versus* control samples.

The relationship between proband age at onset and familial OCD was addressed by (1) dichotomizing OCD probands by age at onset (<18 *versus* $\geqslant 18$ years) and comparing rates of OCD/OC in relatives of the two groups; and (2) introducing proband age at onset as an independent covariate in the proportional hazards analysis. These relationships were analyzed using both age at onset of symptoms and disorder. As results were similar and previous reports have used the symptom onset criterion, only that analysis is presented here. We considered there to be a familial association between OCD and another disorder if: (1) rates of the disorder were significantly increased in relatives of OCD *versus* control probands and (2) the increase was not due to transmission by OCD probands who were co-morbid for the disorder. It should be noted that negative findings in these analyses would not indicate distinctness between OCD and these other disorders, as this would *also* require that relatives of probands with these illnesses did not have an increased rate of OCD (Fyer *et al*. 1995). For all analyses, an α-level of 0·05 was considered significant. To avoid Type II error we report trends at the 0·1 level. All p values are two tailed. Power analyses were done with a PS program (Vanderbilt Medical Center, 2005) using the effect sizes found by Nestadt *et al*. (2000) for definite (11·7% *v*. 2·7%) and probable or definite OCD (16·3% *v*. 3·1%). Direct interview results (without best estimates) on a subset of these data were presented at the First International Congress on OCD Conference (Capri, Italy, 1993) and referred to in Rasmussen (1994).

RESULTS

Probands

Seventy-two OCD and 32 NMI probands were studied. OCD probands were significantly younger and more likely to be male and unmarried than controls (Table 2). Nearly three quarters (71%) reported onset of symptoms, and 46% onset of disorder by age 17 years. Mean onsets of OC symptoms and OCD were 14 ($\pm$11) and 18 ($\pm$12) years respectively. Sixty-four per cent (46/72) of patients reported a chronic course from onset with average duration of 15·9 ($\pm$11) years. Seven (10%) probands had only obsessions, six (8%) only compulsions and 59 (82%) both. The mean clinician rating of OCD-related impairment in this group was 4·3 ($\pm$0·9) with 41% rated as markedly and 44% as extremely impaired. The mean (and median) GAF score was 41 (S.D. $=$13·6). The most prevalent lifetime co-morbid diagnoses

https://doi.org/10.1017/S0033291705005441 Published online by Cambridge University Press

Table 2. *Subject demographics characteristics and interview compliance*

	Proband diagnosis	
	Obsessive–compulsive disorder (OCD)	Never ill controls
Probands, *n*	72	32
Gender (% female)	36	66**
Mean age (yr) (±S.D.)	34·8 (11)	43·6** (15)
College (%)	44	59
Married (%)	36	66**
Total relatives, *n*	268	166
All living relatives, *n*	241	141
Interviewed, *n*	179	112
Gender (% female)	59	53
Caucasian (%)	99	97
Mean age (yr) (±S.D.)	45 (16)	41 (14)*
College (%)	44	45
Married (%)	58	53
Uninterviewed, *n*	62	29
Gender (% female)	47	41
Mean age (±S.D.)	50 (19)	55 (20)
Deceased, *n*	27	25
Combined sample, *n*[a]	263	154
Gender (% female)	53	49
Mean age (yr) (±S.D.)	44 (19)	44 (16)
Compliance of relatives, %		
Interviewed/total	67	67
Interviewed/living	74	79

No diagnostic information was available on 17 relatives (5 of NMI and 12 of OCD probands).

Significance: Fisher's two-tailed * $p<0{\cdot}05$, ** $p<0{\cdot}01$.

[a] Includes all subjects for whom there is either direct interview and/or at least one informant report, total $n=417$.

were: major depression 50%; dysthymia 36%; social phobia 33%; childhood separation anxiety (CSAD) 25%, and specific phobias 22%. Five (7%) probands were diagnosed with tic disorders (four with Tourette's and one chronic tic disorder). In total, 192 acquaintances were screened to identify the 32 NMI probands. There were no gender differences between recruited and not-recruited acquaintances (21/32 *v.* 127/192, 66% *v.* 66%, N.S.). Data on age of not-recruited NMI are not available.

Relatives

Two-thirds (291/434) of all (and 76% of living) first-degree relatives of probands were directly interviewed (Table 2). Informant reports were obtained on an additional 126 relatives. In 116 (92%) of these cases data were obtained from two or more informants. In the remaining 10 only one informant report was available (nine of these were from a proband). Overall, diagnostic information was available on 417/434 of first-degree relatives. Forty-two percent of interviews of relatives of OCD probands were in done in the subject's homes and 58% by telephone. For relatives of NMI these figures were 16% and 84% respectively (between-group difference OCD *versus* NMI relatives: $\chi^2=21{\cdot}9, p<0{\cdot}0001$). Interviewed relatives of the two proband groups did not differ significantly in demographic characteristics except that relatives of NMI were younger (41 *v.* 45 years, $p<0{\cdot}006$) (Table 2). There were no significant between-group age or gender differences in the 'combined' sample (Table 2). Power analyses indicated that our direct interview sample would provide 80% and our combined sample 90% power to detect between-group differences in 'definite' and 'definite or probable' OCD observed by Nestadt *et al.* (2000). Assuming a 1·5% rate of OCD in control relatives and a two-tailed $p=0{\cdot}05$, the directly interviewed sample would have 80% power to detect a six-fold, and the combined sample a slightly greater than five-fold increase in OCD *versus* control relatives.

Table 3. *Rates of obsessive–compulsive disorder (OCD) and symptoms in relatives of obsessive compulsive probands and never mentally ill controls*

	OCD		Never mentally ill	
	%	(*n*)	%	(*n*)
Interviewed relatives				
OCD (definite)	6·2**	(11)	0·0	(0)
OCD (probable/definite)[a]	8·4***	(15)	0·0	(0)
OC symptoms	4·5	(8)	1·8	(2)
OCD or OCD symptoms	12·9***	(23)	1·8	(2)
All relatives[a]				
OCD (definite)	5·3**	(14)	0·0	(0)
OCD (probable/definite)	8·8***	(23)	0·0	(0)
OC symptoms	3·4	(9)	1·3	(2)
OCD or OC symptoms	12·2***	(32)	1·3	(2)
No. of probands	72		32	
No. of interviewed relatives	179		112	
No. of relatives – combined	263		154	

Significance: ** $p<0{\cdot}01$, *** $p<0{\cdot}001$.

[a] A probable or definite OCD.

Familial rates of OCD and OC symptoms

Among interviewed relatives all cases of definite or probable OCD ($n=15$) and most cases of OC symptoms (8/10) occurred in relatives of OCD probands (Table 3). The between-group

https://doi.org/10.1017/S0033291705005441 Published online by Cambridge University Press

Table 4. *Familial obsessive–compulsive disorder (OCD) and OC by proband age of symptom onset*

	Onset <18 years		Onset ⩾18 years		Never mentally ill	
	%	(*n*)	%	(*n*)	%	(*n*)
Interviewed relatives						
OCD (definite)	5·8	(8)	7·5	(3)	0	(0)
OCD (probable/definite)	7·9	(11)	10·0	(4)	0	(0)
OC symptoms	5·8^{+}	(8)	0	(0)	1·8	(2)
OCD or OCD symptoms	13·7	(19)	10·0	(4)	1·8	(2)
All relatives[a]						
OCD (definite)	5·3	(10)	5·5	(4)	0	(0)
OCD (probable/definite)	7·9	(15)	11·0	(8)	0	(0)
OC symptoms	4·7	(9)	0	(0)	1·3	(2)
OCD or OC symptoms	12·6	(24)	11·0	(8)	1·3	(2)
No. of probands	51		21		32	
No. of interviewed relatives	139		40		112	
No. of relatives – combined	190		73		154	

Significance: $^{+}$ $p<0·1$.
[a] Combined sample = best-estimate diagnosis of interviewed relatives with at least one report.

differences were highly significant for both levels of disorder (definite OCD 6·2% *v.* 0, FET $p<0·01$; definite or probable OCD 8·4% *v.* 0, FET $p=0·0001$), but not for OC symptoms alone (4·5% *v.* 1·8%, N.S.). Overall, interviewed relatives of OCD probands had an eight-fold increased risk for OCD/OC symptoms compared to relatives of controls (12·9% *v.* 1·8%, hazard ratio 8·2, $p<0·005$, 95% CI 2–35). A proportional hazards analysis could not be done for definite or probable OCD alone because of the zero cell in relatives of NMI. A similar pattern of familial aggregation was seen in the combined sample (Table 3). This pattern was also seen using the family as the unit of analysis in both the interviewed and combined samples. Using the interviewed sample 14% of families of OCD probands compared to 0 of controls had at least one member affected with OCD (FET $p<0·03$). For probable or definite OCD this contrast was 18% *v.* 0 (FET $p<0·001$) and for OCD/OC symptoms it was 28% *v.* 6% (FET $p<0·02$). The five OCD probands with Tourette's or tics had 14 interviewed relatives. None had definite or probable OCD or tic disorder, but three reported OC symptoms without distress or impairment.

In their summary retrospective assessment, the best estimators considered that informant data was essential for the diagnosis of three and corroborative for seven of the 25 familial cases of OCD/OC symptoms identified in interviewed relatives (9/23 in relatives of OCD probands and one out of two cases in relatives of controls). Informant data about *uninterviewed* relatives contributed an additional nine cases in relatives of the OCD probands, but none in relatives of controls. Removing 'family history essential' cases from the interviewed relative sample did not substantively change our findings in the interviewed (definite/probable OCD 14/179 *v.* 0/112, FET $p<0·02$; 'Any OCD' 22/179 *v.* 1/112, FET $p<0·0002$) or combined datasets.

Proband age at onset and familial OCD/OC symptoms

There were no significant differences between rates of familial OCD or OC symptoms in relatives of probands who reported early (<18 years) *versus* later (⩾18 years) onset of obsessions or compulsions (Table 4). Relatives of the early onset group had higher rates of subdisorder OC symptoms (without disorder), but this difference was not significant in the interviewed group ($p>0·2$) and only reached trend level ($p<0·07$) in the combined sample. The hazards analyses, using relative age and gender as covariates, indicated no significant relationship between proband age at onset and familial aggregation. However, because of the zero cells this could not be done for symptoms alone.

Familial occurrence of other anxiety, affective and substance use disorders

Rates of psychiatric disorders other than OCD were similar in both relative groups (Table 5) with the exception that there were trends ($p<0·10$, two tailed) toward higher rates of

https://doi.org/10.1017/S0033291705005441 Published online by Cambridge University Press

Table 5. *Rates of anxiety and affective disorders in relatives of obsessive–compulsive disorder (OCD) and never mentally ill (NMI) probands*

	Proband diagnosis			
			OCD probands w/o disorder co-morbidity	
	OCD	NMI	%	(no. relatives)
Diagnosis in relatives[a] (%)				
Panic disorder	7†	2	6	(161)
Specific phobia	25	26	25	(144)
Social phobia	30	27	28	(114)
Generalized anxiety disorder	6†	2	6†	(173)
Childhood separation anxiety	7†	2	5	(137)
Post-traumatic stress disorder	6	4	5	(170)
Major depressive disorder	32	26	23	(84)
Dysthymic disorder	16	12	15	(115)
Alcohol dependence	21	30	18*	(157)
Drug dependence	11	11	9	(164)
Tourette's disorder	1	0	1	(167)
No. of probands	(72)	(32)		
No. of relatives	(179)	(112)		

Significance: Fisher's two-tailed: † $p<0{\cdot}10$, * $p<0{\cdot}05$, two-way contrasts between each OCD group and NMI.

[a] Best estimate probable or definite diagnoses of interviewed relatives.

panic disorder (PD), CSAD and generalized anxiety disorder (GAD) among the relatives of the OCD probands. The effect of removing (from each analysis) those OCD probands who also have the disorder under study is shown in the far right-hand column of Table 4. For PD and childhood separation anxiety disorder (CSAD) there are no between-group differences; for GAD a trend ($p<0{\cdot}09$) remained. Hazards analyses controlling for relative age and gender indicated no significant effect of proband OCD on rates of any anxiety or affective disorder other than OCD.

A significantly higher rate of alcohol abuse was also found among relatives of NMI *versus* OCD probands using both direct comparison of rates (30% *v.* 21%, FET $p=0{\cdot}04$) (Table 5) and the hazards analysis ($p<0{\cdot}05$) controlling for gender and age of relatives. Re-examination of the NMI probands indicated a complete absence of subdisorder alcohol abuse/dependence symptoms in these individuals. Despite this the majority of relatives in three NMI families, including one very large family ($n=11$), had alcohol-related illness. Elimination of this latter family from the analyses also eliminated the significant between-group differences in rates of alcohol abuse.

COMMENT

These data indicate moderate familial aggregation of OCD. Rates of subdisorder OC symptoms were also higher in relatives of OCD probands *versus* controls, but this difference did not reach the 0·05 level of significance. We did not see increased familial aggregation of OCD in families of probands who had early (<18 years) *versus* later (⩾18 years) onset of OCD. There was also no evidence for transmission of increased risk for other anxiety or affective disorders to relatives of OCD probands, with the possible exception of GAD.

Our finding of familial aggregation of OCD is consistent with the previous studies of Pauls *et al.* (1995) and Nestadt *et al.* (2000). However, unlike these investigators we did not find a parallel increase in subdisorder OC symptoms (Pauls *et al.* 1995; Nestadt *et al.* 2000). A greater percentage of our interviews of relatives were done over the telephone compared to the other two studies. Comparison of telephone and in-person interviews indicated similar rates of probable and definite OCD among relatives of OCD probands (9·5% *v.* 7·8% respectively). However, the in-person interviews yielded a significantly higher rate of OC symptoms (9·5% *v.* 1%, FET $p<0{\cdot}01$). The only OC symptoms (two cases of subdisorder OC symptoms) found in relatives of controls were in telephone-interviewed subjects. Several previous studies indicate equivalent results in assessment of psychiatric disorders with telephone *versus* in-person interviews (Paulsen *et al.* 1988; Rohde *et al.* 1997; Cacciola *et al.* 1999). However, our data suggest that detection of subdisorder OC symptoms, at least among relatives of OCD probands is particularly vulnerable to this methodological difference. It is also possible that, although the operational criteria for subdisorder diagnosis were quite similar across studies, variation in interpretation of terms such as 'subjective distress' or 'impairment' could account for the observed differences. Alternatively between-study differences might reflect random variations in the ability of subjects to

https://doi.org/10.1017/S0033291705005441 Published online by Cambridge University Press

remember mild and perhaps transient symptomatology.

Our results did not appear to be dependent on informant data. When we removed diagnoses that best estimators indicated were dependent on informant data the difference between rates of OCD/OC symptoms in relatives of OCD probands and controls decreased but remained significant. Using only direct interview data yielded similar results (data not shown). Pauls *et al*. (1995) saw this same pattern of reduced but still significant familial aggregation when they re-best-estimated subjects without the availability of informant data. The risk for OCD in relatives of OCD probands dropped from 10·3 to 6·5, but still remained three-fold greater than the risk (1·9) in relatives of comparison subjects. In contrast, in the study by Black *et al*. (1992) best estimate of direct interview data yielded equal rates of OCD in relatives of OCD and control probands. Proband informants identified OCD in an additional nine individuals who were not initially interviewed. Black *et al*. were subsequently able to interview four of these: one had some subsyndromal OC symptoms; the others had no sign of OCD or OC symptoms on direct interview. Since the meaning of their family history data was unclear they decided to present their direct and informant data separately. Black *et al*. (1992) might have shown familial aggregation if their informant and direct interview data were combined. However, it seems that the main differences between ours and Pauls *et al*. (1995) *versus* Black *et al*. (1992) is in the number of relatives of OCD probands who acknowledged OCD symptoms on direct interview. It is important to note that the data on informant contribution in this report must be interpreted with caution as our only information about the influence of informant reports was from retrospective (i.e. after the estimator had seen data from all sources) ratings and direct interview data depended on the decision of one less experienced clinician.

We did not replicate earlier findings of increased familial aggregation of OCD in families of earlier onset OCD probands (Pauls *et al*. 1995; Nestadt *et al*. 2000). This was not due to a lack of early onset cases in our sample. Median age for symptom onset in our proband group was 12 years. A total of 61% ($n=44$) reported onset by age 14 years, 71% by age 17 years and 79% by age 18 years. This distribution seems quite similar to that in the studies by Pauls *et al*. (1995) (82% ill by age 18) or Nestadt (2000) (75% with symptoms by age 14 and 90% by age 17). However, both Pauls *et al*. and Nestadt *et al*. did have a greater proportion of very early onset probands than our sample. Approximately 40% of their probands, but only 25% of ours were sick by age 9 years. It would be of interest to know if these very early onset probands account for the excess familial cases. We attempted to investigate this within the limits of our sample, but found no difference in familial OCD/OC symptom rates when we subdivided probands by OCD symptom onset $\leqslant 12$ years *versus* >12 years (11/88 *v*. 12/89, N.S.). It may be that a combination of both early onset and certain symptoms patterns (e.g. types of obsessions or compulsions) is necessary for increased familial transmission. Type II error is another possible explanation. Although we had over 95% power to detect the type of difference reported by Nestadt *et al*. (13% *v*. 0%) and 80% power to detect differences such as 25% *v*. 10% or 12% *v*. 1·5%, our power to detect the difference in the combined rates of 'OCD or subthreshold OCD' reported by Pauls *et al*. (21 *v*. 11) was only 46%. Retrospective inaccuracies in dating symptom onset may also contribute to variation in findings in this area.

With the possible exception of GAD, our data do not support a familial relationship between OCD and other anxiety affective disorders. Once proband co-morbidity was taken into account (Table 5, right-hand column) rates of disorders other than OCD did not differ significantly between relatives of OCD *versus* control probands. Although the increase in GAD was only at a trend level ($p<0·1$, two-tailed) it seems worth noting as this relationship has been observed in two previous family studies of OCD (Black *et al*. 1992; Nestadt *et al*. 2001) and the failure to reach the 0·05 significance level in our sample may reflect a Type II error. However, a full investigation of the familial relationship of these disorders would also require comparison of OCD rates in relatives of these other anxiety proband groups.

Interpretation of these data is subject to several limitations. The sample was collected at a metropolitan area research clinic and it may not be appropriate to generalize findings to

https://doi.org/10.1017/S0033291705005441 Published online by Cambridge University Press

other settings. Retrospective reporting on past disorders, symptoms or age at onset may also be subject to inaccuracies in memory as well as, in some cases intentional omissions. The increased rate of alcohol abuse among relatives of our control group most likely reflects the chance inclusion of one large, heavily affected family. It is possible that some well control probands concealed histories of abuse, or that well individuals from families affected by abuse are more likely to consent to participate in research about families and mental health. Rates of other disorders are similar to those in previous population studies (e.g. Kessler *et al.* 1994). We do not believe that this impinges on our main conclusions (e.g. we are not aware of any data suggesting an inverse familial relationship between OCD/OC symptoms and substance abuse disorders, or that substance use obscures OCD/OC symptoms). However, it may be important to keep this observation in mind if the data is referred to in terms of other affective/substance use disorders.

In summary these data indicate moderate familial aggregation of OCD, but do not support increased familial transmission by early onset probands, or a familial relationship between OCD and other anxiety disorders with the possible exception of GAD.

ACKNOWLEDGEMENTS

This work was supported in part by grants PO1 MH-37592 and RO1 MH-44175 from the National Institute of Mental Health.

DECLARATION OF INTEREST

None.

REFERENCES

Alsobrook, J. P., Leckman, J. F., Goodman, W. K., Rasmussen, S. A. & Pauls, D. L. (1999). Segregation analysis of obsessive-compulsive disorder using symptom-based factor scores. *American Journal of Medical Genetics* **88**, 669–675.

APA (1991). *DSM-IV Options Book: Work in Progress*. Task Force on DSM-IV: American Psychiatric Association.

Berthier, M. L., Kulisevsky, J., Gironell, A. & Lopez, O. L. (2001). Obsessive-compulsive disorder and traumatic brain injury: Behavioral, cognitive, and neuroimaging findings. *Neuropsychiatry, Neuropsychology & Behavioral Neurology* **14**, 23–31.

Black, D. W., Noyes, R., Goldstein, R. B. & Blum, N. (1992). A family study of obsessive-compulsive disorder. *Archives of General Psychiatry* **49**, 362–368.

Cacciola, J. S., Alterman, A. I., Rutherford, M. J., McKay, J. R. & May, D. J. (1999). Comparability of telephone and in-person structured clinical interview for DSM-III-R (SCID) diagnoses. *Assessment* **6**, 235–242.

Carey, G. & Gottesman, I. I. (1981). Twin and family studies of anxiety, phobic, and obsessive disorders. In *Anxiety: New Research and Changing Concepts* (ed. D. F. Klein and J. G. Rabkin), pp. 117–136. Raven Press: New York, NY.

Cavallaro, R., Galardi, G., Cavallini, M. C., Henin, M., Amodio, S., Bellodi, L. & Comi, G. (2002). Obsessive compulsive disorder among idiopathic focal dystonia patients: an epidemiological and family study. *Biological Psychiatry* **52**, 356–361.

Chapman, T. F., Mannuzza, S., Klein, D. F. & Fyer, A. J. (1994). Effects of informant mental disorder on psychiatric family history data. *American Journal of Psychiatry* **151**, 574–579.

Childers, M. K., Holland, D., Ryan, M. G. & Rupright, J. (1998). Obsessional disorders during recovery from severe head injury: report of four cases. *Brain Injury* **12**, 613–616.

Fyer, A. J., Endicott, J. E., Mannuzza, S. & Klein, D. F. (1985). Schedule for Affective Disorders and Schizophrenia – Lifetime Version. Modified for the study of Anxiety Disorders (SADS-LA). Anxiety Disorders Clinic, New York Psychiatric Institute: New York, NY.

Fyer, A. J., Mannuzza, S., Chapman, T. F., Martin, L. Y. & Klein, D. F. (1995). Specificity in familial aggregation of phobic disorders. *Archives of General Psychiatry* **52**, 564–573.

Grados, M. A., Riddle, M. A., Samuels, J. F., Liang, K. Y., Hoehn-Saric, R., Bienvenu, O. J., Walkup, J. T., Song, D. & Nestadt, G. (2001). The familial phenotype of obsessive-compulsive disorder in relation to psychotic disorders: the Hopkins OCD family study. *Biological Psychiatry* **50**, 559–565.

Katz, M. M., Secunda, S. K., Hirschfeld, R. M. & Koslow, S. H. (1979). NIMH clinical research branch collaborative program on the psychobiology of depression. *Archives of General Psychiatry* **36**, 765–771.

Kendler, K. S., Silberg, J. L., Neale, M. C., Kessler, R. C., Heath, A. C. & Eaves, L. J. (1991). The family history method: whose psychiatric history is measured? *American Journal of Psychiatry* **148**, 1501–1504.

Kessler, R. C., McGonagle, K. A., Zhao, S., Nelson, C. B., Hughes, M., Eshleman, S., Wittchen, H. U. & Kendler, K. S. (1994). Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Archives of General Psychiatry* **51**, 8–19.

Lenane, M. C., Swedo, S. E., Leonard, H., Pauls, D. L., Sceery, W. & Rapoport, J. L. (1990). Psychiatric disorders in first-degree relatives of children and adolescents with obsessive-compulsive disorder. *Journal of the American Academy of Child & Adolescent Psychiatry* **29**, 407–412.

Lipsitz, J. D., Manuzza, S., Chapman, T. F., Foa, E. B., Franklin, M. E., Goodwin, R. D. & & Fyer, A. J. (2005). A direct interview family study of obsessive–compulsive disorder. II. Contribution of proband informant information. *Psychological Medicine*. doi:10.1017/S003329170500543X.

Mannuzza, S., Fyer, A. J., Endicott, J. & Klein, D. F. (1985). Family Informant Schedule and Criteria. Anxiety Family Study Unit, New York State Psychiatric Institute: New York, NY.

Mannuzza, S., Fyer, A. J. & Klein, D. F. (1993). Assessing Psychopathology. *International Journal of Methods in Psychiatric Research* **3**, 72.1–72.9.

Mannuzza, S., Fyer, A. J., Klein, D. F. & Endicott, J. (1986). Schedule for Affective Disorders and Schizophrenia – Lifetime Version. [Modified for the Study of Anxiety Disorders (SADS-LA): rationale and conceptual development.] *Journal Psychiatric Research* **20**, 317–325.

McKeon, P. & Murray, R. (1987). Familial aspects of obsessive-compulsive neurosis. *British Journal of Psychiatry* **151**, 528–534.

Nestadt, G., Samuels, J., Riddle, M., Bienvenu, J., Liang, K., Labada, M., Walkup, J., Grados, M. & Hoehn-Saric, R. (2000).

https://doi.org/10.1017/S0033291705005441 Published online by Cambridge University Press

A family study of obsessive-compulsive disorder. *Archives of General Psychiatry* **57**, 358–363.

Nestadt, G., Samuels, J., Riddle, M. A., Liang, K. Y., Bienvenu, O. J., Hoehn-Saric, R., Grados, M. & Cullen, B. (2001). The relationship between obsessive-compulsive disorder and anxiety and affective disorders: results from the Johns Hopkins OCD family study. *Psychological Medicine* **31**, 481–487.

Pauls, D. L. & Alsobrook II, J. P. (1999). The inheritance of obsessive-compulsive disorder. *Child and Adolescent Psychiatric Clinics of North America* **8**, 481–496.

Pauls, D. L., Alsobrook, J. P., Goodman, W., Rasmussen, S. & Leckman, J. F. (1995). A family study of obsessive-compulsive disorder. *American Journal of Psychiatry* **152**, 76–84.

Paulsen, A. S., Crowe, R. R., Noyes, R. & Pfohl, B. (1988). Reliability of the telephone interview in diagnosing anxiety disorders. *Archives of General Psychiatry* **45**, 62–63.

Rasmussen, S. A. (1994). Genetic studies of obsessive compulsive disorder. In *Current Insights in Obsessive Compulsive Disorder* (ed. E. Hollander, J. Zohar, D. Marazziti and B. Olivier), pp. 105–117. John Wiley & Sons Ltd: West Sussex, England.

Rohde, P., Lewinsohn, P. M. & Seeley, J. R. (1997). Comparability of telephone and face-to-face interviews in assessing axis I and II disorders. *American Journal of Psychiatry* **154**, 1593–1598.

Rosenberg, D. R. & Hanna, G. L. (2000). Genetic and imaging strategies in obsessive-compulsive disorder: potential implications for treatment development. *Biological Psychiatry* **15**, 1210–1222.

Roy, M. A., Walsh, D. & Kendler, K. S. (1996). Accuracies and inaccuracies of the family history method: a multivariate approach. *Acta Psychiatrica Scandinavica* **93**, 224–234.

Roy, M. A., Walsh, D., Prescott, C. A. & Kendler, K. S. (1994). Biases in the diagnosis of alcoholism by the family history method. *Alcoholism: Clinical and Experimental Research* **18**, 845–851.

SAS Institute Inc. (1986). SUGI Supplemental Library User's Guide, Version 5 edition. SAS Institute Inc.: Cary, NC.

Schleyer, B., Aaronson, C., Mannuzza, S., Martin, L. & Fyer, A. J. (1991). Schedule for Affective Disorders and Schizophrenia – Lifetime Version. [Modified for the Study of Anxiety Disorders.] Anxiety Disorders Clinic, New York State Psychiatric Institute: New York, NY.

Spitzer, R. L. & Endicott, J. (1979). Schedule of Schizophrenic and Affective Disorders – Lifetime Version (3rd edn). Research Assessment and Training Unit, New York State Psychiatric Institute: New York, NY.

Vanderbilt Medical Center (2005). PS: Power and sample size calculation (http://biostat.mc.vanderbilt.edu/twiki/bin/view/Main/PowerSampleSize), version 2.1.31. Accessed May 2005.

Weissman, M. M., Bland, R. C., Canino, G. J., Greenwald, S., Hwu, H. G., Kyoon, C., Newman, S. C., Oakley-Browne, M. A., Rubio-Stipec, M., Wickramaratne, P. J., Wittchen, H. U. & Eng-Kung, Y., for the Cross National Collaborative Group (1994). The cross national epidemiology of obsessive-compulsive disorder. *Journal of Clinical Psychiatry* **55S**, S5–S10.

https://doi.org/10.1017/S0033291705005441 Published online by Cambridge University Press