Childhood parental loss and alcoholism in women: a causal analysis using a twin-family design


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SYNOPSIS Childhood parental loss may be an important risk factor for psychiatric illness in adulthood. While this association has been carefully examined for depression, little is known about the role of parental loss in predisposing to alcoholism. We examined an epidemiological sample of female twin pairs with the same history of continuity or disruption in parent–child relationships (N = 1018 pairs; mean age 30 years), using a range of definitions of alcoholism. Childhood parental loss through separation, but not death, substantially increased the risk in adulthood for all definitions of alcoholism. Furthermore, both paternal and maternal alcoholism substantially increased the probability of parental separation from their children. Proposing a structural equation twin-family model that incorporates childhood parental loss as a specified environmental risk factor, we examined how much of the association between childhood parental loss and alcoholism was causal (i.e. mediated by environmental factors) vs non-causal (mediated by genetic factors, with parental loss serving as an index of parental genetic susceptibility to alcoholism). Both the causal and non-causal paths were significant for all definitions of alcoholism. However, the causal–environmental pathway consistently accounted for most of the association. While a significant proportion of the association is due to non-causal genetic mechanisms, childhood parental loss (or the familial discord that precedes or follows it) is probably a direct and significant environmental risk factor for the development of alcoholism in women.

INTRODUCTION

The loss of a parent in childhood through death or separation has long been considered a prominent risk factor for adult psychopathology. Psychoanalytical theory has focused on parental loss and depression, suggesting that losses experienced in adulthood precipitate depression by reactivating the trauma of early parental separation (Breier et al. 1988; Tennant, 1988). Attachment theory postulates an evolutionarily derived instinctive pattern of attachment behaviour in infancy and childhood, the disruption of which predisposes to a range of psychiatric disorders (Roy, 1985; Keith & Finlay, 1988). While early empirical investigations of this area had many methodological difficulties (Gregory, 1958) an increasingly large and sophisticated body of work has now examined the relationship between childhood parental loss and adult psychopathology, including both clinical and epidemiological samples (Crook & Eliot, 1980; Rutter, 1981; Harris et al. 1986; Tennant, 1988; Tweed et al. 1989).

Most studies of early parental loss have examined its impact on depression (for review, see Tennant, 1988), with a few studies that examine anxiety disorders (Raskin et al. 1982; Tennant et al. 1982; Faravelli et al. 1985; Tweed et al. 1989). Despite the great public health importance of alcoholism, we are aware of only one study, in a small, clinically ascertained sample, which examined the inter-relationship

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between this disorder and premature parental loss (Tennant & Bernardi, 1988).

**Environmental causes of familial aggregation**

While familial aggregation is an almost universal observation for psychiatric disorders, most workers have focused on presumed genetic factors as causes of such aggregation. Environmental sources of familial resemblance have received much less attention. If exposure to an environmental event increases risk for a psychiatric disorder and exposure to that event is correlated in relatives, then the disorder will aggregate in relatives solely as a result of the impact of the familial risk factor (Kendler, 1990). Since alcoholism robustly aggregates in families (Cotton, 1979; Merikangas, 1990), it is worthwhile to enquire to what extent the correlated exposure to childhood parental loss may contribute to this aggregation.

**Premature parental loss and adult psychopathology: the problem of causation**

Most previous studies of the relationship between parental loss in childhood and adult psychopathology have implicitly assumed that the relationship was a causal one. That is, the observed association arose because premature parental loss, or the family disruption that preceded or followed such loss, caused an increased liability to psychiatric illness. While plausible, there are other possible explanations for this association. In particular, individuals with alcoholism are at increased risk for premature death, marital separation and divorce (Vaillant, 1985; Helzer et al. 1991). Since the liability to alcoholism is substantially influenced by genetic factors in men (Merikangas, 1990; McGue, 1994) and recent evidence suggests this is also probably true in women (Kendler et al. 1992a), the observed association between parental loss and alcoholism in the offspring could be entirely non-causal. This would occur if premature death or marital separation was an index of the liability to alcoholism in the parents, which, in turn, was genetically transmitted to their offspring.

This is a familiar conundrum in psychiatric research—correlations in behaviours between family members are observed, but unambiguous causal inferences cannot be drawn. Previous rigorous approaches to this problem have been restricted to adoption studies ideally comprising both intact and adoptive families (e.g. Plomin & DeFries, 1985). Examining the relationship between parental behaviour and offspring characteristics in such families can be quite informative, because, in intact families children can resemble their parents because of both genetic and environmental mechanisms, while in the adoptive families parents impact on their offspring only via environmental processes.

In this paper, we report a data collection and analytical strategy, which, like adoption studies, can move beyond previous correlational analyses by permitting rigorous causal modelling of the inter-relationship between parental characteristics and offspring psychiatric outcome. In a population-based sample of personally interviewed female–female twins and their parents, we seek to answer the following questions about the relationship between parental loss and adult psychopathology.

1. What is the impact of premature parental loss on risk for alcoholism in women and does the impact differ as a function of the kind of loss or the parent involved?

2. Does paternal and maternal alcoholism predict premature parental loss through separation or death?

3. What proportion of the familial aggregation of alcoholism in sisters is due to their correlated exposure to early parental loss?

4. To what degree is the association between parental loss and alcoholism causal (i.e. a direct environmental effect) and how much is non-causal (parental loss as an index of the genetic liability to alcoholism that is transmitted to their offspring)?

**METHOD**

**Sample and diagnostic methods**

As part of a longitudinal study of the genetic and environmental risk factors for common psychiatric disorders in women, we personally interviewed 2163 female twins from the population-based Virginia Twin Registry, where both members had previously returned mailed questionnaires (Kendler et al. 1992b). The sample included both members of 1033 pairs and one
twin from 97 pairs. The mean age (± S.D.) of the participating twins was 30.1 ± 7.6. The refusal rate during the personal interview phase with twins was 8%. Eighty-nine per cent of the interviews were conducted face-to-face, usually in the twin's residence, and 11% by phone. Zygosity was determined by an algorithm based on questionnaire responses, photographs and, where these sources were ambiguous, DNA polymorphisms (Spence et al. 1988) and yielded 590 monozygotic (MZ) pairs, 440 dizygotic (DZ) pairs and three pairs of unknown zygosity.

When interviewing the twins, we requested names and addresses of all living biological parents, so identifying 1698 parents of 1033 twin pairs where both members had been assessed. Attempts were then made to interview these parents; however, at the time of contact 26 were deceased, 33 were too medically ill or demented to be interviewed, five were lost to follow-up and two were adoptive parents. Of the remaining 1632 parents, 1472 (90.2%) were interviewed and 160 (9.8%) refused. Of those interviewed, 855 were mothers and 617 were fathers. Of the completed interviews, 92% were performed face-to-face, nearly always in their home, while 8% were done by telephone. The mean age of the participating parents was 58.6 ± 9.3 years.

All interviews were conducted by individuals with a Master's degree in a mental health related discipline or a Bachelor's degree and at least 2 years clinical experience, who had undergone 80 h of initial training with subsequent training sessions throughout the period of field work. All interviews were conducted by individuals with no prior contact with another family member, so that in complete families (both twins and both parents), four different interviewers were required. Each twin and parent was also asked about a history of alcoholism in their mother and father and spouse and twins, respectively, using the Family History-Research Diagnostic Criteria (FH-RDC) (Endicott et al. 1978).

This report focuses on the 1030 twin pairs of known zygosity and, where available, their interviewed parents (333 mothers and 615 fathers). The sample contains 4 family types: twins only (N = 129), twins and their father (N = 48), twins and their mother (N = 286) and twins and both parents (N = 567).

The personal interviews with both twins and their parents contained the section for alcohol dependence from the Structured Clinical Interview for DSM-III-R Diagnosis (Spitzer et al. 1987). Because of previous evidence that the role of genetic factors in the aetiology of alcoholism in women may differ as a function of severity (Pickens et al. 1991) and because DSM-III-R criteria for alcohol 'dependence' are relatively broad (American Psychiatric Association, 1987), and can, paradoxically, be met by an individual who displays none of the symptoms conventionally associated with dependence, we defined three levels of severity of alcoholism: (i) alcoholism with dependence/tolerance – meets DSM-III-R criteria for alcohol dependence and specifically endorses items relating to alcohol tolerance and/or dependence; (ii) alcoholism without dependence/tolerance – meets DSM-III-R criteria for alcohol dependence but does not endorse any items relating to alcohol tolerance or dependence; and (iii) problem drinking – admits to having had, or to being considered by others as having, a significant ‘drinking problem’ not isolated to single incidents, but does not meet DSM-III-R criteria for alcohol dependence. From these levels of severity, we created three definitions of alcoholism: (i) narrow – alcoholism with dependence/tolerance; (ii) intermediate – alcoholism with or without dependence/tolerance (which corresponds to the DSM-III-R definition of alcohol dependence); and (iii) broad (a) alcoholism with or without dependence/tolerance, or (b) problem drinking.

Inter-rater reliability was measured in 98 randomly chosen twins and parents assessed at a single interview by two raters. Chance corrected agreement (Cohen, 1960) for the diagnosis of alcohol dependence was +0.86. In those twins and parents where both interviewers rated the presence of the nine specific DSM-III-R criteria for alcohol dependence, the two interviewers agreed on their presence or absence with high reliability (κ = +0.90). Inter-rater reliabilities for the family history diagnosis of alcoholism were κ = 1.00 in mothers and κ = +0.87 ± 0.06 in fathers. Chance corrected agreement between alcoholism as assessed by family history and intermediate alcoholism diagnosed at personal interview was ±0.38 ± 0.07 for mothers (N = 843) and ±0.40 ± 0.05 for fathers (N = 607).
Fig. 1. A path diagram of the twin family model for alcoholism with childhood parental loss as a specified form of familial environment used in this paper. The observed phenotypes are in boxes and the latent variables in circles. Three classes of latent variables are postulated: A, additive genetic effects; C, common environmental effects (environmental factors other than parental loss which make twins similar for their liability to alcoholism); and E, individual specific environmental effects (that influence one twin's liability to alcoholism but not her co-twin's). Subscript F or M refers to father, M or m to mother, T1 to twin 1, T2 to twin 2 and T to both twins. Path coefficients (one-headed arrows), which equal standardized regression coefficients, are pictured as lower case letters as follows: a additive genetic factors; c common environmental factors; e individual specific environmental factors; w vertical cultural transmission; s, the influence of alcoholism on risk for parental loss; and d, the influence of parental loss on the common environment. The delta path μ (line with no arrows) reflects assortative mating, here modelled as the tendency for one spouse to select the other on the basis of their liability to alcoholism. Genotype environment correlation is expressed by the correlation (two-headed arrow) ρ and is assumed to be at equilibrium. To express the proportion of variance accounted for in the dependent variable, the path coefficient must be squared.
Definition of parental loss

For this paper, we restricted our sample to those twin pairs where both members had had the same experience of either parental continuity or loss ($N = 1018$). Premature parental loss was defined as the twin living apart from one or both of her natural parents for at least 1 year prior to her seventeenth birthday. Parental loss ($N = 178$ or 17.5% of the sample) was divided into those due to parental death ($N = 62$ or 6.1%) and those due to separation of the parent from the twins for other reasons (termed ‘separation’) ($N = 123$ or 12.1%). We use the term ‘separation’ here to reflect separation of the twins from their natural parents, rather than the more common usage to reflect separation of the parents from one another. In our sample, 92% of ‘parent-child’ separations were associated with parental divorce, the remainder resulting from prolonged parental absence without divorce. In the small number of cases ($N = 7$) where separation preceded death, both events were counted. The age of the twin at parental death or at the first separation was recorded.

The twin family design

The traditional approach to the analysis of twin and family data in psychiatric genetics has been to examine the rates of illness in relatives of ill probands ascertained in a treatment facility. However, our general population sample of twins and their parents were interviewed independent of their psychopathological status. That is, our design contains no identified proband and allows us to assess resemblance both for the tendency to develop illness as well as the tendency to remain well. Our analyses assume a liability threshold model (Pearson, 1901; Falconer, 1965), the strengths and limitations of which have been discussed elsewhere (Kendler et al. 1992b; Neale & Cardon, 1992).

A twin-family model with childhood parental loss as a specified familial environment

Fig. 1 depicts, as a path diagram, the model used for the analysis of these data. This model assumes four latent sources of familial resemblance: (i) additive genetic effects ($a$); (ii) shared or common environmental effects ($c$); (iii) direct vertical cultural transmission (VCT) ($w$); and (iv) assortative mating ($µ$). Direct VCT or ‘parent to child’ environmental transmission would occur if children ‘learned’ to develop alcoholism by observing their parents’ drinking patterns. VCT is allowed to differ from fathers ($w_f$) and mothers ($w_m$).

In addition, this model contains one observed source of parent-offspring transmission of the liability to alcoholism: childhood parental loss. The model assumes that both paternal and maternal alcoholism directly contribute to parental loss by the paths $s_p$ and $s_m$, respectively. Since premature parental loss will always affect both twins, this loss directly contributes to the common environment that may influence the liability to alcoholism by the path $d$.

In our structural equation model, childhood parental loss could be considered an ‘environmental index’. However, it is used in a very different way from that first proposed by Rao et al. (1976). In their original model, environmental indices were used in nuclear families in an attempt to discriminate genetic from cultural transmission. In our model, by contrast, we already possess power to discriminate genetic and cultural transmission and incorporate an ‘environmental’ index in an effort to clarify how this index impacts on childhood characteristics.

In this model, the twin’s common environment that influences liability to alcoholism can be divided into three parts: (i) that due to direct VCT from mother and father, (ii) that resulting from the impact of childhood parental loss; and (iii) that due to other shared familial risk factors such as schools, peer groups, neighbourhood, and social class of rearing.

The model assumes that spousal resemblance for the liability to alcoholism results from phenotypic assortative mating in which spouses select one another (in part) on the basis of their predisposition to alcoholism (Eaves et al. 1984; Heath & Eaves, 1985; Heath, 1987). The correlation in liability to alcoholism in spouses is modelled by a delta path $µ$ (Van Eerdewegh, 1982; Fulker, 1988), which, for this application, is identical to the co-path proposed by Cloninger (Cloninger, 1980). Finally, if both genetic and environmental transmission across generations influences the liability to alcoholism, genotype–environment covariance will occur (i.e. individuals at high genetic risk for alcoholism will
also be exposed to high-risk environments for alcoholism). This is modelled by the path $\rho$.

Statistical analysis – regression and relative risk analyses

Two different analytical methods were used in this report: logistic regression (SAS Institute, 1985) and structural equation model fitting (Loehlin, 1987). In the logistic regression analyses examining the relationship between parental loss and risk for alcoholism, the twin-family was the unit of analysis and the dependent variable was trichotomous: (i) neither twin affected; (ii) one twin affected; and (iii) both twins affected.
The age of the twin at interview and the socioeconomic status of the parents (as indexed by years of education and occupational status) significantly predicted premature parental loss and were, therefore, included as control variables. In addition, we present odds ratios for the impact of parental loss, controlling for the effect of age at interview and parental social class, calculated treating members of the twin pairs as individuals. Because observations from members of a twin pair are not independent, and significance levels are already available from the prior regression analyses with a trichotomous dependent variable, no attempt was made to calculate significance levels for the relative risks. In addition, we conducted logistic regressions examining the impact of parental alcoholism on the risk of parental loss, controlling for parental social class. We conducted these analyses twice, first including only parents with personal interviews and secondly including parents with personal interviews or family histories.

**Statistical analysis – model fitting**

Eight tetrachoric correlation matrices along with standard errors were calculated by the program PRELIS II (Joreskog & Sorbom, 1988) for the four family types (twins with both parents, twins with mother only, twins with father only and only twins) separately for MZ and DZ twins. The sample size of families with fathers only, when divided into the two zygosity groups, was too small to provide stable estimates. Therefore, fathers in these families were eliminated and the twins included in the twin only families. For each definition of illness, models were fitted jointly to these six correlation matrices with their standard errors by the computer Mx (Neale, 1991) using asymptotic weighted least squares. After fitting the full model, we then fitted a series of simpler models, with the goal of explaining the observed data as well as possible with as few parameters as possible. We operationalized this goal with the use of Akaike’s information criterion (AIC) (Akaike, 1987), which equals the \( \chi^2 \) value minus twice the degrees of freedom. In seeking to minimize the value of Akaike’s information criterion, we aimed to find the model that best reflects the balance of goodness of fit and parsimony. We also tested the difference between certain nested models by the \( \chi^2 \) difference tests, where the degrees of freedom equal the number of parameters in the broader model that are constrained in the submodel. Further details of the application of biometrical genetic models to twin and twin family data are outlined by us elsewhere (Eaves et al. 1989; Heath et al. 1989; Neale et al. 1989; Neale & Cardon, 1992).

The final step of twin analysis is to estimate, based on the best fitting model, the proportion of variance in liability to alcoholism due to individual specific environment (\( e_i^2 \)), additive gene action (\( a^2 \)) or common environment (\( e^2 \)) as well as the best estimates for assortative mating (\( u \)). The proportion of variance in liability due to additive genetic effects is often termed ‘heritability’.

The main focus of these analyses, however, is not the transmission of the liability to alcoholism in twins and families, the results of which have been reported elsewhere (Kendler et al. 1992a, 1994). Rather, our major goal is to ‘decompose’ the pathway from childhood parental loss to liability to alcoholism. The causal hypothesis predicts that the association between parental loss and risk for alcoholism in offspring should be mediated by the environmental path \( de \) (from childhood parental loss to the twins’ common environment to the twin offspring liability to alcoholism) (Fig. 2). Assuming, for simplicity, no vertical cultural transmission or genotype–environment covariance, the non-causal hypothesis predicts that the association between parental loss and risk for alcoholism in offspring should be mediated through paths \( 2xu^2 = sa^2 \) (from childhood parental loss to parental alcoholism to parental genetic risk factors for alcoholism to twin offspring genetic risk factors for alcoholism to twin offspring liability to alcoholism – this path occurring through father and/or through mother) (Fig. 3). For the best-fitting model with each definition of alcoholism used, we therefore calculate the total predicted correlation between childhood parental loss and liability to alcoholism, and then the proportion of that correlation that is mediated by causal and non-causal pathways.

**The use of family history diagnoses in model fitting**

We were concerned that by examining only living and cooperative parents, we would undersample those with alcoholism and those who
were separated from the twins. Indeed, a family history diagnosis of alcoholism significantly reduced the probability of obtaining a personal interview in fathers ($\chi^2 = 12.6, \text{df} = 1, P = 0.000$) although not in mothers ($\chi^2 = 2.8, \text{df} = 1, P = 0.10$). Furthermore, being separated from the twins before they reached the age of 17 also lowered the probability of being successfully interviewed in both fathers ($\chi^2 = 9.5, \text{df} = 1, P = 0.002$) and mothers ($\chi^2 = 8.4, \text{df} = 1, P = 0.004$).

Therefore, in addition to the analyses that utilize only parents with personal interviews, we also examined the entire sample of parents using
the following diagnostic algorithm. For those that were personally interviewed, the presence or absence of a diagnosis of alcoholism was assessed from the personal interview. If they were not personally interviewed, then they were given a diagnosis of intermediate alcoholism if, by FH-RDC criteria (Endicott et al. 1978), at least two of the possible three family history informants (twin 1, twin 2 and spouse) reported them as having alcoholism. A diagnosis of broad alcoholism was given if at least one informant reported them meeting FH-RDC criteria for alcoholism. Because the FH-RDC criteria for alcoholism do not contain symptoms that specifically reflect tolerance or dependence, we felt that no valid FH-RDC equivalent for narrowly defined alcoholism could be constructed from our data.

The model fitting analyses that incorporate family history information were done on only two correlation matrices, one for full MZ twin families (N = 585) and one on full DZ twin families (N = 430).

RESULTS
Number of twin families with separation
Of the 1018 twin pairs examined, 178 or 17.5% experienced childhood parental loss (Kendler et al. 1992b). Maternal and paternal death were reported by 13 (1.3%) and 52 (5.1%) pairs, respectively. Maternal separation was experienced by 25 (2.5%) of twin pairs and paternal separation by 112 (11.0%) pairs. The lifetime prevalences of our three definitions of alcoholism based on personal interview in this sample were: narrow – 5.5%, intermediate – 7.9% and broad – 17.2%.

Separation and risk for alcoholism in offspring
The impact of early parental loss through death or separation on risk for alcoholism, expressed as the odds ratio (OR) calculated by logistic regression, is seen in Table 1. Neither any parental death nor paternal death has any significant relationship with alcoholism. Maternal death positively predicted risk for alcoholism, reaching statistical significance only for the narrow definition of illness.

By contrast, parental loss through separation had a robust and consistent relationship with risk for alcoholism. For all definitions of illness, loss through separation of any parent, of father alone, or of mother alone, highly significantly increased the risk for alcoholism. ORs ranged between 2 and 3. In analyses that varied the definitions both of loss and of alcoholism, no significant association was found between age of the twin at the time of parental loss and risk for alcoholism.

The impact of zygosity
Our twin families consisted of two potentially different populations: those with MZ and those with DZ twins. Controlling for age and parental social class, zygosity did not predict maternal or paternal death or separation. The impact of parental death or separation on the risk for narrow, intermediate or broad alcoholism also did not significantly differ in families of MZ v. DZ twins.

Parental alcoholism and risk of parental loss
Table 2 shows the relationship between parental alcoholism and the risk for childhood parental loss in their offspring. For the narrow definition

<table>
<thead>
<tr>
<th>Definition of alcoholism</th>
<th>Death</th>
<th>Separation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any</td>
<td>Paternal</td>
</tr>
<tr>
<td>Narrow</td>
<td>1.12</td>
<td>0.67</td>
</tr>
<tr>
<td>Intermediate</td>
<td>0.89</td>
<td>0.66</td>
</tr>
<tr>
<td>Broad</td>
<td>0.83</td>
<td>0.67</td>
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<table>
<thead>
<tr>
<th></th>
<th>Any</th>
<th>Paternal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narrow</td>
<td>3.19*</td>
<td>2.70***</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2.04***</td>
<td>2.34*</td>
</tr>
<tr>
<td>Broad</td>
<td>1.70</td>
<td>2.31*</td>
</tr>
</tbody>
</table>

Separation here refers to prolonged parent-offspring separation not due to parental death.
Odds Ratio calculated from the logistic regression coefficient.
† Controlling for age at interview and parental social class.
* P < 0.05; ** P < 0.01; *** P < 0.001; **** P < 0.0001.
Table 2. Odds ratios for the impact of parental alcoholism on the risk for childhood parental loss through either death or separation†

<table>
<thead>
<tr>
<th>Parent and definition of alcoholism</th>
<th>Source of information</th>
<th>Death</th>
<th>Separation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Any</td>
<td>Paternal</td>
</tr>
<tr>
<td>Paternal</td>
<td>PI</td>
<td>3.53</td>
<td>—</td>
</tr>
<tr>
<td>Narrow</td>
<td>PI</td>
<td>2.29</td>
<td>—</td>
</tr>
<tr>
<td>Intermediate</td>
<td>PI</td>
<td>0.78</td>
<td>0.70</td>
</tr>
<tr>
<td>Broad</td>
<td>PI</td>
<td>1.09</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>PI + FH</td>
<td>0.74</td>
<td>0.64</td>
</tr>
<tr>
<td>Maternal</td>
<td>PI</td>
<td>1.52</td>
<td>1.52</td>
</tr>
<tr>
<td>Narrow</td>
<td>PI</td>
<td>1.07</td>
<td>1.07</td>
</tr>
<tr>
<td>Intermediate</td>
<td>PI</td>
<td>0.63</td>
<td>0.77</td>
</tr>
<tr>
<td>Broad</td>
<td>PI</td>
<td>2.18</td>
<td>2.18</td>
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<tr>
<td></td>
<td>PI + FH</td>
<td>1.36</td>
<td>1.72</td>
</tr>
</tbody>
</table>

Separation here refers to prolonged parent–offspring separation not due to parental death.
PI, personal interview; FH, family history.
Odds ratio calculated from the logistic regression coefficient.
† Controlling for parental social class; —, indicates no estimate available, as interviewed parents are, of necessity, living; †, model does not converge.
* P < 0.05; ** P < 0.01; *** P < 0.0001.

Table 3. The correlation between childhood parental loss and liability to alcoholism decomposed into causal and non-causal components

<table>
<thead>
<tr>
<th>Definition of alcoholism</th>
<th>Source of information on parents</th>
<th>Total correlation</th>
<th>Causal</th>
<th>Non-causal</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Correlation</td>
<td>% of Total</td>
</tr>
<tr>
<td>Narrow</td>
<td>PI</td>
<td>0.361</td>
<td>+0.316</td>
<td>87.6</td>
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<tr>
<td>Intermediate</td>
<td>PI</td>
<td>0.374</td>
<td>+0.317</td>
<td>84.7</td>
</tr>
<tr>
<td>Broad</td>
<td>PI</td>
<td>0.290</td>
<td>+0.231</td>
<td>79.9</td>
</tr>
<tr>
<td>Intermediate</td>
<td>PI + FH</td>
<td>0.345</td>
<td>+0.283</td>
<td>82.0</td>
</tr>
<tr>
<td>Broad</td>
<td>PI + FH</td>
<td>0.258</td>
<td>+0.176</td>
<td>70.2</td>
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</table>

PI, personal interview; FH, family history.

of alcoholism, we present results only for interviewed relatives, while for the intermediate and broad definitions, results are also shown that include parents evaluated only by family history.

No substantial relationship was found in this sample between parental alcoholism and childhood parental loss through death. While most ORs exceeded one, none reached statistical significance. However, parental alcoholism consistently and significantly predicted parental loss through separation for the intermediate and broad definitions of alcoholism. For the narrow definition, the results were generally in the same direction, but did not reach statistical significance, perhaps due to a smaller sample size.

Paternal alcoholism was generally associated with an approximately two-fold increased risk of separation from father, and a generally lower increased risk of separation from mother. Maternal alcoholism tended to significantly predict both separation from father and separation from mother, with ORs for the latter sometimes exceeding 3.5.

A twin-family model for alcoholism with parental loss as a specified environmental risk factor

We wish to evaluate two hypotheses regarding the observed association between childhood parental loss and alcoholism in adulthood: (i) a causal hypothesis—that parental loss (or the
associated family discord) is an environmental risk factor which directly increases the risk for future alcoholism; and (ii) a non-causal hypothesis – that parental loss is an index of a genetic risk to alcoholism that is transmitted to their children. The detailed results of model fitting are presented in Appendix 1.

Decomposing the path from childhood parental loss to alcoholism in the offspring
From the best fitting model for each of our five definitions of alcoholism (narrow, intermediate and broad using personal interviews in parents only and intermediate and broad using personal interviews or family histories in parents), we calculated the total predicted correlation between childhood parental loss and liability to alcoholism in the twins, and the proportion of that correlation which is direct or causal (Table 3). For narrowly defined alcoholism, the best fit model (model IX in Table A1) predicts that the total correlation in liability between childhood parental loss and alcoholism was +0.361. Of that correlation, +0.316 or 87.6% of the total was via the direct environmental path, while only +0.045 or 12.4% was indirect and mediated by genetic factors.

Results were qualitatively similar for other definitions of illness with the causal pathway accounting for between 70 and 88% of the total association between parental loss and alcoholism. Although the variation in results across definitions was only modest, two trends were noteworthy. First, the broader the definition of alcoholism, the greater the proportion of the association between parental loss and alcoholism that was due to non-causal mechanisms. Secondly, the non-causal pathway tended to be more important when family history information was included versus when the analyses examined only parents with personal interviews.

Childhood parental loss as a cause of the familial aggregation of alcoholism
From the best fitting models for each of the definitions of alcoholism employed (Tables A1 and A2), we could estimate the proportion of correlation in liability in DZ twins that was due to their correlated exposure to childhood parental loss. Examining only parents with personal interviews, this proportion was estimated as follows: narrow definition – 34.5%; intermediate definition – 23.8%; broad definition – 11.6%. Examining parents evaluated by personal interview or family history, the parallel results were: intermediate definition – 20.4%; and broad definition – 10.2%.

DISCUSSION
The goal of this paper was to assess the association between childhood parental loss and risk for alcoholism in women and to clarify the causal mechanisms involved in that association.

The impact of premature parental loss on risk for alcoholism
Controlling for the effect of age at interview and parental social class, parental loss prior to age 17 was highly significantly related to the risk for alcoholism in women. Results differed, however, as a function of the kind of parental loss. Loss through separation had a consistent and robust association with future alcoholism. However, loss through parental death was not significantly predictive of alcoholism in adulthood. A similar pattern of findings has been obtained for parental loss and depression (Tennant, 1988; Kendler et al. 1992b).

Childhood separation from mother and separation from father were about equally strongly associated with later alcoholism. The relationship between parental loss and alcoholism was relatively insensitive to variation in the definition of alcoholism.

Despite the extensive literature on the association between parental loss and mood and anxiety disorders, and a long-standing interest in familial–environmental predictors of later drinking problems (McCord & McCord, 1960; Robins, 1966; Vaillant, 1983), we were able to find only one previous study reporting the impact of parental loss on alcoholism. Tennant & Bernardi (1988) studied 40 patients presenting to an in-patient specialized treatment programme with alcoholism and 123 controls ascertained through general medical practitioners. Their results were broadly consistent with those that we obtained, finding that childhood parental loss through separation but not through death differentiated alcoholic patients from controls. The ORs between parental loss through sep-
aration and alcoholism obtained in this treated and largely male sample (1.92 for maternal loss and 1.66 for paternal loss) were lower than those found in our epidemiological, female sample.

The association between parental alcoholism and childhood parental loss

While it may be appealing to assume that the observed association between parental loss and alcoholism is a causal one, another plausible hypothesis merits consideration. If alcoholism in parents predicts parental loss, then parents separated from their offspring when they are children will have an increased liability to alcoholism. This liability would be genetically transmitted to their children resulting in the observed association between parental loss and alcoholism. In this, a non-causal hypothesis, childhood parental loss is an index of parental liability to alcoholism and is assumed to have no direct impact on risk for alcoholism in offspring.

Our results supported the plausibility of this hypothesis in that parental alcoholism, measured either by direct personal interview or by family history, was generally a strong predictor of parental loss. A diagnosis of intermediate or broad alcoholism in a father or in a mother was generally associated with a 2-3-fold increased risk for parental loss through separation but not through death. Surprisingly, this effect was less robust with a narrow definition of alcoholism.

A twin-family model of parental loss and alcoholism

We developed a twin-family model for alcoholism that incorporated parental loss as a specified environmental risk factor. Since the sample was restricted to those twin pairs who together either experienced parental loss, or, were raised by both their natural parents to the age of 17, parental loss could be modelled as a component of ‘familial’ or ‘common’ environment. The major goal of this model was to permit a full ‘decomposition’ of the association between parental loss and alcoholism in offspring into a ‘direct-environmental’ and an ‘indirect-genetic’ path.

This model differs in two crucial ways from the twin model we previously used to examine childhood parental loss (Kendler et al. 1992b). First, the previous model incorporated diagnostic information only on twins, not on their parents. Secondly, this previous model assumed that the relationship between parental loss and the disorder in offspring was causal. Information was not then available to test that assumption.

Since that time, we have personally interviewed parents of these twins. This has allowed us to construct this more complex, but more realistic model, in which the causal relationship between parental loss and psychiatric illness in offspring can be tested rather than assumed.

Across a wide range of definitions of alcoholism, and including or excluding parents who were only evaluated by family history, model-fitting yielded two major results. First, both the causal-environmental and the non-causal genetic paths were consistently statistically significant. That is, the association between childhood parental loss and alcoholism, however defined, was due in part to both causal and non-causal mechanisms. Secondly, the causal-environmental path was consistently substantially larger than the non-causal genetic path.

For various definitions of alcoholism, the environmental path accounted for between 2-4 and 7 times as much of the correlation between parental loss and alcoholism as did the genetic path.

The non-causal genetic path from childhood parental loss to alcoholism tended to be more important for broader definitions of alcoholism. This is contrary to the widespread (but generally unexamined) assumption in the field of mental health that the ‘milder’ the disorder, the greater the relative aetiological importance of environmental compared to genetic factors.

Degree of familial aggregation of alcoholism due to childhood parental loss

Childhood parental loss can be viewed as an environmental risk factor that contributes to the familial aggregation of alcoholism (Kendler, 1990). Siblings will, on average, be highly correlated for their exposure to parental loss during childhood. Our results suggest that childhood parental loss may account for a modest but non-trivial proportion of the familial aggregation of alcoholism in siblings, that is greater in narrower vs. broader forms of alcoholism. We have previously seen in this sample that childhood parental loss accounts for between 7 and 20% of the sibling correlation for affective and anxiety disorders (Kendler et al.)
Correlated exposure to childhood parental loss appears to be at least as important in explaining familial aggregation of alcoholism as for common psychiatric disorders.

**Early parental loss from a genetic epidemiological perspective**

Childhood parental loss is an intriguing variable for genetic epidemiologists because exposure to this risk factor is perfectly correlated in twin pairs reared together (and very highly correlated in siblings of similar age). By excluding the small number of families where twins were not raised in the same household, we could easily create a data set in which parental loss could be modelled as a specified form of ‘common’ or ‘family’ environment.

Previous psychiatric twin studies have nearly all modelled familial environment as a latent measure. That is, it was never directly observed, but was inferred from the pattern of twin correlations. For traits like psychiatric disorders, most of which have at least moderate heritability, the power to detect family environment modelled as a latent variable is low (Martin et al. 1978). Quite large sample sizes of twins are needed even when the family environment accounts for 15–20% of the variance in liability. By these traditional methods, we could find no unambiguous evidence in our sample for family environment in the aetiology of alcoholism (Kendler et al. 1992a, 1994). However, when we examined childhood parental loss as a specified form of familial environment, our statistical power increased dramatically. We were able to detect the impact of parental loss due to separation on the liability to alcoholism in some models, even though it accounted for as little as 3% of the total variance! These results underscore the large potential gain in analytical power that can occur when genetic–epidemiological models for psychiatric disorders move beyond treating the environment as a latent ‘black box’ to incorporating specific measurable environmental variables.

**Limitations**

These results should be interpreted in the context of seven potential methodological limitations. First, we studied only female twins. As parental loss may impact differently on males and females (Roy, 1985; Keith & Finlay, 1988; McLeod, 1991), and gender is a well documented risk factor for alcoholism (Helzer et al. 1991), results presented here may not extrapolate to males. The impact of parental separation might also differ in twins and singletons.

Secondly, our twin-family model assumed that parental alcoholism predisposed to childhood parental loss rather than the other way around. While the accuracy of retrospective recollection can be doubted, we examined the relative dating of these two events in mothers and fathers where both had occurred and dates were available. In all mothers and 83% of fathers, the onset of alcoholism preceded separation from their children.

Thirdly, estimates of the heritability of liability to alcoholism calculated using the model proposed here are lower than those obtained when analysing the twins alone (Kendler et al. 1992a) or the twins and their parents with a standard twin-family model (Kendler et al. 1994). The goal of the model here used was to decompose covariation between childhood parental loss and alcoholism rather than to estimate the heritability of alcoholism. For simplicity, we constrained to unity the correlation in genetic effects on alcoholism across generations. Relaxing this assumption in these data increases heritability estimates (Kendler et al. 1994). In addition, this model includes genotype–environment covariance, which accounts for some additional variance in liability.

Fourthly, our results are, in at least one important way, incomplete. While we speak of childhood parental loss as ‘directly causing’ alcoholism in adulthood, this is a considerable over-simplification. In fact, our own data suggest that the mere loss of a parent (e.g. by death) does not contribute to later risk for alcoholism. Rather, parental separation probably should itself be considered an index of other familial environmental risk factors, especially marital discord and poor rearing quality (Rutter, 1981; Block et al., 1986; Harris et al. 1986; St Clair & Osborn, 1987; Tennant, 1988). Further work in these and other data sets will be required to clarify the ‘pathway’ through which parental separation impacts on later risk for alcoholism.

Fifthly, our model assumes that parental loss is a ‘shared’ environmental event for members of a twin pair who were reared together. While this is unarguably correct, children in the same
family do not always respond in the same way to parental loss (Hetherington, 1989). Our model, in examining only the ‘main effects’ of parental loss and not interactions between parental loss and prior child characteristics, is therefore almost certainly conservative in its estimation of the total impact of parental loss.

Sixthly, unlike adoption designs, in which the environmental pathway between parental behaviour and offspring characteristics can be directly examined in adoptive families, in the twin-family design this path can only be estimated by a complex model-fitting procedure, the results of which may not be intuitively apparent. While this represents a potential disadvantage of twin-family approach, it must be balanced against limitations of the adoption design (Kendler, 1993). In particular, the very low rates of alcoholism and reduced rates of divorce often seen in adoptive parents (e.g. von Knorring et al. 1983) would substantially limit the power of adoption studies to address the questions examined in this paper.

Finally, our structural equation model assumes that parental genetic factors influence the risk for separation only via the phenotype of alcoholism. Since the risk for divorce is influenced by genotype (McGue & Lykken, 1992), genetic factors for alcoholism might, via some temperamental trait such as irritability or impulsiveness, influence the risk for parental separation directly. Such a relationship can be modelled by replacing paths $s_1$ and $s_m$ in Fig. 1 by direct paths from genetic factors in parents ($A_p$ and $A_s$) to childhood parental loss. Although involving some unlikely assumptions, this alteration produced significant changes in the results. Causal and non-causal effects of childhood parental loss on alcoholism in the twins both remained significant, but the relative importance of the non-causal path increased considerably. For example, using the intermediate definition of alcoholism in the personally interviewed sample, including these direct paths increased the proportion of the association between childhood parental loss and alcoholism in the daughters that was non-causal from 18 to 54%. While unlikely to be exactly correct, these results suggest that by ‘forcing’ the parental genetic effects in our model to impact on separation only via their effect on alcoholism, we may have significantly underestimated the magnitude of the non-causal relationship between childhood parental loss and alcoholism.

**APPENDIX I**

We outlined in detail the results of model-fitting with the narrow definition of alcoholism based on personal interviews (Table A1). These models examine childhood parental loss through separation, and loss is defined as separation from either or both parents. The full model containing the parameters $ACE_{pqw_1w_2s_1s_m}$ produces an excellent fit ($\chi^2 = 14.6$, df = 29, NS, $AIC = -43.4$). As the estimates of the VCT paths ($w_1w_2$) were modest and negative, in model II, we set them both to zero. As expected, the deterioration in fit was slight, with an improvement in the $AIC$ ($\chi^2 = 17.3$, df = 31, $AIC = -44.7$). We then tried to simplify the paths from maternal alcoholism to childhood parental loss in three different ways: (i) set to zero the path from mother ($s_m$) (model III); (ii) set to zero the path from father ($s_f$) (model IV); and (iii) set equal the paths from mother and father ($s_f = s_m = s_0$) (model V). Of these, the third alternative (model V) provided the best fit ($\chi^2 = 17.4$, df = 32, $AIC = -46.6$). In model VI, we set the $d$ path to zero, which assumes that, taking into account genetic effects, there is no direct environmental path from childhood parental loss to liability for alcoholism. This model failed badly ($\chi^2 = 36.0$, df = 33, $AIC = -30.0$), providing a much worse fit than model V ($\chi^2$ difference test = 18.6, df = 1, $P = 0.000$). The assortative mating parameter ($\rho$) was quite small and positive, so starting again with model V, we set, in model VII, that path to zero. This produced an expected improvement in the $AIC$ over model V ($\chi^2 = 17.7$, df = 33, $AIC = -48.3$). In model VIII, we set the path $s$ to zero, which assumes that maternal and paternal alcoholism do not influence the risk for childhood parental loss. The model did not fit as well as model V ($\chi^2 = 19.6$, df = 33, $AIC = -46.4$). In model IX, we constrained the $d$ path to unity, meaning that the only common environmental factor in the model that influenced liability to alcoholism was childhood parental loss. This change further improved the $AIC$ ($\chi^2 = 18.1$, df = 34, $AIC = -49.9$). No further improvement in fit was possible.

Model-fitting results for the intermediate and broad definitions of alcoholism based only on personal interview are also seen in Table A1. Briefly, the results with the intermediate definition followed those found with the broad definition with one major exception. Setting the $d$ path to equal unity, which improved the $AIC$ with the narrow definition of illness, produced a slight decrease in the $AIC$ with the intermediate definition of illness, making model VII instead of model IX the best-fitting model (Table A1). For the broad definition of illness, the results were again somewhat different. With this definition, model III,
which sets to zero the path from mother ($s_m$) to childhood parental loss, fits better than either model IV or V. This result suggests that with this definition of illness, controlling for the impact of paternal alcoholism on parental loss, maternal alcoholism makes no additional contribution. Furthermore, with the broad definition of illness, no other simplifications of the model are possible. Setting the $s, d, p$ paths to zero (models VIII, X and XI, respectively), resulted in a worsening of the AIC. In contrast to the narrower definitions of illness, with the broad definition of illness assortative mating for alcoholism is significant.

Results of model-fitting applied to the twin families including both parental personal interview and family history data are seen in Table A2, the results being identical for the intermediate and broad definitions of illness. VCT was not significant (model II) and the best fitting description of the paths from alcoholism
to childhood parental loss set $s = s_0 = s$ (model V). No further simplification of the model could be made, suggesting in particular that assortative mating was significant and familial environmental factors other than childhood parental loss influenced twin liability to alcoholism.

The parameter estimates from the best fitting models from the five diagnostic approaches to alcoholism that were utilized are outlined in Table A.3.

This work was supported by grants AA-09095 and MH-40828 from the United States National Institutes of Health. The Virginia Twin Registry, established and maintained by Drs. W. Nance and L. Corey, is supported by the United States National Institutes of Health grants HD-26746 and NS-31564. Leroy Thacker assisted in the data analysis.

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