Gender Differences in Schizophrenia: Hormonal Effect or Subtypes?

by David J. Castle, Kathryn Abel, Noriyoshi Takei, and Robin M. Murray

At Issue

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Abstract

Compared with their male counterparts, females with schizophrenia, on average, show better premorbid functioning, later onset, and a more benign course of illness. They are also more likely to have a family history of schizophrenia and/or affective illness, to exhibit “atypical” and affective features, and to show a seasonal pattern of hospital admission that mimics that of patients with mania. However, there exists a paradox. Although schizophrenia in females has much in common with affective disorder, the “schizophrenogenic” effect of maternal influenza also appears to be more significant in female than in male schizophrenia. Perhaps females with a predisposition to affective psychosis who have also been subject to the effects of maternal viral infection during gestation develop some subtle neurodevelopmental damage that renders their psychosis schizophrenia-like.


Schizophrenia has a later onset in females than in males; the difference has been found to be about 5 years in most studies (see Lewine 1988). The sex difference in age at onset is consistent across cultures (Hambrecht et al. 1992) and is robust to definition of “onset” (Loranger 1984; Riecher et al. 1989; Häfner et al. 1991) as well as to definition of illness (Loranger 1984; Shimizu et al. 1988). Furthermore, the age-at-onset distribution curves for schizophrenia differ between women and men. In a study of 392 consecutive first admissions from a defined catchment area with a diagnosis of schizophrenia or paranoid disorder (the ABC study), Häfner and colleagues (1991) found that males showed a single marked peak in their early twenties, while for females there was a second peak of onset in the 45-54-year age group. This finding is echoed in the distribution of pooled data from the World Health Organization Determinants of Outcome study (Hambrecht et al. 1992). We (Castle et al. 1993) recently investigated gender differences in a catchment-area sample of 470 patients with schizophrenia across all ages and found that a surprisingly large number (n = 134, 28%) had an onset of illness after age 45 and even after age 60 (n = 56, 12%). Males had a dramatic early peak followed by a monotonous decline; females showed a second peak in the late forties and an even more emphatic peak in very old age.

Thus, not only do females have a later mean age at onset of illness than males, but the age-at-onset distribution curves for females and males are very dif-
different in shape. This has profound implications for any theory aimed at explaining gender differences in schizophrenia (see Castle and Murray 1993). One possibility is that some factor(s) associated with being female serves to delay the onset of the illness. The factor attracting the most attention has been estrogen; it has been proposed that during the reproductive years women are protected by the antidopaminergic action of estrogens and that the slight peak in the incidence of schizophrenia among women in the 46-55-year age range is the result of the removal of this protection at menopause (see Häfner et al. 1991; Rieber-Rössler and Häfner 1993). An alternative explanation is that the gender differences in age at onset are a clue to subtypes of schizophrenia to which women and men are differentially prone (see Goldstein et al. 1990b; Castle and Murray 1991; Murray et al. 1992). This article will address each of these possibilities in turn.

**The Estrogen Hypothesis**

Animal studies have shown that both D₁ (Hruska and Novak 1988) and D₂ (Di Paolo et al. 1979, 1982a, 1982b, 1984) dopamine receptor numbers increase in response to estrogen treatment, specifically in the lateral caudate-putamen. This effect is seen only after chronic estrogen treatment; in contrast, acute estradiol exposure rapidly converts striatal D₂ receptors from high- into low-affinity states (Levesque and Di Paolo 1988). Estrogen affects not only dopamine systems but also noradrenergic (Johnson et al. 1985), serotonergic (Fischette et al. 1983), and gamma-aminobutyric acid (GABA)-ergic (O’Connor et al. 1988) neurons in a region- and sex-specific manner (McEwen 1991).

Despite the complexity of the influence of estrogen on neurotransmitter systems, the notion that estrogen effects can go some way toward explaining gender differences in schizophrenia has gained currency (see Rieber-Rössler and Häfner 1993). But is there clinical evidence of any relationship between estrogen levels and psychosis? Admission rates to psychiatric hospitals increase for women in the paramenstruum (Janowsky et al. 1969; Abramowitz et al. 1982; Dalton 1982; Blumenthal and Nadelson 1988). Seeman and Lang (1990) proposed that low estrogen levels at this time could precipitate relapse of a schizophrenic illness. However, most studies in this area focused on affective disorders (see Ascher-Svanum and Miller 1990) or included nonpsychotic illnesses, did not employ operational diagnostic criteria, and did not control for time point in the cycle. Also, case reports (Endo et al. 1978; Glick and Steward 1980; Berlin et al. 1985; Brockington et al. 1988; Gerada and Reveley 1989) associating psychosis and the premenstrom all describe affective psychoses, and none of these studies correlated plasma hormone levels with onset of psychotic illness. Indeed, Targum et al. (1991) suggest that the only conclusion that can be drawn is that the menstrual phase may be a nonspecific stressor in mental illness.

Although it is well established that the puerperal period (90 days postpartum) is a particularly vulnerable period for psychotic illness, the increased risk is due mostly to affective psychoses. Thus, Kendell et al. (1987) estimated that women with a past history of schizophrenia have only a 3.4 percent risk of psychiatric admission postpartum, compared with a risk of 13.3 percent in women with a previous history of unipolar depression and 21.4 percent in those with a history of bipolar affective disorder. Pregnancy and the puerperium involve many steroid and peptide hormone changes apart from the simple rise and fall of estrogens; it is likely that puerperal mental disorders result from a complicated interplay of these changes, along with factors involved in the social disruption that childbirth inevitably brings.

The notion that low estrogen levels postpartum increase the risk of schizophrenic relapse goes hand in hand with the idea that high estrogen levels during pregnancy are protective. However, McNeil et al. (1984a, 1984b) found an overall worsening of mental health during pregnancy, which was especially marked in women with schizophrenia; the results of Krener et al. (1989) are congruent with this finding.

Seeman and Lang (1990) posited that at puberty “… the sudden, dramatic hormonal and neurochemical change is a risk period for the development of schizophrenia, which in females is made safer by the protective effects of estrogen” (p. 188). However, the mean age for developing schizophrenia is the late twenties to early thirties in women and the early to midtwenties in men, whereas puberty occurs considerably earlier (Grumbach et al. 1974). Furthermore, if estrogens are protective against a pathogenic overactivity of dopamine systems, then women ought to be similarly protected from mania, which is also
associated with increased dopamine activity (Ashcroft et al. 1972); however, they are not.

The menopause has long been thought to be associated with an increase in psychological morbidity, particularly affective disturbance (see Ballinger 1990). As noted earlier, Häfner and colleagues (1991) reported a small peak in the incidence of schizophrenia in women between the ages of 45 and 54 and a relative decline in male incidence at this age. They attributed this peak to a fall in estrogen levels in women at this time. However, this conclusion is purely inferential, and there were no data on subjects’ menstrual status at the time of psychotic breakdown. Few studies have attempted to correlate the menopause with onset of psychosis, and those that have done so have found no connection between admission for broad diagnostic groups, including schizophrenia, and recent menopause (Tait et al. 1957; Smith 1971). Molnar et al. (1988) found low estrogen levels only in those menopausal psychotic patients with depressive illnesses. The World Health Organization (1981) concluded that no psychological symptoms could be convincingly attributed to a lack of estrogen; treatment studies using estrogens have attested to this opinion (Montgomery and Studd 1991; Schmidt and Rubinow 1991). Indeed, it has been suggested (e.g., Greene and Cooke 1980; MacKinlay et al. 1987) that social life events that coincide with menopause play a greater role in psychiatric disturbance at this time than do biological factors.

As far as we know, the only studies set up to test the hypothesis directly are those of Häfner and colleagues. In rats, Häfner et al. (1991) showed that estradiol reduced behavioral changes induced by both haloperidol and apomorphine and caused a reduction in dopamine receptor affinity for sulpiride. Interestingly, these effects were most marked in neonatal rather than adult rats, and the authors concede that estrogentic effects on brain maturation may be what is most important.

We consider that this hypothesis merits active investigation, as does the role of estrogens in brain degeneration. Rather than estrogens having a protective role, it could be that estrogen withdrawal has adverse effects on the postmenopausal female brain, in, for example, accelerating age-related changes in the medial temporal lobe (Murphy 1994).

**Male-Predominant “Dementia Praecox” Subtype**

We have proposed elsewhere (Castle and Murray 1991; Murray et al. 1992) that males and females are differentially susceptible to at least two different forms of schizophrenia and that the excess of males among early-onset schizophrenia patients is a reflection of a male propensity to a severe early-onset form of the illness that is akin to Kraepelin’s (1896) original conception of “dementia praecox” and a consequence of neurodevelopmental deviance. In support of this hypothesis, we cited evidence of a tendency to worse premorbid functioning (e.g., Zigler and Levine 1973; Klorman et al. 1977; Zigler et al. 1977; Lewine 1981; Childers and Harding 1990; Foerster et al. 1991; Castle et al. 1993) and lower premorbid IQ and poor school performance (Offord 1974; reviewed by Aylward et al. 1984) among males than females who subsequently develop schizophrenia. Obviously, the protective effect of a pubertal estrogen surge in females could not explain these childhood differences.

We also cited evidence of more structural brain abnormalities in male schizophrenia patients than in their female counterparts; we found 10 studies (6 computed tomography and 4 magnetic resonance imaging) pointing in this direction. Flaum et al. (1990) reviewed neuroimaging studies of individuals with schizophrenia in which gender effects were reported; most had small sample sizes and lacked statistical power, but males had larger ventricle-to-brain ratios than females in five of the six studies that found a gender effect. In three of their own four studies, Flaum et al. (1990) found that males had significantly larger ventricles than control subjects but that there was no such effect for females. Andreasen et al. (1993) have shown that in male, but not female, schizophrenia patients, the normal positive correlation between IQ and the volume of various brain structures (e.g., the temporal lobe) is lost, implying greater abnormality in male than female schizophrenia patients. Not all neuroimaging studies of schizophrenia patients have found such a gender difference (e.g., Nasrallah et al. 1990; Gur et al. 1991), and studies have not been designed specifically to address this issue; however, the weight of evidence suggests more brain volume decrements in males than females with schizophrenia.

Johnstone et al. (1994) recently carried out a most interesting reanalysis of post-mortem data on schizophrenia patients for whom there was extensive clinical infor-
There appeared to be two neuropathologic types. In the first, decreased brain size was associated with poor premorbid function, limited academic achievement, prominent negative symptoms, and poor cognitive functions. This pattern is very suggestive of neurodevelopmental impairment.

The second type was more common in women and was associated not with small brains or impaired premorbid function but rather with gliosis and focal brain damage. Johnstone's work raises the question of whether such features are a consequence of acquired brain damage separate from those processes that cause small brain size.

Other characteristics of schizophrenia in males, such as more negative symptoms (reviewed by Bardenstein and McGlashan 1990) and generally worse outcome (for reviews, see Seeman 1986; Goldstein 1988; Angermeyer et al. 1989, 1990), are compatible with the notion that males are more prone to a severe neurodevelopmental form of the illness (see table 1). In etiological terms, males with schizophrenia, expressly those with an early onset of illness, appear more likely than females to have a history of those obstetric complications implicated in the etiology of the condition (see Lewis et al. 1989; Castle and Murray 1991; O'Callaghan et al. 1992).

Kirov et al. studied 73 schizophrenia patients diagnosed according to DSM-III-R (American Psychiatric Association 1987) criteria and found that the mean age at onset was, as expected, significantly earlier in males. However, once those patients (predominantly males) who had a history of obstetric complications were removed from the study, the remaining males and females showed no difference in age at onset of psychosis.

An excess of males is a feature of other neurodevelopmental disorders, such as dyslexia, autism, and hyperkinetic behavior. The reasons for the particular vulnerability of the male brain to neurodevelopmental impairment are poorly understood, but the study of gender differences in rates of cerebral maturation, organization, and structure may provide some of the answers (see McGlone 1980; Diamond 1989; Lewine et al. 1990).

The role of sex hormones (expressly estrogen) in early brain development should be considered in this regard (reviewed by Delisi et al. 1989; see Seeman and Lang 1990; Hafner et al. 1991).

Female monozygotic twins have higher concordance rates for schizophrenia than do male monozygotic twins (Rosenthal 1970; Kringlen 1987), and four recent studies (Bellodi et al. 1986; Goldstein et al. 1990a; Wolyniec et al. 1992; Sham et al. 1993) have shown that the relatives of female schizophrenia probands have a greater risk of developing schizophrenia than do relatives of male schizophrenia probands. This finding might be interpreted as suggesting a greater role for environmental factors (e.g., obstetric complications) in male schizophrenia, a hypothesis that is supported

### Table 1. Gender differences in schizophrenia

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age-at-onset distribution</td>
<td>Early peak with uniform decline</td>
<td>More even distribution throughout adult life</td>
</tr>
<tr>
<td>Symptomatology</td>
<td>More likely to exhibit &quot;typical&quot; and &quot;negative&quot; symptoms</td>
<td>More likely to exhibit &quot;atypical&quot; and affective symptoms</td>
</tr>
<tr>
<td>Season of admission</td>
<td>No clear seasonal pattern</td>
<td>Cyclical pattern as mania</td>
</tr>
<tr>
<td>Premorbid functioning</td>
<td>More likely to show poor premorbid social and occupational functioning and low premorbid IQ</td>
<td>Less likely to have been socially, occupationally, or intellectually compromised</td>
</tr>
<tr>
<td>Neuropathology</td>
<td>More likely to exhibit structural brain changes</td>
<td>Less likely to exhibit structural brain changes</td>
</tr>
<tr>
<td>Course of illness</td>
<td>Tends to be worse in terms of hospitalization and social and occupational functioning</td>
<td>Treatment, social, and occupational outcomes are generally better</td>
</tr>
</tbody>
</table>

Kirov et al. (submitted for publication) have reviewed the evidence that schizophrenia patients with a history of obstetric complications have an earlier onset than those without such a history, and the authors suggest that this fact, together with the greater frequency of such histories in males than in females with schizophrenia, may explain the earlier onset of schizophrenia in male patients.
by the increasing evidence that male, but not female, sporadic schizophrenia patients show larger cerebral ventricular volumes than their familial counterparts (Murray et al. 1994; Vita et al. 1994).

Female Schizophrenia and Affective Disorder

Reviewers have tended to conclude that there is no definitive evidence for an overall sex difference in the incidence of schizophrenia (e.g., Häfner 1987; Lewine 1988). However, when diagnostic criteria of increasing stringency (e.g., Research Diagnostic Criteria [Spitzer et al. 1978], DSM-III-R) are applied to cohorts of schizophrenia patients, more females than males are excluded (e.g., Lewine et al. 1984; Castle et al. 1993). Jones et al. (submitted for publication) have shown that stringent diagnostic criteria for schizophrenia, such as those of the DSM-III-R, define a form of illness associated with early onset and negative symptoms; conversely, 41 percent of females but only 14 percent of males who met Present State Examination/CATEGO (Wing et al. 1974) broad criteria for schizophrenia in Jones et al.'s study were reassigned by DSM-III-R to affective disorder. Bardenstein and McGlashan (1990), reviewing gender differences in schizophrenia and schizoaffective and affective disorders, concluded that the female with schizophrenia is "more likely to receive differential diagnoses of atypical, affective, or manic depressive illness" (p. 160) and that females are overrepresented among patients with a diagnosis of schizoaffective disorder. Also, women are more susceptible to so-called cycloid psychoses, which are characterized by discrete episodes of florid psychosis of abrupt onset that tend to resolve with good return of function between episodes (Cutting et al. 1978). There is some evidence that such patients respond to the prophylactic effect of lithium (Perris 1974).

Recent reviews of the relationship between schizophrenia and affective disorder (e.g., Levitt and Tsuang 1988; Taylor 1992) have pointed out the complexity of the association and the considerable overlap between the two in families. Studies of familial loading in schizoaffective psychoses are difficult to compare because of variability in diagnostic criteria (Pope and Yurgelun-Todd 1993). However, a number of studies suggest that patients with atypical and schizoaffective psychoses show higher than expected familial loading for affective disorder. For example, Tsuang et al. (1976) found that the siblings of their patients with atypical schizophrenia showed a low risk for schizophrenia (1.1%) but a high risk for affective illness (7.4% vs. 6.9% in relatives of patients with bipolar disorders and 1.9% in typical schizophrenia comparison groups). In reviewing the specificity of schizophrenic symptoms, Pope and Lipinsky (1978) found 15 studies in which familiality was compared in good-prognosis and poor-prognosis schizophrenia patients. Those in the good-prognosis groups (mostly patients with atypical, schizoaffective, or schizophreniform psychoses) typically showed two to three times as much familial affective illness as schizophrenia, while the poor-prognosis groups showed a twofold to threefold difference in the opposite direction. A recent family interview study (Pope and Yurgelun-Todd 1993) found high rates of affective disorder in the relatives of patients with schizoaffective illnesses, but not in relatives of those with schizophrenia. Sham et al. (1994), in a Scandinavian data set, found that relatives of females with schizophrenia had a higher rate of manic depression than did relatives of males with schizophrenia.

Another line of evidence in support of the notion that some females with schizophrenia have a form of illness with links to affective disorder is the demonstration of gender differences in season of admission. An excess of admissions for psychosis in summer months is best established for affective psychosis, but studies from a number of countries have shown a similar pattern in patients with schizophrenia (see Takei et al. 1992). Few studies have determined gender effects in seasonality of admission. Takei et al. (1992) examined season of first admission in 17,770 patients with schizophrenia and 20,845 patients with affective disorder in England and Wales between 1976 and 1986 and found a cyclical seasonality with an excess of summer admissions in females, but not male, schizophrenia patients. A similar cyclical pattern was seen in manic patients of both sexes. The finding of a cyclical pattern in female, but not male, schizophrenia patients has been replicated in an independent large data set from Scotland (Takei and Murray 1993).

Effect of Prenatal Exposure to Influenza

Table 2 lists studies that have investigated whether there is an association between prenatal ex-
Table 2. Relationship between 1957 A2 influenza pandemic and birth of individuals who subsequently developed schizophrenia

<table>
<thead>
<tr>
<th>Association and study</th>
<th>Place</th>
<th>Gender effect examined</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mednick et al. (1988)</td>
<td>Helsinki, Finland</td>
<td>Yes</td>
<td>Both</td>
</tr>
<tr>
<td>Kendall and Kemp</td>
<td>Edinburgh, Scotland</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td>O’Callaghan et al.</td>
<td>England and Wales</td>
<td>Yes</td>
<td>Female</td>
</tr>
<tr>
<td>(1991a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kunugi et al. (1992)</td>
<td>Japan</td>
<td>Yes</td>
<td>Male</td>
</tr>
<tr>
<td>Welham et al. (1993)</td>
<td>Queensland, Australia</td>
<td>Yes</td>
<td>Female</td>
</tr>
<tr>
<td>Fahy et al. (1993)</td>
<td>England</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td>Adams et al. (1993)²</td>
<td>England and Wales</td>
<td>No</td>
<td>Female</td>
</tr>
<tr>
<td></td>
<td>Scotland</td>
<td>Yes</td>
<td>Female</td>
</tr>
<tr>
<td></td>
<td>Denmark</td>
<td>Yes</td>
<td>Female</td>
</tr>
<tr>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kendall and Kemp</td>
<td>Edinburgh, Scotland</td>
<td>Yes</td>
<td>Female</td>
</tr>
<tr>
<td>(1989)³</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Torrey et al. (1992)</td>
<td>United States</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td>Crow and Done (1992)</td>
<td>England</td>
<td>No</td>
<td>—</td>
</tr>
</tbody>
</table>

¹The subjects were Afro-Caribbeans.
²These investigators examined three independent data sets from England and Wales, Scotland, and Denmark.
³A reanalysis by Mednick et al. (1990), however, revealed a significantly increased rate of subsequent schizophrenic births in females.
⁴This study was based on the cohort from the National Child Development Study.

Exposure to influenza and later schizophrenia, concentrating on the 1957 A2 influenza pandemic. Of the 10 studies, 7 countries found that fetuses in utero at the time of the pandemic had a higher than expected risk of developing schizophrenia in adulthood. The data of Kendall and Kemp (1989), in Scotland, were originally interpreted as negative, but a reanalysis by Mednick and colleagues (1990) found an effect for females but not males. The possible reasons for the negative findings of Crow and Done (1992) have been discussed elsewhere (O’Callaghan et al. 1991b). Although the issue remains controversial, the weight of evidence appears to support a real association (albeit a modest one) between prenatal exposure to influenza and later schizophrenia. This conclusion is supported by reports of an association between schizophrenic births and influenza epidemics other than the 1957 pandemic (Watson et al. 1984; Torrey et al. 1988; Barr et al. 1990; Sham et al. 1992; Adams et al. 1993; Morris et al. 1993; Takei et al. 1994).

Are there gender differences in susceptibility to the “schizophrenogenic effect” of influenza? Regarding the 1957 pandemic, gender effects were examined in seven data sets; of these, five showed that the effect reached significance only for females (see table 2). Of the researchers looking at influenza epidemics over a long time period, only Takei et al. (1994) investigated the effect of gender; again, the influenza effect was more readily demonstrable in female than in male schizophrenia patients.

We are thus faced with the seeming paradox that females with schizophrenia show evidence of both greater genetic influence (i.e., their relatives show a higher morbid risk of schizophrenia and affective disorder) and greater susceptibility to an early environmental effect (i.e., prenatal exposure to influenza). The mechanism whereby influenza infection in the mother predisposes the fetus to later schizophrenia is far from clear (see Sham et al. 1992). Pulver et al. (1992) found that female schizophrenia patients born in winter or spring (when influenza viruses are most prevalent) had higher than expected familial loading for the illness; one could infer that the influenza effect does not result in “phenocopies,” but rather acts in consort with a genetic diathesis. Intriguingly, Wolyniec et al. (1993) have shown that schizophrenia patients born in winter or spring are significantly more likely than other schizophrenia patients to have a history of manic-like symptoms than are other schizophrenia patients and that this effect is most marked in females. Also, a number of studies (e.g., Myerson 1925; Slater 1936; Rosenthal 1970; Powell et al. 1973; Crow 1986) have reported a higher than expected morbid risk of schizophrenia in the offspring of individuals with affective disorders. Thus, one possibility is that
the prenatal viral effect is due to a "diversion" to schizophrenia of females who would otherwise have developed an affective psychosis. Indeed, Taylor (1992), who recently reviewed the relationship between affective disorder and schizophrenia, suggested that "research should focus on ... nongenetic factors (street drugs, perinatal problems, viral disease) that might alter the clinical expression of a shared genotype" (p. 29).

In a preliminary analysis, Takei et al. (1993), examining first-admission data from England and Wales for the period 1976 to 1986, found that death rates from influenza were associated 5 months later not only with an excess of preschizophrenic births, but with a deficit of births of females, but not males, who later manifested affective psychosis. Of course, such findings need independent replication, but "phenotypic diversion" from affective psychosis to schizophrenia could go some way toward explaining the apparent liability of females to a form of illness resulting from maternal exposure to a virus and the predominance of affective features in females.

Conclusions

We conclude that the evidence points toward a differential susceptibility of males and females to different forms of schizophrenia. In recent years, much attention has been directed toward the severe early-onset form that predominates in males. It is time to focus similar effort on the milder, later-onset form to which women appear particularly susceptible. We are not convinced that this is simply the same illness ameliorated by the antidopaminergic actions of estrogen, but we do believe that the effects of estrogen on cerebral structure at the extremes of life merit attention. Similarly, methodologically rigorous research should be directed toward the hypothesis that some cases of schizophrenia with good outcome may result from an interaction between a genetic diathesis for affective psychosis and environmentally induced brain changes.

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Acknowledgments

David J. Castle and Noriyoshi Takei gratefully acknowledge the support of the Medical Research Council and Wellcome Training Fellowships, respectively. Drs. Jim van Os, Peter Jones, Padraig Wright, Pak Sham, and Shon Lewis provided useful comments on earlier drafts of the manuscript.

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