At Issue: Schizophrenia and Rheumatoid Arthritis: The Negative Association Revisited

by Robert J. Oken and Michael Schulzer

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Abstract

A strong negative association between schizophrenia and rheumatoid arthritis (RA), implying low comorbidity, has been found in 12 of 14 previous studies, which we review. To this literature we add two recently acquired data sets encompassing 28,953 schizophrenia patients, only 31 of whom had comorbid RA. Integrating our new data into those of the previous nine studies, which stratified their populations according to psychiatric diagnosis, we obtain a median frequency of RA in schizophrenia populations of 0.09 percent and a mean frequency of 0.66 percent, well below the expected range of 1 percent. These data robustly support prior studies.

We also present a meta-analysis evaluating the association between the two diseases by integrating information derived from nine data sets, each furnishing an estimate of the relative risk of RA in schizophrenia patients versus that in other psychiatric patients. We find that the estimated rate of RA among schizophrenia patients is only 29 percent of the corresponding rate in other psychiatric patients. Further, the relative risk of RA in schizophrenia patients versus that in the general population is even less than 29 percent and could be as low as one-third of this value.

We present a new hypothesis involving the platelet activating factor system in an effort to account for this negative association and review the suggestions of other investigators toward this end. Finally, we consider the glutamatergic system dysfunction hypothesis of schizophrenia and suggest a possible common pharmacological approach that may ameliorate some of the symptomatology of both schizophrenia and RA.

Key words: Schizophrenia, rheumatoid arthritis, platelet-activating factor system, glutamatergic dysfunction pharmacology.


A substantial body of evidence shows a strong negative association between schizophrenia and rheumatoid arthritis (RA), implying low comorbidity of these disorders. Fourteen epidemiological studies of the prevalence of RA in psychiatric populations were conducted between 1934 and 1985 (reviewed by Eaton et al. 1992). These include the following: Nissen and Spencer (1936); Gregg (1939); Ross et al. (1950); Trevathan and Tatum (1954); Pilkington (1956); Ehrenheil (1957); Rothermich and Philips (1963); Mellson et al. (1974); Osterberg (1978); Baldwin (1980); Mohamed et al. (1982); Ramsay et al. (1982); Krakowski et al. (1983); Allebeck et al. (1985). Twelve of the studies, involving several tens of thousands of subjects, reported a much smaller than expected frequency of RA in populations of schizophrenia patients while two studies covering 665 schizophrenia subjects reported frequencies of RA in the expected range (Ramsay et al. 1982; Krakowski et al. 1983). Five of the twelve studies finding low comorbidity (Nissen and Spencer 1936; Gregg 1939; Trevathan and Tatum 1954; Ehrenheil 1957; Rothermich and Philips 1963) did not stratify their populations according to psychiatric diagnoses but included the schizophrenia patients with other psychotic patients in some studies and with total inpatients in other studies. In the nine studies that did stratify...
their subjects by psychiatric diagnoses (Ross et al. 1950; Pilkington 1956; Mellspot et al. 1974; Osterberg 1978; Baldwin 1980; Mohamed et al. 1982; Ramsay et al. 1982; Krakowski et al. 1983; Allebeck et al. 1985), the median frequency of comorbid schizophrenia and RA was 0.047 percent and the mean frequency was 0.77 percent, both well below the expected level of 1 percent (Spector 1990). Eaton et al. (1992) have suggested focusing on the median frequency of 0.047 percent instead of the mean of 0.77 percent, because the outlier studies of Ramsay et al. (1982) and Krakowski et al. (1983), which contained 665 patients, found frequencies that are higher than often reported for the general population and had no control groups. This article presents two additional data sets and a meta-analysis evaluating the association of RA and schizophrenia, furnishing an estimate of the relative risk of RA in schizophrenia patients versus that in other psychiatric patients and versus that in the general population. We review the previous studies and discuss an additional hypothesis that might account for the negative association.

Methods

Current Studies. Canadian hospital separation statistics for April 1, 1984 through March 31, 1988, covering schizophrenia patients, RA patients, and individuals afflicted with both disorders (ages ≥ 18) were obtained for a 4-year period on an annual basis through record linkage. ICD-9 diagnostic criteria were used for both diseases (World Health Organization 1978).

The raw Canadian hospital separation data give the following total separation counts for 1984 to 1988 (Statistics Canada, Health Section, Cyril Nair, 1997, personal communication): 93,278 schizophrenia patients; 101 comorbid schizophrenia patients with rheumatoid arthritis; 1,137,363 psychiatric patients; 4,743 comorbid psychiatric patients with rheumatoid arthritis. These gross numbers must be reduced to distinct individual patients to allow inclusion of this data set in the overall meta-analysis. In accordance with the mathematical techniques described in the appendix, we obtained 27,630 as the estimated number of distinct individuals represented by the 93,278 recorded hospital separations.

Under the Canadian national health care system, each medical facility forwards its patient data to the Health Statistics Section of Statistics Canada, where the information is recorded on computer discs. The quality of the medical care, research, and teaching in Canada are on a par with that of the United States and Western Europe, so it is highly unlikely that the prominent symptoms of RA would be overlooked in the modern hospital setting (McGeer et al. 1990).

On July 24, 1993, we visited the Pilgrim State Psychiatric Center in West Brentwood, New York, and found that of an inpatient population of 1,984 subjects, 1,323 individuals were diagnosed with schizophrenia according to DSM-III-R criteria (American Psychiatric Association 1987). One patient with schizophrenia also had RA (American Rheumatism Association diagnostic criteria) as established by clinical, radiographic, and serological means. This yields a schizophrenia to RA comorbidity frequency of 0.076 percent. Of the 661 nonschizophrenia inpatients, 2 had comorbid RA, a frequency of 0.30 percent. The patients in this study were diagnosed by and regularly examined by psychiatrists and nurses, and the results were recorded on charts and computers. Patients with clinical evidence of arthropathy underwent examination at an arthritis and rheumatism clinic. We reviewed the computerized diagnostic data on the overall hospital statistics of patients' medical records and various patient charts.

Previous Studies. The earlier studies of this subject reported results similar to ours. Nissen and Spencer (1936) reported a zero frequency of arthritis of all types in a psychiatric hospital with 2,200 inpatients afflicted with various mental disorders.

Gregg (1939) queried nine Massachusetts hospital superintendents about cases of seriously arthritic patients and was informed that of 10,993 patients with psychosis over age 40, only 18 subjects had comorbid severe arthritis, a frequency of 0.164 percent. This was only 2 percent of the frequency of rheumatism in the general population of that State. Importantly, Gregg also found that in 3,000 autopsies of subjects with psychosis, the state pathologist observed no arthritic joints. Finally, Gregg found no cases of seriously afflicted arthritis patients in a group of 1,962 inpatients of a State school for the “feeble minded.”

Ross and coworkers (1950) stratified their study group by psychiatric diagnosis and considered RA specifically. Neither the diagnostic criteria for schizophrenia or for RA were furnished. Employing medical records, they found no comorbid RA and schizophrenia in 800 inpatients and 4 cases of RA in 808 nonschizophrenia psychiatric subjects, a frequency of 0.49 percent. Trevathan and Tatum (1954) studied discharge records of 9,000 patients from a neuropsychiatric hospital and found only 1 case of comorbid psychosis and RA, a frequency of 0.011 percent.

Pilkington (1956) reported on physical examinations of 318 women over 40 years of age with various psychiatric diagnoses; 130 of them had schizophrenia, and only
1 had comorbid RA (frequency 0.77%). Of the other 188 patients, 5 had comorbid RA (frequency 2.7%). Ehrentheil (1957) studied the medical records of 4,500 inpatients in a neuropsychiatric hospital for a diagnosis of RA. The group was not stratified by psychiatric diagnosis. Only one case of comorbid RA was encountered, a frequency of 0.22 percent.

Rothermich and Philips (1963) studied 20,494 psychiatric inpatients for RA using ARA diagnostic criteria. Suspected subjects were tested with the standard diagnostic techniques. In the group of 16,000 psychotic subjects, the RA frequency was 0.08 percent. The RA frequency among the other 4,494 psychiatric patients was 0.38 percent. These investigators also reported an RA frequency of 0.22 percent in a group of 4,040 prisoners and no patients with RA out of 1,391 patients in a hospital for the criminally insane.

Mellsop et al. (1974) examined 301 Australian women with schizophrenia, ages 40 to 65, for RA and found no cases. They also found a lower than expected rate of osteoarthritis in this group. Osterberg (1978) reviewed the discharge diagnoses of over 180,000 Swedish psychiatric inpatients for arthropathy. The frequency of RA was 0.047 percent in schizophrenia and 0.11 percent in other psychiatric diagnoses.

Baldwin (1980) studied clinical records of patients from two counties in England from an 8-year period. He found that of 2,314 schizophrenia patients, only 0.09 percent had comorbid RA. In all other psychiatric diagnoses, he found an RA comorbidity frequency of 0.43 percent. The comorbidity frequency of osteoarthritis in schizophrenia patients in comparison with other psychiatric patients was 0.22 percent versus 0.65 percent.

Mohamed et al. (1982) studied a Canadian inpatient group of 111 schizophrenia subjects and 51 psychiatric inpatients with other diagnoses. No RA was found in the former group, and three cases of probable RA were found in the latter (frequency 5.8%). They also found a negative association for osteoarthritis and mental disorders. Ramsay et al. (1982) did not find an unusually low prevalence of RA in a group of 354 Canadian and U.S. schizophrenia patients, ages 20 to 70. The RA comorbidity frequency was 3.4 percent.

Krakowski et al. (1983), proceeding in the same manner as Ramsay et al. (1982), found that among 311 Polish schizophrenia subjects, ages 20 to 70, the frequency of comorbid RA was 2.6 percent, within the expected range.

Allebeck et al. (1985) reviewed the records of all patients discharged from treatment facilities in Stockholm County, Sweden, during 1971 with diagnoses of schizophrenia, affective psychosis, and neurosis. They found records of 1,190 schizophrenia patients, 2 with comorbid RA (0.17% frequency); 621 patients with affective psychoses, 2 with comorbid RA (0.32% frequency); and 3,978 patients with neurosis, 17 with comorbid RA (0.43% frequency). Further details of the above 16 studies, including diagnostic criteria and a statistical summary in the form of a frequency analysis, are found in table 1.

While these studies provide strong evidence for an inverse relationship between schizophrenia and RA, several methodological problems should be pointed out. First, 8 of the 16 studies discussed have no control group (Nissen and Spencer 1936; Gregg 1939; Trevathan and Tatum 1954; Ehrentheil 1957; Rothermich and Philips 1963; Mellsop et al. 1974; Ramsay et al. 1982; Krakowski et al. 1983). The other eight studies stratified their patients by psychiatric diagnoses, and the nonschizophrenia groups were used as controls (Ross et al. 1950; Pilkington 1956; Osterberg 1978; Baldwin 1980; Mohamed et al. 1982; Allebeck et al. 1985; Oken and Schulzer, two studies).

Five of the 16 studies furnish no diagnostic criteria for either RA (Ross et al. 1950; Trevathan and Tatum 1954; Ehrentheil 1957) or arthropathy (Nissen and Spencer 1936; Gregg 1939). With respect to schizophrenia, diagnostic criteria are provided for only 8 of the 16 studies (Mellsop et al. 1974; Osterberg 1978; Baldwin 1980; Mohamed et al. 1982; Ramsay et al. 1982; Krakowski et al. 1983; Oken and Schulzer, two studies). In view of the recent narrowing of schizophrenia diagnostic criteria, some loss of comparability between the older population samples and the more recent ones has doubtless occurred.

It is possible that many cases of arthropathy in psychiatric inpatients may have been overlooked in the time period of the earlier studies. In 5 of the 14 studies reporting a negative association, the prevalence of comorbid psychiatric disease and RA is quite low (Nissen and Spencer 1936; Gregg 1939; Trevathan and Tatum 1954; Ehrentheil 1957; Rothermich and Philips 1963). In the eight studies that stratified their subjects by psychiatric diagnosis, the schizophrenia patients had the lowest rate of comorbid RA and the frequency of comorbidity of the other psychiatric diagnoses and RA was also considerably lower than expected (see table 1). Nine of the studies relied solely on medical records or unspecified screening for diagnoses of arthritis or RA.

Gender was not controlled in 14 of the 16 studies. This is important because the prevalence of RA is considerably higher in females than in males and because schizophrenia may have a different etiology in men than in women. Age should be controlled, as most initial schizophrenia presentations occur in the 15 to 34 age range, and RA generally begins between ages 25 and 55. Only 7 of the 16 studies specified age ranges (Gregg 1939; Pilkington 1956; Mellsop et al. 1974; Mohamed et al.
<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Sample</th>
<th>Other psychiatric diagnoses</th>
<th>Method of ascertainment for RA</th>
<th>Frequency of RA, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nissen and Spencer (1936)</td>
<td>Not reported</td>
<td>—</td>
<td>2,200 inpatients</td>
<td>Not reported</td>
<td>0.0</td>
</tr>
<tr>
<td>Gregg (1939)</td>
<td>Massachusetts</td>
<td>—</td>
<td>10,993 psychotic inpatients age &gt; 40 yrs</td>
<td>Questionnaire sent to hospital</td>
<td>0.16</td>
</tr>
<tr>
<td>Ross et al. (1950)</td>
<td>Quebec</td>
<td>800 inpatients</td>
<td>808 inpatients</td>
<td>Medical records, history, physiological and radiological exams</td>
<td>0.0 0.49</td>
</tr>
<tr>
<td>Trevathan and Tatum (1954)</td>
<td>Alabama</td>
<td>—</td>
<td>9,000 inpatients</td>
<td>Discharge diagnosis</td>
<td>0.011</td>
</tr>
<tr>
<td>Pilkington (1956)</td>
<td>England</td>
<td>130 female inpatients, age &gt; 40 yrs</td>
<td>188 female inpatients, age &gt; 40 yrs</td>
<td>History, physical, radiological and ESR ARA criteria</td>
<td>0.77 2.7</td>
</tr>
<tr>
<td>Ehrentheil (1957)</td>
<td>Massachusetts</td>
<td>—</td>
<td>4,500 inpatients</td>
<td>Medical records</td>
<td>— 0.22</td>
</tr>
<tr>
<td>Rothermich and Philips (1963)</td>
<td>Ohio</td>
<td>—</td>
<td>16,000 psychotic inpatients; 4,494 nonpsychotic inpatients</td>
<td>Unspecified screening; physical, radiological, and serological exams; ARA criteria</td>
<td>— 0.08 0.38</td>
</tr>
<tr>
<td>Mellsop et al. (1974)</td>
<td>Australia</td>
<td>301 female inpatients, ages 40–65</td>
<td>— —</td>
<td>History; physical, radiological and, serological exams; ARA criteria</td>
<td>0.0 7.72</td>
</tr>
<tr>
<td>Osterberg (1978)</td>
<td>Sweden</td>
<td>40,426 inpatients</td>
<td>142,406 inpatients</td>
<td>Case records, discharge diagnoses, ARA criteria</td>
<td>0.047 0.11</td>
</tr>
<tr>
<td>Baldwin (1980)</td>
<td>England</td>
<td>2,314 inpatients</td>
<td>5,404 inpatients</td>
<td>Oxford Record Linkage Study, ICD–8 revision criteria</td>
<td>0.09 0.43</td>
</tr>
<tr>
<td>Mohamed et al. (1982)</td>
<td>Ontario</td>
<td>111 inpatients</td>
<td>51 inpatients</td>
<td>Structured diagnostic interview, serological and radiological exams, ARA criteria</td>
<td>0.0 5.8</td>
</tr>
<tr>
<td>Ramsay et al. (1982)</td>
<td>Toronto and New York</td>
<td>354, ages 20–70</td>
<td>— —</td>
<td>History, unspecified lab tests, radiological exam</td>
<td>3.4 —</td>
</tr>
<tr>
<td>Krakowski et al. (1983)</td>
<td>Poland</td>
<td>311, ages 20–70</td>
<td>— —</td>
<td>History, unspecified lab tests, radiological exam</td>
<td>2.6 —</td>
</tr>
<tr>
<td>Allebeck et al. (1985)</td>
<td>Stockholm County</td>
<td>1,190 inpatients</td>
<td>621 affective psychosis; 3,978 neurosis; 10,152 medical</td>
<td>Stockholm Record Linkage ICD Swedish version</td>
<td>0.17 0.32 0.43 0.43</td>
</tr>
</tbody>
</table>
Social class should be controlled because schizophrenia is more prevalent in the lower class (Eaton 1985) and because lifestyles connected to social class may be related to the etiology of arthritides, as pointed out by Eaton et al. (1992). Neuroleptic exposure will be considered later.

Despite the faulty methodology of several of these 16 studies, the inverse relationship of schizophrenia and RA prevalence is one of the strongest phenomena in the literature of schizophrenia epidemiology.

### Meta-analysis

Meta-analytic techniques can be used to combine individual estimates of effects or associations from independent studies into a single, overall estimate with considerably greater precision. We wish to evaluate the association between schizophrenia and RA by synthesizing information derived from nine independent observational studies and data sets, each providing an estimate of the relative risk of rheumatoid arthritis in schizophrenia patients versus that in other psychiatric patients. The odds ratio (OR) is the best choice for measuring this association (Fleiss 1981; Cooper and Hedges 1994). The OR offers a close approximation to the relative risk; it is a stable quantity; and it is estimable from data collected according to many different study designs. Finally, the OR is widely used in combining measures of association from independent studies meta-analytically because of the optimal statistical properties associated with its logarithm (Cooper and Hedges 1994).

We include in our analysis 7 of the 14 studies reviewed in table 1 of Eaton et al. (1992, p. 182) that contain sufficient data for this purpose. These are the studies by Ross et al. (1950), Pilkington (1956), Melissop et al. (1974), Osterberg (1978), Baldwin (1980), Mohamed et al. (1982), and Allebeck et al. (1985). In addition, we also analyze results from 4 consecutive years of Canadian hospital separation data (Statistics Canada Health Section, Cyril Nair, 1997, personal communication) and Pilgrim hospital data (Medical Records Dept., 1993, personal communication). A modified and adapted portion of Eaton's table 1 (1992, p. 182) is reproduced in our table 1. The data used in our meta-analysis are presented in table 2.

### Table 1. Studies reporting frequencies of rheumatoid arthritis in psychiatric populations—Continued

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Method of ascertainment for RA</th>
<th>Other psychiatric diagnoses</th>
<th>Other psychiatric patients</th>
<th>Frequency of RA, %</th>
<th>Social Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oken and Schulzer</td>
<td>Canada</td>
<td>ICD-9 criteria, medical records</td>
<td>202,342 patients</td>
<td>661 patients</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>Oken and Schulzer</td>
<td>New York</td>
<td>ARA criteria, physical exam</td>
<td>1,323 patients</td>
<td>661 patients</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Summary</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0-3.4</td>
<td></td>
</tr>
<tr>
<td>Eaton et al. (1992)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0-7.7</td>
<td></td>
</tr>
</tbody>
</table>

Note—Unless otherwise indicated, patient populations consist of males and females. — = subjects with schizophrenia were not reported separately from other psychiatric groups; ICD = International Classification of Diseases. The table is modified and adapted from Eaton et al.'s (1982) estimate of reference group (medical inpatients). 1982; Ramsay et al. 1982; Krakowski et al. 1983; Oken and Schulzer 1999 (Canadian study). Social class should be controlled because schizophrenia is more prevalent in the lower class (Eaton 1985) and because lifestyles connected to social class may be related to the etiology of arthritides, as pointed out by Eaton et al. (1992). Neuroleptic exposure will be considered later.

Despite the faulty methodology of several of these 16 studies, the inverse relationship of schizophrenia and RA prevalence is one of the strongest phenomena in the literature of schizophrenia epidemiology.
Table 2. Studies reporting the sample sizes, frequencies of RA, ORs, and corresponding 95% CIs and p values in schizophrenia and other psychiatric populations

<table>
<thead>
<tr>
<th>Data Source</th>
<th>Sample Size</th>
<th>Schizophrenia</th>
<th>Other psychiatric diagnoses</th>
<th>RA frequency, n (%)</th>
<th>OR</th>
<th>CI</th>
<th>p (2-tail)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ross et al. (1950)</td>
<td>800</td>
<td>808</td>
<td></td>
<td>0</td>
<td>4 (0.49)</td>
<td>0.11</td>
<td>0.006–2.08</td>
</tr>
<tr>
<td>Pilkington (1956)</td>
<td>130</td>
<td>188</td>
<td></td>
<td>1 (0.77)</td>
<td>5 (2.66)</td>
<td>0.28</td>
<td>0.03–2.46</td>
</tr>
<tr>
<td>Mellsop et al. (1974)</td>
<td>301</td>
<td>3,157</td>
<td></td>
<td>0</td>
<td>234 (7.41)</td>
<td>0.02</td>
<td>0.001–0.33</td>
</tr>
<tr>
<td>Osterberg (1978)</td>
<td>40,426</td>
<td>142,406</td>
<td></td>
<td>19 (0.047)</td>
<td>149 (0.10)</td>
<td>0.45</td>
<td>0.28–0.72</td>
</tr>
<tr>
<td>Baldwin (1980)</td>
<td>2,314</td>
<td>5,404</td>
<td></td>
<td>2 (0.09)</td>
<td>23 (0.43)</td>
<td>0.20</td>
<td>0.05–0.86</td>
</tr>
<tr>
<td>Mohamed et al. (1982)</td>
<td>111</td>
<td>51</td>
<td></td>
<td>0</td>
<td>3 (5.88)</td>
<td>0.06</td>
<td>0.003–1.23</td>
</tr>
<tr>
<td>Allebeck et al. (1985)</td>
<td>1,190</td>
<td>4,599</td>
<td></td>
<td>2 (0.17)</td>
<td>19 (0.41)</td>
<td>0.41</td>
<td>0.09–1.74</td>
</tr>
<tr>
<td>Oken and Schulzer (1999)</td>
<td>27,630</td>
<td>202,342</td>
<td></td>
<td>30 (0.11)</td>
<td>900 (0.44)</td>
<td>0.24</td>
<td>0.17–0.35</td>
</tr>
<tr>
<td>Canadian Separations (1984–88)</td>
<td>1,323</td>
<td>661</td>
<td></td>
<td>1 (0.08)</td>
<td>2 (0.30)</td>
<td>0.25</td>
<td>0.02–2.75</td>
</tr>
</tbody>
</table>

Note.—CI = confidence interval; OR = odds ratio; RA = rheumatoid arthritis.
1 Counts derived from Mellsop et al. (1974), Table 2.
3 Counts adjusted for deaths and readmissions, see Methods.

percent confidence interval contains the value 1, no statistically significant association between schizophrenia and rheumatoid arthritis can be detected in that study (at a 2-tail significance level of 5%).

Odds ratios are combined across studies by using appropriate weights, with the ORs derived from larger studies being more heavily weighted than those from smaller ones. Technically, the logarithm of the OR for each study is weighted by the inverse of its estimated variance (i.e., by the reciprocal of the square of its standard error). Thus, the more precisely it is measured (e.g., in large sample studies), the smaller its variance is likely to be, and therefore the larger the corresponding weight and the contribution to the final combined estimate. Along with the combined OR estimate, an overall 95 percent confidence interval for the combined OR is also calculated. This interval is considerably tighter than the intervals estimated for the individual component studies, reflecting the gain in precision of the combined estimate. The statistical significance of the combined OR can also be calculated. Thus, an OR significantly less than 1 indicates a significant negative association between the factors studied.

To ensure that the independent studies included are in fact reasonably comparable; that is, that they are sufficiently similar in attempting to estimate the same population parameter in relation to the common association sought, a chi-square test of homogeneity is carried out. Generally, when this test yields a nonsignificant p value (e.g., p > 0.10), one may conclude that the results from the individual component studies are reasonably consistent with a common association parameter, and thus a combined estimate of the common OR may be meaningfully calculated.

Another concern in research synthesis is the potential effect of "publication bias": the tendency to publish selectively studies with significant results, and to omit from publication, and file away "null studies," that is, studies demonstrating lack of association between the factors studied. The extent of the possible biasing effect of such potential omissions on the pooled estimate of the association derived from published studies may be evaluated by the "file-drawer method" (Rosenthal 1979; Hedges and Olkin 1985; Cooper and Hedges 1994). This method determines the number of unpublished null studies that would have been needed to offset the significance of the meta-analytically derived estimate. If this number is large enough that it is unlikely that so many unpublished studies exist, one may safely conclude that the significance of the observed association is unchallengeable (Cooper and Hedges 1994).
Results

Using the statistical comorbidity frequency data of the 16 studies described previously, we adjusted and enlarged Eaton et al.'s table 1 (1992, p. 182). We found the median schizophrenia and RA comorbidity frequency to be 0.09 percent and that of the other psychiatric diagnoses and RA to be 0.32 percent. The mean schizophrenia and RA comorbidity is computed to be 0.66 percent, and that for the other psychiatric patients group is 0.79 percent, all frequencies well below that of definite RA in the general population of 1 percent (Spector 1990).

A test of homogeneity of all nine studies gave a $p$ value of 0.3039, ensuring that the component studies are reasonably homogeneous for the purposes of synthesis.

Figure 1 shows the ORs calculated cumulatively from the nine independent studies as they are sequentially and chronologically combined. Each cumulative estimate is enclosed within a corresponding 95 percent confidence interval on a logarithmic scale. The final OR combined from all nine studies is 0.2883 ($p < 0.0001$), indicating that the estimated rate of RA among schizophrenia patients is only 29 percent of the corresponding rate in other psychiatric patients. The 95 percent confidence interval for the combined OR extends from 0.2199 to 0.3779, that is, from 22 percent to 38 percent, giving a tighter interval than any of the individual confidence intervals shown in table 1, indicating the increased precision of the estimate due to the pooling of the individual results.

The file-drawer method was applied to the combined OR estimate to address the issue of publication bias: 124 unpublished null studies would have been required to offset the significance of the pooled OR derived above.

Our estimated OR indicates that RA occurs among schizophrenia patients at a rate of only 29 percent of the
corresponding prevalence in other psychiatric patients. Our analysis is based entirely on comparisons among hospitalized patients. Thus any possible confounding effects that hospitalization may have on diminishing the rate of development of RA (see e.g., Eaton et al. 1992) have been controlled for in our estimate.

The prevalence of definite RA in the general population is reported to be 1 percent worldwide (Spector 1990). The median estimate of the prevalence of RA in nonschizophrenia psychiatric patients, derived from Eaton’s enlarged and adjusted table (table 1), is 0.32 percent. It follows, a fortiori, that the relative risk of rheumatoid arthritis in schizophrenia patients versus the general population is even lower than 0.2883 and could well be as low as one-third of this value.

Discussion

In an attempt to account for the intriguing negative association between these disorders, we add a new hypothesis to the literature. Our candidate molecular system comprises the platelet-activating factor (PAF; 1-O-alkyl-2-acetyl-sn-glycero-3-phosphocholine), its phospholipase A₂-inactivating enzyme cytosolic PAF-acetylhydrolase, the PAF receptor, their proteinaceous biosynthetic precursors (including, but not limited to, lysophospholipase [Nakagawa et al. 1992]), 2-lyso-PAF:acetyl-CoA acetyltransferase (Villani et al. 1991), diacylglycerol lipase (Blank et al. 1990), choline phosphotransferase (Blank et al. 1988), and 1-alkyl-2-lyso-sn-glycero-3-phosphocholine:acetyl-CoA acetyltransferase (Lee et al. 1984). Other enzymes relevant to this area of investigation have been reviewed by Snyder (1988).

PAF and PAF-acetylhydrolase appear to be important in the formation of the brain cortex during differentiation and development (Hattori et al. 1994) and therefore in neuronal migration and synaptic connectivity (Bazan 1995; Akbarian et al. 1996; Ho et al. 1997). Thus, dysfunction of the PAF, PAF-acetylhydrolase system, for example through insufficient bioavailability of PAF, could disrupt both neuronal migration and synaptic connectivity, a major neurodevelopmental insult. This in turn could set the stage for schizophrenia at a later date (e.g., LaFosse and Mednick 1991; Nowakowski 1991; Bullmore et al. 1998; Sachdev 1998 and references therein) and be protective against future RA. PAF is a potent proinflammatory phospholipid that activates cells involved in inflammation (e.g., Ho et al. 1997). It has been found in synovial fluids from patients with inflammatory joint diseases (Pettipher and Blake 1995) and may have detrimental effects on cartilage (Howat et al. 1990). All the above phenomena are important in RA.

Several of the mechanisms by which PAF could affect neuronal migration have been discussed by Albrecht et al. (1996) and Sapir et al. (1997). By way of precedent and analogy, the devastating Miller-Dieker lissencephaly syndrome, a neuronal migration disorder characterized by a virtually smooth cortex and absence of gyri and sulci (see Hattori et al. 1994; Bazan 1995); results from a hemideletion of the gene LIS-1, which codes for a subunit of a brain PAF-acetylhydrolase (Clark et al. 1997). These considerations support our recommending the study of the genes encoding the proteins listed above for polymorphic variants as possible schizophrenia susceptibility genes. Bell et al. (1997) studied the plasma PAF-acetylhydrolase gene in a group of schizophrenia patients and controls and found no association of this gene with schizophrenia. But the cytosolic brain PAF-acetylhydrolase gene and the genes encoding the associated proteins previously noted (especially the PAF receptor, mapped to chromosome 1) were not studied. These would likely be more relevant candidates for schizophrenia susceptibility genes, as plasma-PAF and cytosolic-PAF-acetylhydrolases have quite different amino acid sequences and structures (Tjoelker et al. 1995).

Some pharmacological considerations follow. Perhaps a portion of the negative association of schizophrenia and RA is attributable to medication. Six of the 16 studies of this subject were conducted prior to or early in the neuroleptic era (Nissen and Spencer 1936; Gregg 1939; Ross et al. 1950; Trevathan and Tatum 1954; Pilkington 1956; Ehrentheil 1957). The timing of these studies has led to the assumption that the negative association is unrelated to the effects of medications, an assumption that is perhaps unjustified. We consider the glutamatergic system dysfunction hypothesis of schizophrenia. Evidence from numerous studies has recently implicated the glutamatergic system in the pathophysiology of schizophrenia (Deutsch et al. 1989; Carlsson and Carlsson 1990; Wachtel and Turski 1990; Ulas and Cotman 1993; Olney and Farber 1995; Bartha et al. 1997; Eastwood et al. 1997; Goff and Wine 1997). Several of these authors suggested that glutamate- and/or glutamate receptor-mediated neurotoxicity may underlie schizophrenia and schizophreniform disorders. Grilli and colleagues (1996) have recently reported that plasma concentrations of aspirin and sodium salicylate sufficient to treat chronic inflammatory disorders such as RA provided protection against glutamate-induced neurotoxicity in rat primary neuronal culture and hippocampal slices. The mechanism of action appears to be the inhibition of glutamate-mediated induction of the nuclear transcription factor NF-κB. Work by Ghosh and Kopp (1995) suggests that the corticosteroids, also used in RA therapy, might well be effective via a similar mechanism. To the extent
that the glutamatergic system dysfunction hypothesis of schizophrenia is valid, then aspirin, salicylate, corticosteroids, and possibly other antiinflammatory agents or inhibitors of nuclear transcription factors may be useful agents against both schizophrenia and RA. Salicylate would be preferable to aspirin, as it crosses the blood-brain barrier much more efficiently. While the suggestion of the possible utility of such agents in schizophrenia therapy may appear radical, it should be pointed out that there is considerable evidence that many antipsychotic drugs are immunomodulators (e.g., Ferguson et al. 1978; Lovett et al. 1978; Zarrabi et al. 1979; Gowdy 1980; Jones-Brando et al. 1997) and, thus, their use might reduce the risk for RA, which is widely regarded as an autoimmune disease. Further, the structure and pharmacological actions of the atypical neuroleptic clozapine are consistent with its being a prostaglandin E analog. The E-prostaglandins are stimulators of cAMP generation (Abramson et al. 1985). cAMP inhibits phospholipase A$_2$ and aspirin and salicylate stimulate cAMP generation. Thus, aspirin and salicylate application would inhibit phospholipase A$_2$ activity and, under the membrane phospholipid dysfunction hypothesis of schizophrenia (Horrobin 1998), might result in clinical improvement in schizophrenia. Supporting this, a recent case report (Puri and Steiner 1998) describes sustained remission of positive and negative symptoms of schizophrenia following treatment with eicosapentaenoic acid, a phospholipase A$_2$ inhibitor and a precursor of docosahexaenoic acid, an essential fatty acid (EFA) found to be deficient in brain membranes of schizophrenic patients (Horrobin 1998). Studies by Mellor et al. (1996) and Peet et al. (1996, 1997) also support the membrane hypothesis of schizophrenia (Horrobin 1998). Gattaz et al. (1990, 1996) and others have found elevated phospholipase A$_2$ levels and activity in schizophrenia patients, presumably associated with neuronal membrane phospholipid degradation. That aspirin and salicylate inhibit phospholipase A$_2$ activity (as do various neuroleptics, including clozapine) further supports our suggestion of the possible utility of these agents against schizophrenia. Finally, Canadian hospital separation data (Statistics Canada, Health Section, Cyril Nair, 1997, personal communication) (data not shown) demonstrate a very low prevalence (0.11%) of schizophrenia in RA patients. These RA patients were treated with antiinflammatory drugs, some of which are nuclear transcription factor inhibitors as well.

Several suggestions from the literature have been offered to account for the negative association of schizophrenia and RA. It has been suggested, for example, that neuronal membrane phospholipid abnormalities in schizophrenia might be responsible for the low occurrence of RA. Horrobin (1998) and colleagues have evolved a membrane hypothesis of schizophrenia in a series of 18 papers beginning in 1977 (Horrobin et al. 1995, p. 612, references 27-43 and Horrobin 1998). Building upon this foundation, Horrobin (1998) recently pointed out that in schizophrenia there is evidence for an increased rate of loss of the EFAs arachidonic acid and docosahexaenoic acid from neuronal membranes, possibly as a result of elevated levels of a cytoplasmic phospholipase A$_2$. These EFAs are metabolic precursors of prostaglandins and leukotrienes by the cyclooxygenase and lipoxygenase enzyme-related systems. Inasmuch as RA is associated with excessive prostaglandin and leukotriene production (McMillan et al. 1995), a schizophrenia-associated membrane deficiency of arachidonic and docosahexaenoic acids suggests a concomitant prostaglandin and leukotriene deficiency, which would be protective against RA.

Other researchers have looked at the genetic association of schizophrenia and the human leukocyte antigen (HLA) DRB1 gene locus on chromosome 6p21.3. Wright et al. (1996a) have recently investigated the HLA DRB1*04 gene in schizophrenia patients, as it is positively associated with RA. They conducted a study of 94 unrelated schizophrenia patients and 92 mothers of children with schizophrenia who were unrelated to either the patients or each other. They found that the frequency of HLA DRB1*04 alleles was significantly lower in both the schizophrenia patients and mothers than in healthy controls. Wright et al. (1996b) had previously reported an excess of autoimmune diseases in the first-degree relatives of schizophrenia patients. They suggested that this excess may represent a tendency for autoimmune diseases in families having a member with schizophrenia and that the presence of HLA DRB1*04 alleles in some members of such a family predisposes to RA, while their absence in others permits schizophrenia to be expressed.

Other histocompatibility factors have also been studied as possible contributors to the low schizophrenia-RA association. Gattaz et al. (1980, 1981) found no schizophrenia in arthritic patients with HLA-B27 and no arthritis in schizophrenia patients with HLA-B27. He postulated that the HLA-B27 antigen is a protective factor in both schizophrenia and RA.

Eaton et al. (1992) suggested that institutionalization per se might be protective against RA because of the low exposure to joint trauma, a risk factor for RA. While this may indeed contribute to the negative association, it cannot account for the fact that we found a schizophrenia-RA comorbidity of only 29 percent of that in other psychiatric patients. Our analysis was based entirely on comparisons among hospitalized patients, so the institutionalization effect was controlled for.

Prostaglandin abnormalities have been suggested to play a role in the negative association (Vinogradov et al.
1. Adjustment for schizophrenia patients.

Let \( x \) be the average number of discharges for a schizophrenia patient in 4 years, and let \( y \) be the mortality rate of schizophrenia patients over a period of 4 years. The total number of separations \( (N) \) of schizophrenia patients in 4 years consists of a number of live separations \( (L) \) and a certain number \( (M) \) of separations due to deaths. Thus,

\[
N = L + M. \tag{1}
\]

Note that \( L \) contains some separations that terminated in some of the \( M \) deaths, as well as a number of separations experienced by \( z \) distinct live individuals. Thus, the total number of distinct individuals, live and dead, that accounted for the \( N \) separations, is given by \( z + M \). Of these individuals, a proportion \( y \) will have died in the 4-year interval, so that

\[
M = y (z + M). \tag{2}
\]

Now each of the \( z \) live individuals is represented, on average, \( x \) times in the total number of live separations \( L \). Assuming that the \( M \) individuals who died followed a uniform distribution of deaths over the 4-year interval, each of these individuals is represented, on average \( x/2 \) times in \( L \), before being represented once more in the count \( M \) of separations due to deaths. Thus,

\[
L = x z + x/2 M. \tag{3}
\]

Equations (1), (2), and (3) can be readily solved simultaneously. The solution is given by \( M = 2yN / (2x + 2y - xy) \) and by \( Z = M (1/y - 1) \).

To estimate \( x \), the survival function in figure 1 ("real world") of Weiden and Olifson (1995) was used. Assuming (approximately) that this survival function follows an exponential distribution, describing the proportion of schizophrenia patients surviving to a given period of time without relapse, and noting that only some 18 percent of patients do not relapse within 24 months, the mean relapse time per patient can be estimated to be approximately 14 months, yielding an estimated average of 3.43 discharges in a 4-year period.

To estimate \( y \), Brown (1997) gives a crude mortality rate for schizophrenia patients of 189/10,000 per year, resulting in a 4-year value for \( y \) of 0.0756. Substituting these estimates for \( x \) and \( y \) in equations (1), (2), and (3) above, with \( N = 93,278 \), one obtains \( M = 2,089; z = 25,541 \); and \( Z + M = 27,630 \) as the estimated number of distinct individuals represented by the 93,278 separations recorded.

An analogous adjustment can be applied to the 101 comorbid separations (schizophrenia patients with...
rheumatoid arthritis), resulting in an estimate of 30 distinct comorbid individuals.

2. Adjustment for psychiatric patients.

Since these patients form a very mixed group of psychiatric diagnoses, only a simple overall adjustment to the separation counts was attempted. In Johansen et al. (1996, p. 28, figure 1) it is reported that the mean number of discharges per patient per year in the category of “mental disorders” in Canadian hospitals was 1.29. Thus, in a 4-year period, an average of 5.16 discharges would be expected. The separation figures for total psychiatric (nonschizophrenia) patients and for comorbid psychiatric (nonschizophrenia) patients with rheumatoid arthritis were adjusted downward by this factor.

It should be noted that the above adjustments to the separation counts do not affect the calculation of the odds ratio (OR) itself. They do affect the estimation of the corresponding standard error, however, and therefore reduce slightly the weight assigned to this OR in the calculation of the meta-analytically combined overall OR.

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