Mortality in Schizophrenia: Clinical and Serological Predictors

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Persons with schizophrenia have a reduced life expectancy largely due to death from natural causes. Factors that have been previously associated with excess mortality include cigarette smoking and antipsychotic medication. The role of other environmental factors such as exposure to infectious agents has been the subject of only limited investigation. We prospectively assessed a cohort of persons with schizophrenia with a clinical evaluation and a blood sample from which antibodies to human herpes viruses and Toxoplasma gondii were measured. Mortality was determined with data from the National Death Index following a period of up to 11 years. We examined the role of demographic, serological, and clinical factors on mortality. A total of 25 (5%) of 517 persons died of natural causes. The standardized mortality ratio was 2.80 (95% CI 0.89, 6.38). After adjusting for age and gender, mortality from natural causes was predicted in separate models by cigarette smoking (relative risk [RR] = 4.66, \( P = .0029 \)); lower cognitive score (RR = 0.96, \( P = .013 \)); level of antibodies to Epstein–Barr virus (RR = 1.22, \( P = .0041 \)) and to Herpes Simplex virus type 1 (RR = 1.19, \( P = .030 \)); immunologic disease (RR = 3.14, \( P = .044 \)); and genitourinary disease (RR = 2.70; \( P = .035 \)). Because cigarette smoking confers an almost 5-fold risk of mortality, smoking cessation is an urgent priority. Having an elevated level of antibodies to Epstein–Barr virus and to Herpes Simplex virus type 1 are also significant predictors of death from natural causes.

Key words: premature death/cigarette smoking/Epstein–Barr virus

Introduction

Persons with schizophrenia have a life expectancy that is 15–25 years shorter than those in the general population and have a 2- to 3-fold greater mortality rate.1–5 Despite extremely high rates of suicide in schizophrenia relative to the general population, most of the excess mortality is due to death from natural causes.2,3,5,6 Circulatory and respiratory diseases contribute most to the excess mortality.2,6,7

The underlying reasons for premature death from natural causes in this population are not known with certainty. Persons with schizophrenia have elevations in 6 leading modifiable risk factors for mortality: smoking, hypertension, raised blood levels of glucose, physical inactivity, obesity, and dyslipidemia.5,8 In addition, mortality in schizophrenia may be increased by drug and alcohol abuse, found to be disproportionately high in this population, as well as by suboptimal medical treatment and the overall social disadvantages experienced by many persons with the disorder.5,9,10 Adverse effects of antipsychotic medications have also been identified as a cause of excess mortality in some but not other studies.5,6,8,11

Many of the risk factors for excess mortality in schizophrenia are interrelated, and their independent role is difficult to establish. However, cigarette smoking has been identified as an important independent predictor of mortality. In a study of persons with schizophrenia and related disorders admitted to state of Maryland hospitals between 1994 and 2000, Kelly and colleagues9 found that cigarette smoking contributed to an increased risk of death especially in persons aged 35–54 (hazards ratio [HR] = 2.06, \( P < .007 \)); in this age group, the odds of cardiac death were increased by 12-fold in smokers relative to nonsmokers (HR = 12.4, \( P < .0005 \)). Smoking has also been found to be predictive of mortality in cohort studies of schizophrenia when adjusting for other relevant variables.6,8 In a study consistent with findings of increased mortality, we previously reported that persons with serious mental illness who smoked cigarettes had a significantly higher 10-year Framingham cardiovascular disease risk score than nonsmokers (13.2% vs 7.4%) and were more likely to have abnormalities in blood pressure and lipid markers.12

Recent studies have shown that some individuals with schizophrenia have increased rates of exposure to some microbial agents and increased levels of immune markers.
in the blood and in the central nervous system.\textsuperscript{13-15} However, the association between exposure to specific infectious agents and premature death in schizophrenia has been the topic of only limited investigation. In an earlier version of the schizophrenia cohort described in this study, we found an association between serological evidence of \textit{Toxoplasma gondii} and risk of dying of natural causes (HR = 4.7, \( P = .02 \)).\textsuperscript{16} The role of other infectious agents in schizophrenia mortality has not been previously investigated.

The purpose of the current investigation was to identify the determinants of mortality in a cohort of individuals with schizophrenia assessed at baseline with an in-person clinical evaluation and a blood sample from which antibodies to infectious agents were measured. Mortality and causes of mortality were determined with data from the National Death Index (NDI) following a period of up to 11 years. We examined the role of demographic and clinical factors including cigarette smoking, exposure to infectious agents, and other potentially modifiable risk factors for mortality.

\section*{Methods}

\subsection*{Participants}

Participants were individuals with schizophrenia who were enrolled by the Stanley Research Program at Sheppard Pratt in Baltimore, Maryland between February 1, 1999 and December 31, 2009 in a study directed at defining the association between antibodies to infectious agents and schizophrenia. At the time of their enrollment in the study, all participants were receiving services at treatment programs affiliated with Sheppard Pratt or at other psychiatric programs in central Maryland. All participants met the following additional inclusion criteria: (1) diagnosis of schizophrenia or schizoaffective disorder made by a board-certified psychiatrist based on the Structured Clinical Interview for Diagnosis for Axis I disorders\textsuperscript{17}; and (2) age 18–65. Exclusion criteria were (1) primary diagnosis of substance abuse or dependence, (2) any history of intravenous substance abuse, (3) mental retardation, (4) clinically significant medical disorder that would affect cognitive performance such as history of encephalitis or head trauma, (4) immunodeficiency condition such as HIV or cancer chemotherapy, and (5) onset of schizophrenia within the previous 2 years.

All participants provided written informed consent, and the study was approved by the Institutional Review Boards of Sheppard Pratt and Johns Hopkins School of Medicine following established guidelines.

\subsection*{Measures}

All participants were interviewed at study enrollment. Information was obtained about demographic variables including age, race, and education. Information about the participant’s age at the onset of the psychiatric disorder was obtained from self-report and medical records. Participants were also asked about the presence of co-occurring medical conditions with a review of systems and about their current smoking status. Participants were categorized as to whether or not they had a history of substance abuse, apart from nicotine, based on their response to interview questions about the use of alcohol and drugs and on the medical record. Current medications were determined from participant self-report and medical records. Participants were interviewed and rated on the Positive and Negative Syndrome Scale (PANSS)\textsuperscript{18} to determine psychiatric symptom severity. Cognitive functioning was assessed with the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS),\textsuperscript{19} a brief cognitive battery that was individually administered.

Each participant provided a blood sample at the time of the study visit. Blood samples were tested by enzyme immunoassay tests for immunoglobulin G class antibodies to the human herpes viruses (Herpes Simplex virus type 1 [HSV-1], Cytomegalovirus [CMV], Epstein–Barr virus [EBV]) and to the protozoan \textit{T. gondii}. These infectious agents were selected for inclusion because they are capable of establishing latency in the central nervous system and have been studied as to their possible role in the etiology of schizophrenia and its associated symptoms. The antibody level was measured by immunoassay tests by means of the reaction of test serum to solid-phase antigen; the amount of antibody in each sample was expressed in terms of the ratio of optical density of the test sample to the standard sample using previously described methods.\textsuperscript{20}

\subsection*{Mortality Status at Follow-up}

In order to determine the individuals in the schizophrenia sample who had died since the time of the original assessment, follow-up of the patients in the schizophrenia sample was done through the NDI. This index provided the date and cause of death for decedents. Data from the NDI were available through December 31, 2009, and this date was used as the endpoint for the observation period. The duration of observation was calculated for each patient as the time between the study visit and December 31, 2009 or the date of death.

\subsection*{Data Analyses}

Standardized mortality ratios (SMRs) were calculated to compare the numbers of deaths per year for the cohort as a whole and for gender and racial subgroups with those that would be expected in the overall US population. The total number of deaths in 2005 due to all causes that would be expected in the overall US population. The total number of deaths in 2005 due to all causes and this date was used as the endpoint for the observation period. The duration of observation was calculated for each patient as the time between the study visit and December 31, 2009 or the date of death.

\textsuperscript{21} The total population counts for gender and racial subgroups were obtained from the
US Census Bureau estimates for 2005. The year 2005 was chosen because that was the midpoint of the observation period. Due to the low numbers of observed deaths per year in our sample, exact 95% confidence limits for the SMRs were calculated using published 95% confidence limits for the Poisson parameter method.

Bivariate independent predictors of mortality from natural causes were calculated with predictors shown as risk ratios with 95% CI. Baseline variables included in these analyses were age, gender, race (Caucasian vs other), education, cigarette smoking status at baseline (yes/no), number of packs per day smoked; PANSS total symptom score; RBANS total cognitive score; receipt of first-generation antipsychotic medication; receipt of second-generation antipsychotic medication; receipt of clozapine; serological status to CMV, EBV, HSV-1, and T. gondii; and comorbid conditions in the categories, cardiovascular, dermatologic, endocrine, gastrointestinal, genitourinary, hematologic, immunologic, musculoskeletal, neoplastic, neurological, and respiratory diseases.

To develop a multivariate model of predictors of mortality from natural causes, each predictor that was statistically significant at the <0.1 level in bivariate analyses was included in a Cox proportional hazards regression model along with age and gender. There were too few deaths from unnatural causes to study this group.

Results

Description of the Sample

The study sample consisted of 517 individuals: 25 who died of natural causes, 6 who died of unnatural causes, and 486 who remained alive throughout the observation period. Sample characteristics are shown in Table 1. The mean follow-up interval was 2270 days or 6.22 years; the total follow-up for the cohort was 3218 person years.

Almost all of the participants (511/517, 99%) were receiving antipsychotic medication at the time of the baseline assessment. A total of 176 (34%) were receiving a first-generation antipsychotic and 342 (66%) a second-generation antipsychotic; among the latter group, 146 (26% of the total) were receiving clozapine.

Causes of Natural Death

The cause of death for each of the persons who died of natural causes is shown in Table 2.

Standardized Mortality Ratios

Based on expected deaths in the overall US population by age, race, and gender groups, the SMR was 2.80 (95% CI 0.89, 6.38) for the overall sample; 5.27 (95% CI 0.68, 20.40) for Caucasian females; 3.57 (95% CI 0.10, 20.97) for non-Caucasian females; 2.19 (95% CI 0.30, 9.04) for Caucasian males; and 0.30 for non-Caucasian (95% CI 0.00, 4.19).

Table 1. Demographic and Clinical Characteristics of the Study Population at Baseline (N = 517)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD) or n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>42.2 (±9.9)</td>
</tr>
<tr>
<td>Gender, male</td>
<td>315 (61%)</td>
</tr>
<tr>
<td>Race, Caucasian</td>
<td>326 (63%)</td>
</tr>
<tr>
<td>Education (y)</td>
<td>12.3 (2.5)</td>
</tr>
<tr>
<td>Maternal education (y)</td>
<td>12.5 (2.9)</td>
</tr>
<tr>
<td>Age of illness onset</td>
<td>20.9 y (±7.6)</td>
</tr>
<tr>
<td>Duration of illness</td>
<td>21.2 y (±10.2)</td>
</tr>
<tr>
<td>Drug alcohol abuse, current or</td>
<td>271 (52%)</td>
</tr>
<tr>
<td>by history</td>
<td></td>
</tr>
<tr>
<td>Current cigarette smoker</td>
<td>331 (64%)</td>
</tr>
<tr>
<td>Packs per day among smokers</td>
<td>1.1 (±0.7)</td>
</tr>
<tr>
<td>PANSS total symptom score</td>
<td>71.2 (13.3)</td>
</tr>
<tr>
<td>RBANS total cognitive score</td>
<td>65.8 (13.6)</td>
</tr>
<tr>
<td>Antipsychotic medications</td>
<td></td>
</tr>
<tr>
<td>First-generation antipsychotic</td>
<td>176 (34%)</td>
</tr>
<tr>
<td>Second-generation antipsychotic</td>
<td>342 (66%)</td>
</tr>
<tr>
<td>Clozapine</td>
<td>146 (28%)</td>
</tr>
</tbody>
</table>

Note: PANSS, Positive and Negative Syndrome Scale; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status

Bivariate Predictors of Death From Natural Causes

The bivariate predictors of death from natural causes are shown in Table 3.

Multivariate Model for Predicting Death From Natural Causes

To develop a model of predictors of mortality, each predictor that was statistically significant at the <0.1 level in bivariate analyses was included in a Cox proportional hazards regression model along with age and gender. The baseline variables that were significantly associated with excess mortality after adjusting for both age and gender were being a smoker (relative risk [RR] = 4.66, 95% CI 1.61, 19.7, P = .0029); lower RBANS total cognitive score (RR = 0.96, 95% CI 0.93, 0.99, P = .013); level of antibodies to EBV (RR = 1.22, 95% CI 1.08, 1.35, P = .0041); level of antibodies to HSV-1 (RR = 1.19, 95% CI 1.02, 1.37, P = .030); genitourinary disease (RR = 2.70, 95% CI 1.08, 6.27, P = .035); and endocrine disease (RR = 3.14, 95% CI 1.03, 7.87, P = .044). The following variables had a bivariate association with mortality (P < .10) but were not significant (P < .05) in a model that also included age and gender: level of antibodies to T. gondii, cardiovascular disease, musculoskeletal disease, endocrine disease, and hematologic disease.

Discussion

This report describes the results of a prospective cohort study of 517 individuals with schizophrenia followed for up to almost 11 years. In this period, a total of 25 persons
died from natural causes, the majority from diseases of the circulatory system. Participants who smoked cigarettes were almost 5 times more likely than nonsmokers to die of natural causes during the observation period. Participants having an immunologic disease or genitourinary disease at study entry were also at increased risk. The level of serum antibodies to EBV and to HSV-1 was also associated with the risk of dying from natural causes.

Our results about the contribution of cigarette smoking to mortality in schizophrenia are consistent with those of previous investigations. The RR of smoking at baseline on mortality in the follow-up period was 4.66 in our study compared with 2.1 in the Kelly and colleagues study for persons aged 35–54, 4.29 in the Suvisaari and colleagues study, and 2.16 in the Brown and colleagues study. These findings underscore the life-shortening effects of smoking in this population and the urgent need to more vigorously promote smoking cessation.

We found that the level of antibodies to EBV was independently associated with mortality. EBV, also known as human Herpesvirus 4, is a gamma Herpesvirus with a worldwide distribution. Acute infection with EBV in immune competent hosts can be asymptomatic or may be associated with fever, pharyngitis, and lymphadenopathy (infectious mononucleosis). Acute infection is generally followed by the establishment of latency in B-cells, which are the primary cell for viral replication. This latency is generally lifelong and can be associated with periods of reactivation. Replication of EBV has been closely linked with malignancies such as Burkitt’s lymphoma and nasopharyngeal carcinoma. Exposure to EBV has also been associated with autoimmune disorders, particularly multiple sclerosis and systemic lupus. EBV can cause myocarditis and has been associated with fatal or near-fatal consequences in some cases. The mechanisms underlying the occurrence of serious effects of EBV infection in some individuals are not known with certainty but may be related to the underlying immune state of the host, as well as the timing of infection and the infectious dose. The effect of EBV exposure on a population of immune competent individual has not been previously reported. There are a number of available and experimental medications that can inhibit the replication of EBV, and experimental vaccines directed at EBV have been developed and evaluated in phase 1 trials. The better understanding of the role of EBV in mortality might

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**Table 2. Causes of Death for Individuals Who Died of Natural Causes (N = 25)**

<table>
<thead>
<tr>
<th>Age (y) at Death/Gender</th>
<th>International Classification of Diseases-10 Cause of Death and Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 47/M</td>
<td>Unknown but natural</td>
</tr>
<tr>
<td>2. 43/F</td>
<td>I21.9 Acute myocardial infarction (diseases of circulatory system, ischemic heart disease)</td>
</tr>
<tr>
<td>3. 63/F</td>
<td>I21.9 Acute myocardial infarction (diseases of circulatory system, ischemic heart disease)</td>
</tr>
<tr>
<td>4. 46/M</td>
<td>I21.9 Acute myocardial infarction (diseases of circulatory system, ischemic heart disease)</td>
</tr>
<tr>
<td>5. 44/M</td>
<td>D61.9 Aplastic anemia, unspecified (diseases of the blood)</td>
</tr>
<tr>
<td>6. 44/M</td>
<td>I25.0 Atherosclerotic cardiovascular disease (diseases of circulatory system, ischemic heart disease)</td>
</tr>
<tr>
<td>7. 64/F</td>
<td>I25.0 Atherosclerotic cardiovascular disease (diseases of circulatory system, ischemic heart disease)</td>
</tr>
<tr>
<td>8. 66/F</td>
<td>I25.1 Atherosclerotic heart disease (diseases of circulatory system, ischemic heart disease)</td>
</tr>
<tr>
<td>9. 48/F</td>
<td>I25.1 Atherosclerotic heart disease (diseases of circulatory system, ischemic heart disease)</td>
</tr>
<tr>
<td>10. 55/M</td>
<td>J44.0 Chronic obstructive pulmonary disease with infection (diseases of the respiratory system)</td>
</tr>
<tr>
<td>11. 53/M</td>
<td>J44.0 Chronic obstructive pulmonary disease with infection (diseases of the respiratory system)</td>
</tr>
<tr>
<td>12. 49/F</td>
<td>J44.0 Chronic obstructive pulmonary disease with infection (diseases of the respiratory system)</td>
</tr>
<tr>
<td>13. 66/F</td>
<td>A04.7 Enterocolitis due to <em>Clostridium difficile</em> (infectious and parasitic diseases)</td>
</tr>
<tr>
<td>14. 59/F</td>
<td>K25.5 Gastric ulcer chronic or unspecified with perforation (diseases of the digestive system)</td>
</tr>
<tr>
<td>15. 54/F</td>
<td>I13.1 Hypertensive heart and renal disease with renal failure (diseases of circulatory system)</td>
</tr>
<tr>
<td>16. 54/F</td>
<td>C50.9 Malignant neoplasm of breast (neoplasms)</td>
</tr>
<tr>
<td>17. 63/F</td>
<td>C34.9 Malignant neoplasm of bronchus and lung (neoplasms)</td>
</tr>
<tr>
<td>18. 62/F</td>
<td>C34.9 Malignant neoplasm of bronchus and lung (neoplasms)</td>
</tr>
<tr>
<td>19. 45/F</td>
<td>I34.0 Mitral valve insufficiency (diseases of circulatory system, other forms of heart disease)</td>
</tr>
<tr>
<td>20. 40/F</td>
<td>I34.1 Mitral valve prolapse (diseases of circulatory system, other forms of heart disease)</td>
</tr>
<tr>
<td>21. 46/F</td>
<td>I80.2 Phlebitis and thrombophlebitis of deep vessels of lower extremities (diseases of circulatory system, disease of veins)</td>
</tr>
<tr>
<td>22. 42/M</td>
<td>I26.9 Pulmonary embolism without mention of cor pulmonale (diseases of circulatory system, pulmonary heart disease)</td>
</tr>
<tr>
<td>23. 64/F</td>
<td>I64 Stroke, not specified as hemorrhage or infarction (diseases of circulatory system, cerebrovascular disease)</td>
</tr>
<tr>
<td>24. 54/M</td>
<td>I62.0 Subdural hemorrhage, acute, nontraumatic (diseases of circulatory system, cerebrovascular disease)</td>
</tr>
<tr>
<td>25. 68/F</td>
<td>F05.9 Delirium, not induced by alcohol or other substances (mental disorder with known physiological cause)</td>
</tr>
</tbody>
</table>
lead to new methods for the prevention of excess mortality in some susceptible populations.

The finding of an association between HSV-1 and mortality is curious as there are no previous studies which we could identify that report an association between HSV-1 and mortality in an otherwise immune competent population. In previous studies, we have found a robust effect of HSV-1 seropositivity on cognitive functioning in schizophrenia. Because we examined the effect of HSV-1 and of cognitive functioning separately on mortality, it is possible that the HSV-1 is exerting its effect via cognitive impairment. Another possibility is that HSV-1 may be reactivated in pneumonia.\textsuperscript{37,38}

In a previous study of mortality in a schizophrenia cohort studied for a shorter time period, we found an association between antibodies to \textit{T. gondii} and mortality.\textsuperscript{16} In this study, the level of \textit{T. gondii} antibodies was associated with mortality in the bivariate analysis but not when adjusting for age and gender. In our previous report, the strength of the increased risk conferred by toxoplasma seropositivity was HR = 4.7. However, in the earlier study, toxoplasma seropositivity was assessed dichotomously that may explain some of the difference from the mortality risk associated with toxoplasma seropositivity in the current study, RR = 1.47. In addition, the RR in this study is within the 95% CI of that found

\begin{table}
\centering
\caption{Characteristics of Alive and Deceased Participants From Natural Causes and Bivariate Predictors of Mortality (\textit{N} = 517)}
\begin{tabular}{llll}
\hline
Characteristic & Alive (\textit{n} = 486) & Dead from Natural Causes (\textit{n} = 25) & Bivariate Predictors of Mortality From Natural Causes RR (95% CI) \textit{P} Value\
\hline
Demographics\textsuperscript{c} & & & \\
Age at entry (y) & 41.9 ± 10.0 & 48.9 ± 7.8 & 1.09 (1.04-1.14) .0002 \\
Caucasian race & 61.9\% & 80.0\% & 1.59 (0.64 – 4.82) .33 \\
Female gender & 37.7\% & 68.0\% & 3.26 (1.45–7.98) .004 \\
Education (y) & 12.3 ± 2.5 & 11.8 ± 2.1 & 0.89 (0.78 – 1.03) .13 \\
Substance use & & & \\
Cigarette smoker & 63.2\% & 88.0\% & 4.41 (1.53-18.62) .0041 \\
Packs per day & 0.7 ± 0.7 & 1.1 ± 0.7 & 1.70 (1.09-2.44) .020 \\
Drug/alcohol abuse & 52.7\% & 48.0\% & 0.93 (0.42–2.08) .91 \\
Psychiatric & & & \\
PANSS & 71.3 ± 13.1 & 71.0 ± 13.6 & 1.00 (0.97–1.03) .93 \\
RBANS & 65.8 ± 13.7 & 62.6 ± 10.0 & 0.97 (0.94–1.00) .059 \\
Clozapine & 25.7\% & 24.0\% & 0.83 (0.30–1.96) .68 \\
First-generation antipsychotic & 34.4\% & 32.0\% & 1.00 (0.41–2.24) .99 \\
Second-generation antipsychotic & 66.3\% & 64.0\% & 1.15 (0.52–2.72) .74 \\
Infectious diseases\textsuperscript{d} & & & \\
Cytomegalovirus\textsuperscript{e} & 1.5 ± 1.6 & 1.5 ± 1.4 & 0.98 (0.74–1.22) .89 \\
Toxoplasma\textsuperscript{f} & 0.5 ± 0.7 & 0.9 ± 1.2 & 1.47 (1.02–1.93) .042 \\
Epstein–Barr virus\textsuperscript{g} & 2.0 ± 2.0 & 3.6 ± 2.7 & 1.13 (1.03–1.21) .019 \\
Herpes simplex virus type 1\textsuperscript{h} & 1.7 ± 1.9 & 2.9 ± 2.5 & 1.22 (1.05–1.41) .013 \\
Other diseases & & & \\
Cardiovascular & 44.4\% & 60.0\% & 2.50 (1.13–5.76) .023 \\
Dermatologic & 6.6\% & 4.0\% & 0.53 (0.03–2.49) .49 \\
Endocrine & 37.5\% & 52.0\% & 2.00 (0.91–4.43) .086 \\
Gastrointestinal & 13.2\% & 20.0\% & 1.92 (0.64–4.76) .22 \\
Genitourinary & 8.6\% & 32.0\% & 4.35 (1.78–9.79) .0022 \\
Hematologic & 5.8\% & 12.0\% & 3.46 (0.81–10.07) .085 \\
Immunologic & 4.7\% & 20.0\% & 4.50 (1.50–11.10) .010 \\
Musculoskeletal & 10.5\% & 24.0\% & 3.24 (1.18–7.71) .025 \\
Neoplastic & 3.3\% & 12.0\% & 2.88 (0.68–8.34) .13 \\
Neurological & 17.3\% & 32.0\% & 2.04 (0.83–4.59) .11 \\
Respiratory & 17.3\% & 24.0\% & 1.72 (0.63–4.08) .27 \\
\hline
\end{tabular}
\footnotesize{Note: Abbreviations are explained in the first footnote to table 1.}
\footnotesize{\textsuperscript{a}The \textit{N} = 517 also includes \textit{n} = 6 persons who died of unnatural causes.}
\footnotesize{\textsuperscript{b}Significant (\textit{P} < .05) bivariate predictors are shown in bold.}
\footnotesize{\textsuperscript{c}Values in table are mean ± SD or percentage.}
\footnotesize{\textsuperscript{d}The antibody level was measured by immunoassay tests by means of the reaction of test serum to solid-phase antigen; the amount of antibody in each sample was expressed in terms of the ratio of optical density of the test sample to the standard sample.}
\footnotesize{\textsuperscript{e}Antibodies to Cytomegalovirus.}
\footnotesize{\textsuperscript{f}Antibodies to \textit{T. gondii}.}
\footnotesize{\textsuperscript{g}Antibodies to Epstein–Barr virus.}
\footnotesize{\textsuperscript{h}Antibodies to \textit{Herpes simplex virus type 1}.}
\end{table}
in the previous investigation (1.27, 17.31). The study of larger samples might identify additional infectious agents associated with mortality.

Not surprisingly, we found that a number of disease categories were associated with mortality. The presence of an immunologic condition at baseline was a significant mortality predictor in the multivariate model. In our data set, the most common immunologic condition at baseline was insulin-dependent diabetes (16 of 33 persons in this category). Suvisaari\(^6\) also found that diabetes was a predictor of schizophrenia mortality, though in that study the predictor was diabetes type 2, which may or may not involve insulin dependence. And diabetes is a known risk factor for mortality in the general population.\(^2\) We also found that the presence of a genitourinary condition was predictive of mortality. The mostly common condition in this category among persons in our sample was urinary tract infection. It is of note that urinary tract infections have been found to be highly prevalent in persons with acute psychotic symptoms.\(^3\) Urinary tract infections have also been associated with increased mortality in elderly women unselected for medical problems.\(^4\)

We found that women in our cohort were at significantly greater risk of dying from natural causes than were men. This finding is curious as most schizophrenia studies have not found a sex difference in mortality risk or have found a higher risk for males. However, one recent study from Norway\(^4\) found that women with schizophrenia who had been hospitalized showed an increased difference in mortality risk relative to the general population in the period 1992–2006 compared with an earlier period, 1980–1992; in the recent time period, women were also found to have an increase in absolute mortality compared with the earlier period, approaching that of men. It has also been noted that women with schizophrenia may be at particular risk for cardiovascular disease and associated mortality. A recent study from Finland\(^2\) found that women with schizophrenia had a 6.9-fold risk for coronary heart disease compared with a 2.4 risk for men in comparison with the general population. The mechanisms of this differential mortality are not known but may be related to particularly high rates of cardiovascular risk factors, metabolic syndrome, and abdominal obesity, in women with schizophrenia.\(^5\) Our study was not sufficiently powered to look at the interaction of gender and specific causes of mortality.

The SMR in our cohort, based on expected deaths in the overall US population was elevated for the sample as a whole, consistent with the results of other studies.\(^1,6,8\) Looking at subgroups of our cohort, we found elevated SMRs for Caucasian females, non-Caucasian females, and Caucasian males (5.27, 3.57, 2.19, respectively). We found a lower than expected mortality (SMR of 0.30) in our non-Caucasian male schizophrenia group, almost all of whom were African American. The interaction between race and mortality in schizophrenia has not been the focus of systematic investigation. Kelly and colleagues\(^9\) found that African American patients with schizophrenia admitted to a state of Maryland hospital had a 40% lower mortality risk than whites, but this study did not report on comparisons with the general population. It may be that the overall health disadvantage for African Americans in our society, especially African American men, is offset by the attention to health and by the medical treatment afforded patients with schizophrenia who are in a psychiatric system of care, as was the case for all of the participants in our study. A better understanding of the health disparities in subgroups of persons with schizophrenia, and of the comparison with health disparities in the general population, is needed.

We did not find that receipt of second-generation antipsychotic medications, and clozapine in particular, had any significant effect on mortality in bivariate analyses. The fact that all of our patients were in a system of psychiatric care at baseline and that the majority were receiving second-generation antipsychotic medications limited the impact of this variable on mortality. We were not able to examine the effect on mortality of all of the individual medications given the very small number of decedents within each medication group. Also, participants were prescribed so many different combinations of medication that any meaningful analysis of these combinations was not possible. In addition, we do not have information on the medications received during the observation period between the baseline and the follow-up.

Limitations of the study include the fact that we did not measure or evaluate all of the potential health factors that may have affected mortality such as obesity and physical inactivity. We also did not assess other blood-based markers that would be of interest and relevant to mortality such as C-reactive protein, lipid levels, and blood glucose. Some of these limitations are based on the fact that we did not obtain samples from fasting individuals and some markers are unstable after long periods of storage. In addition, while we collected information about baseline co-occurring somatic disorders, we do not know the extent to which these disorders were adequately treated. Finally, we note that the sample size precluded our fitting a full multivariate model and also our comparing persons with schizophrenia and those in the general population on specific causes of death.

Strengths of the study include our detailed clinical assessment at baseline and the inclusion of blood-based antibody markers. To our knowledge, this is the first prospective study of mortality in schizophrenia that has included these markers.

Conclusions

There is increased mortality in schizophrenia that is due to a number of factors of which smoking is the strongest modifiable factor. Because cigarette smoking confers an almost
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5-fold risk of mortality, smoking cessation is an urgent priority. A better understanding of the factors associated with mortality might lead to preventative measures and to the reduction of premature deaths in this population.

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