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MORTALITY AFTER FIRST DIAGNOSIS OF PSYCHOTIC DISORDER IN ADOLESCENTS AND YOUNG ADULTS

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Abstract

Importance—People with psychotic disorders experience increased mortality, and recent research suggests a marked increase shortly after diagnosis.

Objective—Use population-based data to examine overall and cause-specific mortality after first diagnosis of psychotic disorder.

Design—Cohort study using health system records.

Setting—Five integrated health systems serving over 8 million members in five states.

Participants—Members aged 16 through 30 receiving first lifetime diagnoses of psychotic disorder between 9/30/2009 and 9/30/2015, along with two comparison groups matched for age, sex, health system, and year of diagnosis, selected from all members making an outpatient visit and from all receiving a first diagnosis of unipolar depression.

Exposure—First recorded diagnosis of schizophrenia, schizoaffective disorder, mood disorder with psychotic symptoms, or other psychotic disorder in any outpatient, emergency department, or inpatient setting.

Main Outcome—Death over three years following index diagnosis or visit date, ascertained from health system electronic health records, insurance claims, and state mortality records.

Results—11,713 members with first psychotic disorder diagnoses (60% male, 20% aged 15–17 and 80% aged 18–30) were matched to 35,576 outpatient service users and 23,415 members with first diagnosis of unipolar depression. During the year after first diagnosis, all-cause mortality was 54.6 per 10,000 in the psychotic disorder group compared to 20.5 per 10,000 in the unipolar depression group and 6.7 per 10,000 in the general outpatient group. After adjustment for race,

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ethnicity, and pre-existing chronic medical conditions, the relative hazard of death in the psychotic disorder group compared to the general outpatient group was 34.9 (95% CI 8.2 – 149.1) for self-inflicted injury or poisoning and 4.67 (95% CI 2.06 – 10.86) for other type of injury or poisoning. Risk of death attributed to heart disease or diabetes did not differ significantly different between the psychotic disorder group and the general outpatient group (HR=0.78, 95% CI 0.15 – 3.96). In the psychotic disorder group, all-cause mortality and mortality due to injuries or poisonings declined by half between the first and third year after diagnosis, but both rates remained three times as high as in the general outpatient group.

Conclusions and Relevance—Marked increases in early mortality underscore the importance of systematic intervention for young people experiencing first onset of psychosis. Clinicians should attend to markedly elevated suicide risk following first diagnosis.

People with psychotic disorders experience significant excess mortality. Among people with serious mental illnesses, including schizophrenia and affective psychoses, all-cause mortality rates are two to three times those in the general population [1–5]. Consequently, people with psychotic disorders can expect to die, on average, ten to fifteen years sooner than their peers[4–6].

Much of the concern regarding excess mortality in people with psychotic disorders has focused on chronic illness, especially cardiovascular disease. Long-term studies find that the majority of excess mortality in psychotic disorders can be attributed to various “natural” causes, especially cardiovascular disease[1,4,7]. Excess cardiovascular mortality has been attributed to a mix of factors, including adverse health behaviors (smoking, sedentary lifestyle), adverse metabolic effects of medications, and poorer access to effective general medical care [1,4,8,9].

More recent research suggests an even more marked increase in mortality soon after initial diagnosis of psychotic disorder[10–14]. In a sample of people aged 16–30 with first diagnoses of psychotic disorder in US commercial insurance claims, mortality over the following 12 months was more than 20 times the expected rate based on US general population statistics [14]. In that sample, data were not available regarding specific causes of death. National registry studies in Denmark[11], Finland[13], and Sweden[10] have all found elevated mortality following first hospitalization for psychotic disorder. In a combined analysis using data from all three of those national registries, all-cause mortality over an average follow-up period of four years was two to three times greater than in the general population. The most marked increases were seen in mortality due to suicide (15- to 30-fold increase) and other external causes (three- to six-fold increases) [12].

Here we use population-based records data from five large integrated health systems in the US to examine mortality in adolescents and young adults after first diagnosis of psychotic disorder in any treatment setting. We address five specific questions: How does overall mortality in the year after first diagnosis of psychotic disorder compare to mortality in matched control groups of members from the same health systems? Is excess mortality specific to psychotic disorder or common to other mental health conditions? What specific causes of death account for excess mortality? Is excess mortality explained by differences in

prevalence of pre-existing chronic medical conditions? How do patterns of overall and cause-specific mortality change over time following first diagnosis of psychotic disorder?

METHODS

Participating study sites included five regions of Kaiser Permanente (Colorado, Northern California, Southern California, Northwest, and Washington), all members of the Mental Health Research Network (MHRN). All five healthcare systems provide pre-paid comprehensive care (including general medical and specialty mental health care) to defined populations, totaling over 8 million members in 5 states. In each system, members are representative of service area populations in terms of age, sex, and race/ethnicity [15–17]. In 2012, the source of insurance coverage for members of these health systems was Medicaid for 6%, Medicare for 13%, individual insurance (including subsidized low-income plans) for 5%, and group commercial insurance for 76%.

As members of MHRN, all health systems maintain standardized research databases organized according to the Health Care Systems Research Network Virtual Data Warehouse model [18]. In each system, electronic medical records (for services provided at healthcare system-operated facilities) and insurance claims (for services provided by external providers and paid for by the healthcare system) are organized into a virtual data warehouse for research [18]. Identifiable data remain at each healthcare system, but common data specifications facilitate multi-site research using pooled de-identified data. Responsible Institutional Review Boards for each health system approved a waiver of consent for use of de-identified records data in this research.

Cases of newly diagnosed psychotic disorder included all health system members aged 16 through 30 receiving a first recorded diagnoses of psychotic disorder in any health care setting between 9/30/2009 and 9/30/2015. During the study period, billing or encounter diagnoses from all outpatient and inpatient encounters in each health system (including emergency department, mental health specialty, primary care, and other general medical settings) were used to identify the first-ever lifetime diagnosis of any psychotic disorder (including schizophrenia-spectrum disorders, mood disorders with psychotic symptoms, and other psychotic disorders) among enrolled health plan members. Eligible International Classification of Disease, Ninth Edition, Clinical Modification (ICD9-CM) diagnoses included any recording (primary or otherwise) of diagnostic codes 295.0 through 295.9, 296.04, 296.14, 296.24, 296.34, 296.44, 296.54, 296.64, 297.1, 297.3, 298.1, 298.3, 298.4, 298.8, or 298.9. Patients with other mental health diagnoses preceding the first recorded diagnosis of psychotic disorder were not excluded. Diagnoses of substance-induced psychotic symptoms were not included, but patients with diagnoses of substance use disorder or a record of substance use accompanying an eligible psychotic disorder diagnosis were included. To exclude those with pre-existing diagnoses of psychotic disorder, cases were limited to those continuously enrolled in the health system for at least 12 months prior to first occurring diagnosis. As previously reported [19], the positive predictive value of this case definition (validated against detailed review of full-text medical records) was approximately 80%.

For each case with a new diagnosis of a psychotic disorder, three matched controls were identified from all health system members making at least one outpatient visit, regardless of diagnosis, during the study period. General outpatient controls were frequency matched to cases by sex, health system, year of eligibility (plus or minus 2 years), and age (plus or minus 2 years).

To examine whether any mortality differences were specific to psychotic disorder, two additional matched controls per case were selected from health system members receiving a first recorded diagnosis of unipolar major depression without psychotic symptoms (ICD9-CM codes 296.20, 296.21, 296.22, 296.23, 296.30, 296.31, 296.32, and 296.33) during the same time period. Controls with unipolar depression were frequency matched to cases by sex, study site, year of diagnosis (plus or minus 2 years), and age (plus or minus 2 years).

In the psychotic disorder case group and the unipolar depression control group, the first-appearing diagnosis (of psychotic disorder or depression) was considered the index date for ascertainment of subsequent mortality. For the general outpatient control group, the first qualifying outpatient visit during the eligibility year was considered the index date.

For all three groups, deaths occurring during the three-year period following the index date were identified from any of three different sources: health system electronic health records and insurance claims for deaths occurring in hospitals or emergency departments, health insurance enrollment records for deaths reported to health plans by payers or purchasers, and state death certificate data. Information on specific cause of death was available for deaths ascertained from state death certificate data or electronic health records, but cause of death was not available for deaths ascertained solely from insurance enrollment records. Specific causes of death, when known, were classified as suicide or self-inflicted injury (ICD-10 codes U03, X60-X84, Y87.0), accidental injury or poisoning (ICD-10 codes V01-X59, Y85-Y86), assault (ICD-10 codes U01-U02, X85-Y09, Y87.1), cancer (ICD-10 codes C00-C97), diabetes and cardiovascular disease (ICD-10 codes E10-E14, I00-I09, I11, I20-I51).

Chronic medical conditions prior to the index diagnosis or index date were identified using the Charlson Comorbidity Score[20,21] categories, calculated using all outpatient or inpatient diagnoses recorded during the 12 months prior to index date.

Primary analyses considered deaths over the one year following each person's index date. Initial descriptive analyses examined baseline demographic and clinical characteristics in case and control samples. Additional descriptive analyses examined point estimates and confidence intervals for all-cause mortality and for specific causes of death over 12 months in all three groups. Cox proportional hazard regression was used to compare hazard of all-cause mortality and cause-specific mortality over 12 months, comparing cases to each of the control groups and adjusting for race/ethnicity and pre-existing chronic medical conditions. Secondary analyses examined all-cause mortality and cause-specific mortality over three years following index date (the longest period for which data were available for more than half of the case sample).

RESULTS

The criteria described above identified 11,713 health system members with new diagnoses of psychotic disorder. Initial diagnoses were schizophrenia-spectrum disorder for 1172 (10)%, mood disorder with psychosis (including schizoaffective disorder) for 2577 (22%), and other psychotic disorder for 7964 (68%). The care setting of initial diagnosis was a hospitalization in 2692 (23%), an emergency department visit in 2328 (20)%, a mental health outpatient visit in 4899 (42)%, and a general medical outpatient visit in 1794 (15%). Baseline characteristics of cases with psychotic disorder and the general outpatient and depression control groups are shown in Table 1. Distributions of age and sex were similar in cases and controls, reflecting the matching process described above. Compared to either control group, cases with first diagnosis of psychotic disorder were more often African American and less often Non-Hispanic White. Chronic lung disease (including asthma) was the only chronic illness with an overall prevalence greater than one percent. In general, prevalence of pre-existing chronic illnesses in those with a first diagnosis of psychotic disorder was similar to that in those receiving a first diagnosis of unipolar depression and higher than seen in the general outpatient control group.

All-cause and cause-specific mortality rates in cases and controls over 12 months following the first diagnosis date or index date are shown in Table 2. Overall mortality after first diagnosis of psychotic disorder was approximately eight times that in the general outpatient comparison group, with deaths attributed to injury or poisoning (including self-harm, accidents, and assaults) accounting for most of that difference. Overall mortality in those with a first diagnosis of psychotic disorder was almost three times that observed in the matched control group with first diagnoses of unipolar depression. Again, deaths attributed to self-harm, accidents, and assaults accounted for most of that difference.

Results of proportional hazards regression models with and without adjustment for race, ethnicity, and medical comorbidity prior to diagnosis are shown in Table 3. After adjustment, overall mortality in the year following a first psychotic disorder diagnosis was approximately seven times the overall mortality observed in the matched general outpatient comparison group and approximately 2.5 times that observed in the matched unipolar depression comparison group. Deaths due to self-inflicted injury or poisoning were over thirty times as likely in the group with new psychotic disorder diagnoses as in the general outpatient control group, but self-harm mortality was not significantly more likely in the psychosis group than in the unipolar depression comparison group (i.e. confidence limit for hazard ratio included one).

Figure 1 shows overall and cause-specific mortality rates over three years following each person’s first diagnosis or index date. In the group with first diagnoses of psychotic disorder, overall mortality declined steadily over three years following diagnoses, but deaths due to injury or poisoning continued to account for approximately half of all mortality. After three years, however, overall mortality remained more than twice as high as that in the unipolar depression comparison group and more than three times as high as that in the general outpatient comparison group. Similarly, mortality due to injury or poisoning remained more

than twice as high as that in the unipolar depression comparison group and five times as high as that in the general outpatient comparison group.

DISCUSSION

In this population-based sample of health system members receiving first diagnoses of psychotic disorder in any care setting, we observed an all-cause mortality rate approximately eight times that observed in a matched control group of outpatient service users and three times that observed in a matched control group of members receiving first-ever diagnoses of unipolar depression. Compared to the general outpatient control group, excess mortality during the year following a first diagnosis of psychosis was largely attributable to injuries and poisonings, including those attributed to self-harm, accident, or assault. In those with new diagnoses of psychotic disorder, both overall mortality and mortality due to injuries and poisonings declined gradually over three years following diagnosis. But overall mortality and mortality due to injury or poisoning remained elevated in comparison either to outpatient service users or to health plan members with a new diagnoses of unipolar depression.

Our data clearly indicate a marked increase in risk of death following first diagnosis of psychotic disorder in adolescents and young adults, but the eight-fold increase in mortality seen in this sample is smaller than the twenty-fold increase reported by Schoenbaum and colleagues[14]. Some of that discrepancy may represent random variation, given the small number of deaths in this sample. Some of the discrepancy may reflect differences in methods. Mortality data were obtained from electronic health records, state vital records and insurance coverage data rather than from Social Security Administration records, so deaths among patients disenrolling from the health system and moving to a different state could be missed. A control group selected from outpatient service users would be expected to have a higher mortality rate than a general population sample. Even the lower estimate of an eight-fold difference in mortality, however, represents a dramatic increase in risk among adolescents and young adults soon after first clinical presentation with psychotic symptoms.

Approximately 75% of members of these health systems were enrolled through commercial insurance, and the sample reported by Schoenbaum and colleagues [14] was limited to those covered by commercial insurance. We might observe even greater excess mortality in a population with a higher proportion of low-income or disadvantaged patients.

New diagnoses of psychotic disorder could sometimes reflect misdiagnosis of primary psychotic disorder in people with psychotic symptoms attributable to medical illness. In this scenario, subsequent excess mortality would be due to that underlying illness rather than causally related to psychotic disorder. We do observe a higher rate of pre-existing medical illness in the psychotic disorder group compared to the general outpatient control group, but accounting for differences in pre-existing illness had only minimal effect on mortality differences.

Limitations

We should acknowledge possible misclassification in our identification of new diagnoses of psychotic disorder. Given the large sample of cases, it was not possible to individually confirm all diagnoses using full-text medical records. Consequently, we relied on a strict definition found to have high confirmation rate or positive predictive value in our previous research [19]. Nevertheless, this definition may also have a false positive rate of up to 20%. Our previous research suggests that most false positives are due to over-diagnosis of psychotic symptoms (i.e. recording of a psychotic disorder diagnosis when psychotic symptoms are not clearly present) with a small number due to newly-recorded diagnoses in people with history of prior diagnosis or treatment (i.e. chronic rather than new cases). A significant number of false positives in our psychotic disorder group would lead to a conservative bias (i.e. under-estimating the excess mortality after first diagnosis of psychotic disorder).

We should also emphasize that many of those receiving first diagnoses of psychotic disorder may have experienced symptoms of psychosis for months or years prior to receiving a formal diagnosis [22–24]. The records data available to us do not allow assessment of unrecognized or untreated psychotic symptoms. Diagnoses of psychotic disorder could have been recorded prior to the 12-month enrollment window required for inclusion in this sample. Sensitivity analyses limiting the sample to those with longer prior enrollment yielded similar results (see online appendix). Any errors in dating the onset of psychosis would likely introduce a conservative bias by mixing those with truly new symptoms (where mortality risk appears to be highest) and those with longstanding symptoms only recently diagnosed. We cannot, of course, examine mortality in those developing psychotic symptoms who died before those symptoms were ever diagnosed[11].

Context

Excess mortality in people with first diagnoses of psychotic disorder was less striking when compared to that observed in people with unipolar depression. Nevertheless, both overall mortality and mortality due to injuries or poisonings (the largest single category) were more than twice as high following diagnosis of a psychotic disorder than following diagnosis of unipolar depression. This difference was maintained over three years. While confidence limits were wide for less common causes of death, mortality rates for most categories were higher following psychotic disorder diagnosis.

Our data are consistent with previous epidemiologic research that describes elevated risk of death due to injury or poisoning soon after the onset of psychotic disorder [10–13,25–27]. Those previous studies have also found markedly elevated rates of suicide death or death due to unnatural causes soon after first diagnosis. Similar to findings in our sample, approximately half of all early deaths after first diagnosis of psychotic disorder were attributable to suicide or other types of injury or poisoning.

Our data and other recent reports [11,12] indicate that causes of excess mortality soon after diagnosis differ significantly from the chronic illnesses responsible for long-term increases in mortality among people with psychotic disorders [7,9]. In our sample, deaths attributed to

diabetes or cardiovascular disease accounted for a small proportion of all mortality within three years after first diagnosis of psychotic disorder. Furthermore, the rate of death due to diabetes or heart disease was no different soon after a first diagnosis of psychotic disorder than the rate observed in a matched sample selected from outpatient service users. While previous research has demonstrated high prevalence of cardiovascular risk factors at or soon after first diagnosis of psychotic disorder [28,29], mortality impact of those risk factors would not be expected to appear for many years.

Conclusions

Our findings support the importance of systematic early intervention for young people experiencing first onset of psychosis. Strong evidence supports the effectiveness of coordinated specialty care programs for improving both clinical and functional outcomes [30–32]. Observational studies suggest that continuous treatment with antipsychotic medication may reduce mortality in people with psychotic disorders [33,34]. Unfortunately, few young people with new diagnoses of psychotic disorder actually receive coordinated or continuous care [14]. These findings also underscore the specific importance of suicide and other injury or poisoning deaths soon after first diagnosis of psychotic disorder. Early intervention programs should give special attention to assessing and addressing risk of self-harm. Clinicians caring for young people with psychotic symptoms should be aware that the one or two years following first onset is a period of especially high risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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KEY POINTS

Question

What is responsible for the increased risk of death after diagnosis of psychotic disorder?

Findings

In people aged 16–30 with a first diagnosis of psychotic disorder, overall mortality was 7 times as high as in health system outpatients, with injuries and poisonings accounting for most of the excess mortality.

Meaning

The period soon after a first diagnosis of psychotic disorder in an especially high-risk time for suicide and other deaths due to injury or poisoning.

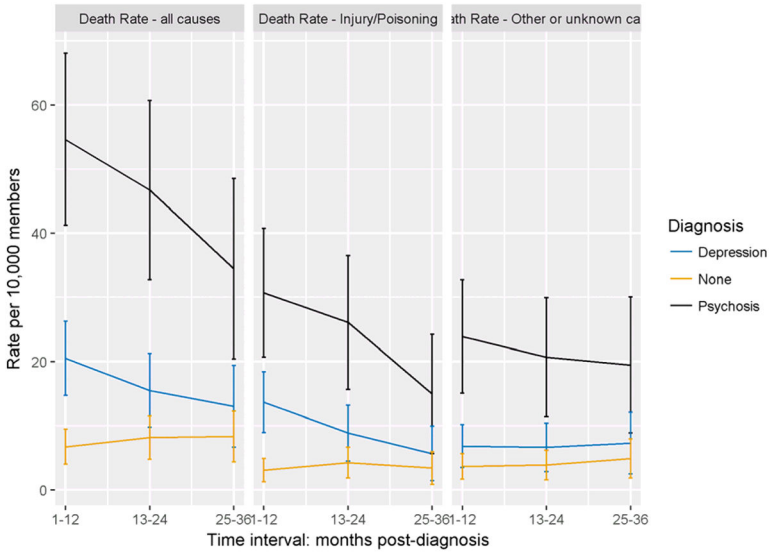

Figure 1.

Mortality trends over 3 years health plan members receiving first diagnosis of psychotic disorder and matched comparison groups selected from members making at least one outpatient visit and members receiving a first diagnosis of unipolar depression.

Table 1

Baseline characteristics of health plan members receiving first diagnosis of psychotic disorder compared to matched control groups selected from members making at least one outpatient visit and members receiving a first diagnosis of unipolar depression.

	1st Diagnosis of Psychotic Disorder		1st Diagnosis of Unipolar Depression		General outpatient	
	N	%	N	%	N	%
Male	6976	59.6	13626	58.2	20881	58.7
Age						
15–17	2368	20.2	5041	21.5	7845	22.1
18–25	7501	64.0	14411	61.6	21741	61.1
26–30	1844	15.7	3963	16.9	5990	16.8
Race/Ethnicity						
White	5060	43.2	11930	51.0	13974	39.3
Black	1722	14.7	1825	7.8	3249	9.1
Hispanic	3030	25.9	6202	26.5	10590	29.8
Asian	948	8.1	1957	8.4	4375	12.3
Native American/Alaskan Native	73	0.6	159	0.7	167	0.5
Hawaiian or Pacific Islander	113	1.0	185	0.8	335	0.9
Other or Unknown	767	6.6	1376	5.9	3262	9.2
Any Mental Health Diagnosis in Prior Year	6748	57.6	10667	45.6	2695	7.6
Any Substance Use Disorder Diagnosis in Prior Year	2972	25.4	2275	9.7	621	1.7
Charlson Comorbidity Score						
Score >=1	1569	13.4	2718	11.6	2247	6.3
Score >=2	179	1.5	227	1.0	190	0.5
Specific Chronic Conditions						
Chronic pulmonary disease	1303	11.1	2309	9.9	1848	5.2
Diabetes	115	1.0	268	1.1	219	0.6
Any malignancy	48	0.4	57	0.2	83	0.2
Cerebrovascular disease	57	0.5	41	0.2	21	0.1
Renal disease	31	0.3	44	0.2	42	0.1
Rheumatic disease	24	0.2	23	0.1	38	0.1

	1st Diagnosis of Psychotic Disorder		1st Diagnosis of Unipolar Depression		General outpatient	
	N	%	N	%	N	%
Hemiplegia or paraplegia	35	0.3	26	0.1	16	<0.1

Table 2

Total and cause-specific mortality rates over 12 months in health plan members receiving first diagnosis of psychotic disorder compared to matched control groups selected from members making at least one outpatient visit and members receiving a first diagnosis of unipolar depression.

	1st Diagnosis of Psychotic Disorder (n=11713)		1st Diagnosis of Unipolar Depression (n=23415)		General outpatient (n=35576)	
	N	**Rate per 10,000 per year (95% CI)**	**N**	**Rate per 10,000 per year (95% CI)**	**N**	**Rate per 10,000 per year (95% CI)**
Total deaths	64	54.6 (41.3, 68.0)	48	20.5 (14.7, 26.3)	24	6.7 (4.0, 9.4)
Self-inflicted Injury/Poisoning	22	18.8 (10.9, 26.6)	26	11.1 (6.8, 15.4)	2	0.6 (0.0, 1.3)
Accidental Injury/Poisoning	11	9.4 (3.9, 14.9)	5	2.1 (0.3, 4.0)	6	1.7 (0.3, 3.0)
Assault	3	2.6 (0.0, 5.5)	1	0.4 (0.0, 1.3)	3	0.8 (0.0, 1.8)
Cancer	8	6.8 (2.1, 11.6	2	0.9 (0.0, 2.0)	5	1.4 (0.2, 2.6)
Heart disease / Diabetes	2	1.7 (0.0, 4.1)	4	1.7 (0.0, 3.4)	6	1.7 (0.3, 30)
Other Known Cause	9	7.7 (2.7, 12.7)	3	1.3 (0.0, 2.7)	2	0.6 (0.0, 1.3)
Cause Unavailable	9	7.7 (2.7, 12.7)	7	3.0 (0.8, 5.2)	0	0

Table 3

Relative hazard of death over 12 months in health plan members receiving first diagnosis of psychotic disorder compared to matched control groups selected from members making at least one outpatient visit and members receiving a first diagnosis of unipolar depression.

	Vs. General outpatient				Vs. 1st Depression Diagnosis			
	Unadjusted		Adjusted*		Unadjusted		Adjusted*	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Total deaths	8.06	5.04–12.90	6.92	4.30–11.14	2.63	1.80–3.83	2.55	1.77–3.72
Self-inflicted Injury/Poisoning	32.36	7.59–138.0	34.9	8.19–149.1	1.62	0.92–2.87	1.62	0.91–2.88
Other Injury/Poisoning	4.76	2.06–10.99	4.67	2.01–10.86	4.67	1.79–12.16	4.66	1.79–12.12
Heart disease / Diabetes	1.02	0.21–5.05	0.78	0.15–3.96	1.00	0.18–5.46	0.94	0.17–5.15
Other Known Cause	7.46	3.09–17.99	4.63	1.89–11.33	6.81	2.51–18.46	6.11	2.25–16.58
Cause Unavailable	**		**		2.58	0.96–6.92	2.50	0.93–6.72

*Adjusted for Charlson Score (0 vs 1+) and race/ethnicity (Non-Hispanic White, Native American/Alaskan Native, and other /unknown vs. Black, Asian, Hispanic, Native Hawaiian/Pacific Islander)

**Cannot estimate due to zero events in comparison group.