UC Irvine

UC Irvine Previously Published Works

Title

Cardiovascular Disease Mortality of Medicaid Clients with Severe Mental Illness and a Co-occurring Substance Use Disorder.

Permalink

<https://escholarship.org/uc/item/9mb0p0x3>

Journal

Administration and policy in mental health, 44(2)

ISSN

0894-587X

Authors

Bruckner, Tim A
Yoon, Jangho
Gonzales, Marco

Publication Date

2017-03-01

DOI

10.1007/s10488-016-0722-9

Peer reviewed

Cardiovascular Disease Mortality of Medicaid Clients with Severe Mental Illness and a Co-Occurring Substance Use Disorder

Abstract

Increasing attention focuses on cardiovascular disease (CVD) among persons with SMI. We examined, among persons with SMI, whether co-occurring substance use disorder (SUD) elevates the risk of CVD death. We linked 2002 to 2007 Medicaid claims data on 121,817 persons with SMI to cause and date of death information. We applied a proportional hazards model that controls for co-morbidity at baseline, atypical antipsychotic prescription medications, age, gender and race/ethnicity. Results among persons with co-occurring SUD indicate a 24% increased risk of CVD death (Hazard Ratio = 1.24; 95% Confidence Interval=1.17 — 1.33). We encourage further coordination of services for this population.

KEYWORDS: substance use, severe mental illness, comorbidity, cardiovascular death

Introduction

Persons hospitalized with severe mental illness (SMI) live, on average, fifteen to twenty years less than persons without SMI (Osborn et al., 2007; Wahlbeck, Westman, Nordentoft, Gissler, & Laursen, 2011). This reduced lifespan among persons with SMI arises in part from the increased risk of other chronic diseases such as cardiovascular disease (CVD). CVD ranks as the leading cause of death in the developed world (Alwan, 2011) and among persons with SMI (Colton & Manderschied, 2006). Whereas CVD mortality in the U.S. has declined for the general population, persons with SMI show a two-fold increased risk of CVD death relative to persons without SMI (Newcomer & Hennekens, 2007; Brown, Inskip, & Barraclough, 2000). The heightened incidence of CVD among persons with SMI not only raises the risk of death but also portends costly health care services in both in- and out-patient settings. An increasing body of research has begun to identify pathways that connect SMI to CVD morbidity (Newcomer & Hennekens, 2007; Ray, Chung, Murray, Hall, & Stein, 2009). Here we build on this research base and test the hypothesis that, among persons with SMI, co-occurring substance use disorder (SUD) increases the risk of CVD death.

SMI often co-occurs with alcohol and illicit substance use in that an estimated thirty to fifty percent of persons with SMI report at least one SUD (Mueser et al., 2000; Regier et al., 1990; Grant et al., 2004). SUD may increase the risk of chronic disease including CVD among persons with SMI via several pathways. SUD may result in poor adherence to medications to treat chronic disease. In addition, SUD may act as a barrier to seeking preventive care (American Pharmacists Association, 2013). These pathways may co-occur in conjunction with physiological mechanisms by which SUD (e.g., alcohol abuse and use of illicit drugs) increases CVD risk among persons with SMI. For instance, alcohol abuse increases the risk of hypertension and arrhythmia, heroin and other opiates elevate the risk of arrhythmia and noncardiac pulmonary

Running Head: CVD Death in persons with Substance Use and Severe Mental Disorders

edema, and overdose of cocaine may lead to myocardial ischemic events (Frishman, Del Vecchio, Sanal, & Ismail, 2003; Hollander & Hoffman, 1992).

We set out to test whether a documented SUD places persons with SMI at an increased risk of death due to CVD. We test this hypothesis using a longitudinal Medicaid claims dataset in California of over 120,000 clients with SMI. Our research contributes to the literature in two ways. First, linkage of a large publicly-funded claims database to the California cause-of-death file among persons with SMI allows for the first estimates, to our knowledge, of the SUD comorbidity / CVD mortality relation in the SMI population. Second, we examine death due to CVD—the leading cause of death in developed countries. Use of death information precludes substantial measurement error that could arise from reliance on reimbursement claims data to estimate CVD morbidity (Nestor & Knecht, 2007; Jollis et al., 1993).

Methods

Variables and Data: We retrieved reimbursable medical claims data on persons with SMI aged 18 to 64 participating in Medi-Cal, California's version of the publicly funded federal Medicaid program. California processes approximately one million mental health-related claims per month for Medi-Cal eligible persons aged 18 to 64 years. The State of California, Department of Health Care Services (CA-DHCS) makes these data available to University of California researchers. CA-DHCS provided us with claims data for 72 months spanning January 2002 to December 2007. These data comprise the longest time span of claims that we could link to cause of death information (if deceased). The Medi-Cal dataset also includes social and demographic variables of their participants. The State of California, Committee for the Protection of Human Subjects, CA-DHCS, and the University of California, Irvine approved the

Running Head: CVD Death in persons with Substance Use and Severe Mental Disorders

use of this dataset for this study (Protocol numbers 08-12-57, 12-10-0813, and 2010-7472, respectively).

County and health care providers file claims to the State for services provided to Medi-Cal patients. Because the State reimburses claims to the county and/or the provider, pharmacy and procedure claims more than diagnostic codes appear reliably reported. We base this judgment on the measurement validity of these codes in Medicaid claims data relative to the “gold standard” of detailed clinical reports (Crystal, Akincigil, Bilder, & Walkup, 2007). We used these claims in conjunction with diagnoses to define SMI (Crystal, Akincigil, Bilder, & Walkup, 2007). Based on extensive discussions with CA-DHCS staff, we identified patients as ever having SMI during our study period if they met any one of the following criteria: (i) received a prescription for at least one second generation antipsychotic drug, (ii) underwent a procedure classified as specialty mental health care (either in an inpatient, outpatient, or community-based setting), or (iii) received a primary or secondary diagnosis of schizophrenic disorder, affective psychosis, paranoid states and delusional disorders, other non-organic psychoses, panic disorder, obsessive-compulsive disorder, generalized anxiety disorder, somatization disorder, or antisocial personality (ICD-9 codes: 295-297, 298.9, 300.0, 300.1, 300.21, 300.3, 300.81, and 301.7). Based on this strategy, we classified 121,817 persons with SMI, of which we identified 41% from prescriptions, 36% from specialty mental health care, and 23% from diagnostic data.

First generation antipsychotics have specific side effects related to serious movement disorders including muscle spasms and parkinsonism. Such side effects led to a phasing out of these drugs before, and including, the study period, which makes it difficult to track continuity of care among persons taking first generation antipsychotics (relative to those taking second generation antipsychotics). For this reason we focused on second-generation antipsychotics for

Running Head: CVD Death in persons with Substance Use and Severe Mental Disorders

the SMI inclusion criteria. We, however, acknowledge that not including persons taking first-generation antipsychotics reduces our sample size. In addition, given the incomplete nature of diagnostic codes, overlap in diagnoses, and the difficulty of deriving a diagnosis from procedure and pharmacy codes only, we did not classify persons with SMI by specific condition.

For patients enrolled in Medi-Cal at any time from 2002 to 2007 and no longer alive on December 31, 2007, we linked their claims data to cause-of-death information. The California Death Statistical Master File lists exact date of death, as well as underlying cause of death, for all California residents even if they died in other states. CA-DHCS staff linked Medi-Cal claims to death records in the CA Death File using a combination of Social Security number, family name and date of birth information.

We coded a CVD death if the underlying cause of death on the Death File listed any of the ICD-10 death codes classified as “circulatory” (i.e., I-00 to I-99) (American Heart Association, 2007). We examined CVD death rather than the onset of CVD morbidity given the documented under-detection of CVD cases using reimbursement claims data (Goff, Pandey, Chan, Ortiz, & Nichaman, 2000). For the SUD exposure variable, we classified SMI clients as having SUD if they met any of the following criteria: (i) a diagnostic claim indicated alcohol or drug dependency (excluding tobacco); (ii) a procedure claim listed alcohol or drug rehabilitation, detoxification, or intervention; or (iii) a pharmacy claim showed a prescription for methadone. These exposure criteria appear more inclusive than prior literature which focuses only on diagnostic codes (Dickey & Azeni, 1996). The noted under-reporting of non-reimbursable diagnosis codes in Medi-Cal, however, led us to classify SUD with additional procedural and pharmacy claims (Busch, Frank, Lehman, & Greenfield, 2006).

Analysis: We used survival analytic methods to examine, among persons with SMI, whether co-occurring SUD varies positively with the risk of CVD death. We treated CVD death

Running Head: CVD Death in persons with Substance Use and Severe Mental Disorders

as a time-to-event outcome with age as the time axis. Persons with SMI could survive to the end of follow-up or die of another cause. In this context, CVD death and mortality due to other causes represent competing risks. We therefore specified a Cox proportional hazards model with adjustment for competing risks. The Cox model also permits adjustment for potential confounders.

Each patient contributes person-time at risk of CVD death beginning at their initial eligibility date in Medi-Cal (in our case, January 2002 or later) and ending on December 31, 2007 or death, whichever comes first. We analyzed person-time for both continuously and periodically enrolled Medi-Cal clients, since we could link the California Death File to subjects regardless of their duration of Medi-Cal enrollment.

We classified persons as having SUD based on claims data from only their first year of enrollment during our study period. A patient could enter Medicaid in, for example, 2004 and would be followed for 365 days thereafter to assess SUD status. Classification of SUD exposure in this fashion—independent of the subject's actual length of follow-up—avoids bias that may arise from differential person-time contributions (Hernan, Hernandez-Diaz, Robins, 2004). If we instead had examined full follow-up for each subject, persons surviving six years would have a much greater opportunity to be classified as SUD relative to persons surviving one year. In this case, we may find a spurious negative association between SUD and CVD death if we had classified SUD according to full length of follow-up. We minimized this bias by fixing the exposure window to the first year of eligibility. In addition, our definition of SUD coheres with the notion that SMI/SUD comorbidity often persists (Kessler, 2004).

In estimating the SUD / CVD relation we first plot the unadjusted survival curves. Next, we control for other comorbidities at baseline that may increase CVD mortality. We also control for the independent risk among the SMI population of atypical antipsychotics increasing sudden

Running Head: CVD Death in persons with Substance Use and Severe Mental Disorders

cardiac death (Ray, Chung, Murray, Hall, & Stein, 2009; Newcomer & Haupt, 2006). We included a Charlson co-morbidity score (range: 1-29), recommended in the literature, which captures illness severity and predicts premature death (Sundararajan et al., 2004). Next, we included as a covariate a prescription rate of atypical antipsychotic drugs (milligrams per day) given their documented relation to CVD death [6]. We derived this rate using formulation, date and dose information on atypical antipsychotic drugs from Medi-Cal pharmacy prescription claims. We standardized all drugs to chlorpromazine equivalents to permit aggregation across various medications (Woods, 2003). We, consistent with prior literature, then categorized atypical antipsychotic drugs into dose quartiles (e.g., low—including no use, medium-low, medium-high, and high) (Ray, Chung, Murray, Hall, & Stein, 2009).

We further included race/ethnicity and gender in the survival analysis. Given the strong age-dependence of CVD mortality, we controlled for differences in subject age at entry using the ENTRYTIME option in SAS (Gail, Graubard, Williamson, & Flegal, 2009). For this reason, and consistent with the statistical literature, we did not specify age at entry as a covariate (Thiebaut & Benichou, 2004).

We performed several sensitivity analyses to assess the robustness of the findings. First, we examined the extent to which confounding by smoking, a strong independent risk factor for CVD, could affect results. We applied the Breslow and Day (1980) method to assess potential confounding by smoking in the absence of tobacco information in the Medi-Cal claims data. Second, we assessed whether the competing risk of diabetes death artificially inflated CVD mortality risk among SMI persons with co-occurring SUD. Third, given that clinicians may prescribe second generation antipsychotics as hypnotics among non-SMI persons for short-term use, we restricted the SMI population to persons taking higher doses and/or more frequent prescriptions of these antipsychotics. Difficulty with sleep reflects a symptom for which

clinicians may prescribe second generation antipsychotics as hypnotics for short-term use. A more reliable proxy for SMI may therefore involve a higher dose of antipsychotics, which we assess with a sensitivity analysis (i.e., persons with greater than 3,750 mg of prescribed antipsychotics, which lies above the 10th percentile of the distribution). Fourth, we restricted the analysis to persons with low co-morbidity scores to determine whether “outlier” clients with severe and extensive comorbidities account for results. We conducted all statistical analyses in SAS (version 9.2, SAS Institute, Cary, NC).

Results

Table 1 describes the demographic and health characteristics of our study population. We identified 121,817 persons with SMI who enrolled in Medi-Cal at some point between 2002 and 2007. Of these subjects, 24.2% show a co-occurring SUD. CVD ranks as the leading cause of death over the study period in that it accounts for 23.5% of the observed 22,609 deaths. Non-Hispanic whites comprise 45% of the sample, followed by Hispanics and non-Hispanic blacks. At study entry, about 40% of persons with SMI show a Charlson co-morbidity score of one or greater. Three-quarters of persons with SMI remain continuously enrolled, which coheres with the notion that these clients appear less likely than other Medi-Cal enrollees to gain employer-based private health insurance coverage (McAlpine & Mechanic, 2002).

Figure 1 plots the unadjusted survival curves for CVD mortality by SUD status among SMI clients over the six years (i.e., 312 weeks) of observation. Whereas the curves remain statistically indistinguishable for the first two years, survival especially among persons with SMI and SUD falls thereafter. At the end of follow-up, we observe an unadjusted survival probability of 89.5% among the SMI/SUD group as compared with 92.8% for the SMI/non-SUD group. This difference exceeds conventional levels of statistical significance ($p < .001$).

Running Head: CVD Death in persons with Substance Use and Severe Mental Disorders

Table 2 displays the results of our fully adjusted Cox proportional hazards model.

Persons with SMI and a co-occurring SUD appear at elevated risk of CVD mortality relative to persons without SUD (Hazard Ratio [HR] = 1.24; 95% Confidence Interval [CI] = 1.17 — 1.33, $p < .0001$). This finding remains essentially unchanged when we restrict the sample to only continuously enrolled Medicaid subjects (results available upon request).

Comorbidities at baseline, as reflected by the Charlson index, also vary positively with the risk of CVD death. Consistent with the literature, several demographic characteristics predict CVD death. Females show a reduced risk of CVD mortality relative to males (HR = 0.59; 95% CI = 0.56 — 0.63). Non-Hispanic black clients, by contrast, appear more likely than non-Hispanic white clients to die of CVD. The highest quartile of atypical antipsychotic medication prescriptions (relative to the lowest quartile) also varies positively with the risk of CVD death.

Given incomplete information on smoking in Medi-Cal claims, there remains a possibility that the SUD / CVD mortality relation includes residual confounding due to smoking. We therefore assessed the sensitivity of our results by applying the Breslow and Day (1980) confounding risk ratio method for an unmeasured variable. We assumed a smoking prevalence of 70% for SMI/SUD (Lasser et al., 2000) and 61% prevalence for SMI /non SUD (Kalman, Morissette, & George, 2005). We then, consistent with the literature, specified a two-fold increased risk of CVD death among smokers (Ray, Chung, Murray, Hall, & Stein, 2009). Application of the Breslow-Day calculation yields a confounding risk ratio of 1.07. This result suggests that our SUD findings in Table 1 are seven percent greater than if we completely controlled for smoking. This exercise indicates that smoking cannot fully explain the magnitude of our discovered SUD / CVD mortality relation (see Appendix for details). Our sensitivity analysis, moreover, may overestimate the influence of smoking given that the Charlson index

Running Head: CVD Death in persons with Substance Use and Severe Mental Disorders

captures many of the mediating co-morbidities (e.g., myocardial infarction, heart failure) by which smoking increases the risk of CVD death.

One assumption of the hazards model with competing risks of death involves the statistical independence of competing risks from the principal outcome of interest. Given that CVD and another cause of mortality—diabetes—share a common precursor (i.e., metabolic syndrome), this assumption may not hold (Wilson, D'Agostino, Parise, Sullivan, & Meigs, 2005). We therefore assessed the robustness of our results by reclassifying the key outcome as *either* CVD or diabetes death. We reasoned that, among both persons with diabetes and/or CVD, SUD may reduce the ability to properly manage either chronic condition via mechanisms described in the Introduction. Results from the adjusted model (Table 3) do not change inference from the original test, although the SUD result appears somewhat attenuated.

The unadjusted survival plot (Figure 1) indicates increased CVD mortality as a function of SUD only after 1.5 years of follow-up. We therefore assessed this possibility in the adjusted hazard analysis by restricting the test to before and after 1.5 years of follow-up. Results using the multivariable hazard model (not shown) support this inference, as well as the notion that the risk of CVD mortality increases over time among those classified as SUD.

Given that a more reliable proxy for SMI may involve a higher dose of antipsychotics, we then restricted the SMI study population to persons with greater than 3,750 mg of prescribed antipsychotics (i.e., >10th percentile of the distribution) and re-ran the hazard analysis. The hazard ratio for CVD death among SMI persons with co-occurring SUD became slightly stronger than in the original test (HR= 1.26; 95% CI: 1.18, 1.35, p<.0001).

We restricted the analysis to persons with low co-morbidity scores to determine whether “outlier” clients with severe and extensive comorbidities account for results. Outlier clients may include those who receive a variety of prescriptions (including methadone) for chronic pain from

Running Head: CVD Death in persons with Substance Use and Severe Mental Disorders

other conditions. Use of administrative claims data may render it difficult to accurately classify the outlier clients' SUD status. For this reason, we excluded all clients with a Charlson co-morbidity score of greater than three and re-ran the hazard analysis. Whereas the hazard ratio for CVD death among SMI persons with co-occurring SUD attenuated slightly (HR= 1.17; 95% CI: 1.08, 1.26), results indicate that potential misclassification of SUD status among severely co-morbid SMI persons does not account for our findings.

Discussion

Recent research on persons with SMI focuses on reducing the morbidity and health care costs of cardiovascular disease (Goff et al., 2005; Jackson, Covell, Drake, & Essock, 2007), the most common cause of death worldwide (Alwan, 2011). Given that SMI often co-occurs with alcohol and illicit substance use, we tested whether persons with SMI and substance use disorder (SUD) show an elevated risk of CVD mortality relative to persons with SMI but no documented SUD. Results from over 120,000 persons with SMI enrolled in California's Medicaid system show a nearly 25 percent elevated risk of CVD death among those with co-occurring SMI/SUD.

Strengths of our analysis include the large Medicaid sample of persons with SMI and the six year follow-up window, which provides strong statistical power to examine CVD death. Linkage of the California death file to the Medi-Cal database also permits accurate classification of the timing of a clearly defined health endpoint. This circumstance avoids the limitation of using reimbursement claims data to identify incident morbidity (Nestor & Knecht, 2007; Jollis et al., 1993). Results, moreover, remain robust to control for potential confounders (e.g., pre-existing conditions at baseline, level of atypical antipsychotic drugs prescribed) known to elevate the risk of CVD mortality. In addition, continuous enrollment of three-quarters of persons with

Running Head: CVD Death in persons with Substance Use and Severe Mental Disorders

SMI over the six year period allows strong statistical power while also minimizing bias due to selective loss to follow-up.

The unadjusted survival plot (Figure 1) indicates that co-occurring SUD increases the risk of CVD mortality after 1.5 years of follow-up but not before. Our reported hazard ratio for SUD in Table 2, therefore, reflects the elevated risk of CVD mortality averaged over the entire time period (i.e., 2002 to 2007) and does not describe narrow time intervals. We speculate that the pattern of results arises from the risk of CVD death increasing commensurately with duration of SUD. We encourage more precise collection of SUD data among the SMI population to further refine and test the potential time dependence of CVD risk.

As with all analyses using administrative claims data, limitations involve incompleteness of SMI and SUD diagnoses. Based on discussions with Medi-Cal staff and clinicians, we opted for an inclusive definition of SMI that used pharmacy, diagnostic, and procedure codes so as to detect the entire SMI population. This process may have expanded the study population to include persons with milder mental disorders that would not qualify as SMI if true prevalence data were available. If there exists a weaker association between SUD and CVD mortality for non-SMI persons than for SMI persons, our inclusive definition of the study population attenuates the discovered SUD coefficient towards the null. We, however, note that in our discussions with CA-DHCS we did not select major depressive disorder for inclusion into the SMI definition. We, therefore, caution the reader against making direct comparisons between our SMI population and others used in the literature. In this regard, our decision to exclude persons taking first generation antipsychotics also limits generalizability of our results to SMI populations who continue to use first generation antipsychotic medications.

We also analyzed SMI and SUD in aggregate, rather than treating each component disorder of either SMI or SUD separately. We did not examine specific diagnoses for two main

Running Head: CVD Death in persons with Substance Use and Severe Mental Disorders

reasons. First, many conditions co-occur (among SMI, and separately, among SUD) which would make it challenging to examine each diagnosis in isolation. Second, Crystal and colleagues document lower measurement validity of diagnostic claims in the Medicaid database (Crystal, Akincigil, Bilder, & Walkup, 2007). This aggregation, however, likely obscures differences in severity and type of SUD. In addition, we cannot distinguish from the dataset persons whose substance use reflects either a self-medication or “sensation-seeking” pattern. Previous research indicates that many persons with SMI self-medicate with substances to cope with their mental disorder, which may make addressing SUD in this population quite challenging (Leshner, 1999). We anticipate that the integration of data from California’s former Alcohol and Drug Program into the Department of Health Care Services data warehouse will permit testing of more refined hypotheses regarding specific patterns and types of substance use disorder among persons with SMI.

We further relied on a combination of diagnostic, procedural, and pharmacy claims variables to identify SMI and SUD. Our reported 24% prevalence of SUD among persons with SMI appears slightly lower than that of other SMI populations (Rosenthal, Nunes, & Le Fauve, 2012). This lower prevalence indicates potential misclassification of “true” SUD as non-SUD. Such exposure misclassification likely attenuates our SUD finding towards the null. Our work is also limited in that we included any methadone prescription as SUD despite the possibility that persons may receive methadone for pain control.

Lack of information on smoking also precludes a specific analysis on the contribution of smoking to CVD. Our sensitivity analysis using the Breslow and Day method (1980), however, suggests that confounding due to smoking among persons with SMI does not account for the discovered relation between SUD and CVD death. Additionally, research documents the neurobiological overlap of obesity and SUD (Volkow, Wang, Tomasi, & Baler, 2013), which

Running Head: CVD Death in persons with Substance Use and Severe Mental Disorders

suggests that obesity may contribute to the discovered SUD / CVD relation. Medi-Cal claims data contain no information on body mass index or other obesity measures. However, to the extent that obesity precedes diabetes, myocardial infarction, or peripheral vascular disease, inclusion of the Charlson co-morbidity score in our hazard analysis controls for such obesity-related morbidities.

Our research provides a first step in describing the contribution of co-occurring SUD and SMI to the exacerbation of CVD and diabetes. In future work we hope to identify specific causal mechanisms by which SUD may increase CVD risk. One hypothesized pathway involves the receipt of fragmented or uncoordinated health care especially among persons with co-morbid SMI/SUD. Failure to receive integrated care may impede early diagnosis and treatment of CVD. Untreated SUD among persons with SMI may also reduce adherence to medications to treat chronic disease and act as a barrier to seeking preventive care (American Pharmacists Association, 2013). An ideal dataset would contain longitudinal information on incident SUD and its duration over the life course, as well as data on CVD morbidity and health care utilization. We know of no such dataset. As an alternative, we used Medicaid data to estimate CVD morbidity at baseline (with the Charlson index) as well as presence of SUD. Future linkage of health care claims to morbidity and mortality information, such as that described in this manuscript, will permit further identification of the onset and duration of SUD, SMI and CVD.

Recently, the US Centers for Medicare and Medicaid Services (2014) redoubled efforts to coordinate care as a means to achieving the “Triple Aim” of improving quality, controlling costs, and enhancing population health. Newly developed models of health care delivery and financing for Medicaid programs, such as coordinated care organizations in Oregon and regional care collaborative organizations in Colorado, emphasize improved coordination of services and management of chronic disease for Medicaid patients with SMI (Oregon Health Authority, 2014;

Running Head: CVD Death in persons with Substance Use and Severe Mental Disorders

Colorado Department of Health Care Policy and Financing, 2014). Such delivery models recognize that SMI often co-occurs with SUD and various chronic physical illnesses. Improved management and streamlined delivery of health services could promote health of these Medicaid beneficiaries while also containing overall costs.

Our results support the continued integration of somatic and psychiatric care that involves general CVD (and diabetes) risk reduction efforts among persons with SMI. Additionally, SMI/SUD persons in particular may benefit from the Medicaid Health Home State Plan Option, authorized under the Patient Protection and Affordable Care Act. California, for instance, recently opened its Health Homes Program for Patients with Complex Needs (California Department of Health Care Services, 2015). This program focuses on the high-utilizing Medicaid group with multiple co-morbidities (including SUD) that account for a disproportionately high share of service use and costs. A combination of general integration of CVD risk reduction among SMI, along with the “high-risk” Health Home targeting approach among persons with SMI/SUD, has gained favor by the California Department of Health Care Services. Given that most persons with SMI receive specialty care under publicly funded health insurance programs (McAlpine & Mechanic, 2000), we encourage careful implementation and rigorous assessment of these dual approaches before determining their effectiveness at reducing morbidity and mortality among persons with SMI and SMI/SUD.

References

Alwan, A. (2011). *Global status report on noncommunicable diseases 2010*. The World Health Organization. Geneva. Available at: http://www.who.int/chp/ncd_global_status_report/en/ (Accessed on 3/12/14).

American Heart Association. (2007). Heart Disease and Stroke Statistics—2007 Update: A Report From the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2007, 115, e69-e171.

American Pharmacists Association (2013). Improving medication adherence in patients with severe mental illness. *Pharmacy Today*, 19, 69-80.

Breslow N.E., & Day, N.E. (1980). *Statistical methods in cancer research: Volume 1, The analysis of case-control studies*. 74 ed. Lyon, France: International Agency for Research on Cancer.

Brown, S., Inskip, H., & Barraclough, B. (2000). Causes of the excess mortality of schizophrenia. *Br J Psychiatry*, 177, 212-217.

Busch, A. B., Frank, R. G., Lehman, A. F., & Greenfield, S. F. (2006). Schizophrenia, co-occurring substance use disorders and quality of care: the differential effect of a managed behavioral health care carve-out. *Adm Policy Ment Health*, 33(3), 388-397.

California Department of Health Care Services. (2015). Health Homes Program. Available at:

Running Head: CVD Death in persons with Substance Use and Severe Mental Disorders

<http://www.dhcs.ca.gov/services/Pages/HealthHomesProgram.aspx> (Accessed on 1/13/16).

Colorado Department of Health Care Policy and Financing (DHCPF). (2014). Accountable Care Collaborative. Available at: <http://www.colorado.gov/cs/Satellite/HCPF/HCPF/1233759745246> (Accessed on 3/12/14).

Colton, C.W. & Manderscheid, R.W. (2006). Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states. *Prev Chronic Disease*, 3(2), 1-14.

Crystal, S., Akincigil, A., Bilder, S., & Walkup, J. T. (2007). Studying prescription drug use and outcomes with medicaid claims data: strengths, limitations, and strategies. *Med Care*, 45(10 Supl 2), S58-65.

Dickey, B., & Azeni, H. (1996). Persons with dual diagnoses of substance abuse and major mental illness: their excess costs of psychiatric care. *Am J Public Health*, 86(7), 973-977.

Frishman, W. H., Del Vecchio, A., Sanal, S., & Ismail, A. (2003). Cardiovascular manifestations of substance abuse: part 2: alcohol, amphetamines, heroin, cannabis, and caffeine. *Heart Dis*, 5(4), 253-271.

Gail, M. H., Graubard, B., Williamson, D. F., & Flegal, K. M. (2009). Comments on 'Choice of time scale and its effect on significance of predictors in longitudinal studies' by Michael J.

Pencina, Martin G. Larson and Ralph B. D'Agostino, *Statistics in Medicine* 2007; 26:1343-1359.

Stat Med, 28(8), 1315-1317.

Goff, D. C., Pandey, D. K., Chan, F. A., Ortiz, C., & Nichaman, M. Z. (2000). Congestive heart failure in the United States: is there more than meets the I(CD code)? The Corpus Christi Heart Project. *Arch Intern Med*, 160(2), 197-202.

Goff, D. C., Sullivan, L. M., McEvoy, J. P., Meyer, J. M., Nasrallah, H. A., Daumit, G. L., et al. (2005). A comparison of ten-year cardiac risk estimates in schizophrenia patients from the CATIE study and matched controls. *Schizophr Res*, 80(1), 45-53.

Grant, B. F., Stinson, F. S., Dawson, D. A., Chou, S. P., Dufour, M. C., Compton, W., et al. (2004). Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Arch Gen Psychiatry*, 61(8), 807-816.

Hernan, M. A., Hernandez-Diaz, S., & Robins, J. M. (2004). A structural approach to selection bias. *Epidemiology*, 15(5), 615-625.

Hollander, J.E., Hoffman, R.S. (1992). Cocaine-induced myocardial infarction: an analysis and review of the literature. *J Emerg Med*, 10, 169-177.

Jackson, C. T., Covell, N. H., Drake, R. E., & Essock, S. M. (2007). Relationship between diabetes and mortality among persons with co-occurring psychotic and substance use disorders. *Psychiatr Serv*, 58(2), 270-272.

Jollis, J. G., Ancukiewicz, M., DeLong, E. R., Pryor, D. B., Muhlbaier, L. H., & Mark, D. B. (1993). Discordance of databases designed for claims payment versus clinical information systems. Implications for outcomes research. *Ann Intern Med*, 119(8), 844-850.

Kalman, D., Morissette, S. B., & George, T. P. (2005). Co-morbidity of smoking in patients with psychiatric and substance use disorders. *Am J Addict*, 14(2), 106-123.

Kessler, R. C. (2004). The epidemiology of dual diagnosis. *Biol Psychiatry*, 56(10), 730-737.

Lasser, K., Boyd, J. W., Woolhandler, S., Himmelstein, D. U., McCormick, D., & Bor, D. H. (2000). Smoking and mental illness: A population-based prevalence study. *Jama*, 284(20), 2606-2610.

Leshner, A. I. (1999). Science-based views of drug addiction and its treatment. *Jama*, 282(14), 1314-1316.

McAlpine, D. D., & Mechanic, D. (2000). Utilization of specialty mental health care among persons with severe mental illness: the roles of demographics, need, insurance, and risk. *Health Serv Res*, 35(1 Pt 2), 277-292.

Mueser, K. T., Yarnold, P. R., Rosenberg, S. D., Swett, C., Jr., Miles, K. M., & Hill, D. (2000). Substance use disorder in hospitalized severely mentally ill psychiatric patients: prevalence, correlates, and subgroups. *Schizophr Bull*, 26(1), 179-192.

Nestor, J. R., & Knecht, J. G. (2007). On the efficacy of programmatic searching of medical claims for the occurrence of hospital admissions for coronary artery disease. *Dis Manag*, 10(5), 293-303.

Newcomer, J. W., & Haupt, D. W. (2006). The metabolic effects of antipsychotic medications. *Can J Psychiatry*, 51(8), 480-491.

Newcomer, J. W., & Hennekens, C. H. (2007). Severe mental illness and risk of cardiovascular disease. *Jama*, 298(15), 1794-1796.

Oregon Health Authority. (2014). Oregon's Health System Transformation Quarterly Progress Report 2013. Available at <http://www.oregon.gov/oha/Metrics/Documents/report-november-2013.pdf> (Accessed on 3/12/14).

Osborn, D. P., Levy, G., Nazareth, I., Petersen, I., Islam, A., & King, M. B. (2007). Relative risk of cardiovascular and cancer mortality in people with severe mental illness from the United Kingdom's General Practice Research Database. *Arch Gen Psychiatry*, 64(2), 242-249.

Ray, W. A., Chung, C. P., Murray, K. T., Hall, K., & Stein, C. M. (2009). Atypical antipsychotic drugs and the risk of sudden cardiac death. *N Engl J Med*, 360(3), 225-235.

Regier, D. A., Farmer, M. E., Rae, D. S., Locke, B. Z., Keith, S. J., Judd, L. L., et al. (1990). Comorbidity of mental disorders with alcohol and other drug abuse. Results from the

Running Head: CVD Death in persons with Substance Use and Severe Mental Disorders

Epidemiologic Catchment Area (ECA) Study. *Jama*, 264(19), 2511-2518.

Rosenthal, R. N., Nunes, E. V., & Le Fauve, C. E. (2012). Implications of epidemiological data for identifying persons with substance use and other mental disorders. *Am J Addict*, 21(2), 97-103.

Sundararajan, V., Henderson, T., Perry, C., Muggivan, A., Quan, H., & Ghali, W. A. (2004). New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. *J Clin Epidemiol*, 57(12), 1288-1294.

Thiebaut, A. C., & Benichou, J. (2004). Choice of time-scale in Cox's model analysis of epidemiologic cohort data: a simulation study. *Stat Med*, 23(24), 3803-3820.

US Centers for Medicare and Medicaid Services. (2014). The Institute for Healthcare Improvement Triple Aim Initiative. Available at:
<http://www.ihl.org/Engage/Initiatives/TripleAim/Pages/default.aspx> (Accessed on 3/12/14).

Wahlbeck, K., Westman, J., Nordentoft, M., Gissler, M., & Laursen, T. M. (2011). Outcomes of Nordic mental health systems: life expectancy of patients with mental disorders. *Br J Psychiatry*, 199(6), 453-458.

Woods, S. W. (2003). Chlorpromazine equivalent doses for the newer atypical antipsychotics. *J Clin Psychiatry*, 64(6), 663-667.

Running Head: CVD Death in persons with Substance Use and Severe Mental Disorders

Wilson, P. W., D'Agostino, R. B., Parise, H., Sullivan, L., & Meigs, J. B. (2005). Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. *Circulation*, 112(20), 3066-3072.

Table 1. Health and demographic characteristics of SMI clients enrolled in California's Medicaid program between 2002 and 2007 (n= 121,817 clients).

	n	% of total
Substance use disorder	29,438	24.2
Death before 2008 (any cause)	22,609	18.6
CVD death before 2008	5,328	4.4
Female	73,650	60.5
Age		
18-29 years	30,882	25.3
30-44 years	39,496	32.4
45 to 54 years	29,110	23.9
55 to 64 years	22,329	18.3
Charlson co-morbidity score at baseline		
0	73,026	60.0
1	20,333	16.7
2 through 5	21,336	17.5
6 through 10	6,573	5.4
>10	549	0.4
Race/ethnicity		
Non-Hispanic white	55,244	45.3
Non-Hispanic black	19,347	15.9
Hispanic	27,615	22.7
Asian	8,011	6.6
Other	11,600	9.5
Continuous Medi-Cal eligibility	91,501	75.1

Note: column percents may not sum to 100% due to rounding and non-exhaustive nature of categories.

Figure 1. Unadjusted survival plot of death due to cardiovascular disease for 121,817 persons with SMI, by co-occurring SUD status, 2002 to 2007. The black line shows persons with SMI and SUD, and the light gray line shows persons with SMI only.

Table 2. Cox proportional hazards model of **CVD death** among persons with SMI as a function of a co-occurring substance use disorder, comorbidity index at baseline, and other covariates.

Variable	Hazard Ratio	(95% CI)
Substance use disorder	1.24	(1.17 — 1.33)
Female	0.59	(0.56 — 0.63)
Charlson co-morbidity score at baseline	1.06	(1.05 — 1.07)
Atypical Antipsychotic Use		
1 st quartile (lowest, including no use)	ref.	
2 nd quartile	1.07	(0.98 — 1.16)
3 rd quartile	1.07	(0.98 — 1.17)
4 th quartile (highest)	1.20	(1.10 — 1.30)
Race/ethnicity		
Non-Hispanic white	ref.	
Non-Hispanic black	1.27	(1.18 — 1.37)
Hispanic	0.77	(0.71 — 0.85)
Asian	0.56	(0.49 — 0.63)
Other	1.07	(0.98 — 1.18)

χ^2 likelihood ratio for inclusion of covariates = 902.8, $p < .0001$.

Table 3. Cox proportional hazards model of **CVD or diabetes death** among persons with SMI as a function of a co-occurring substance use disorder, comorbidity index at baseline, and other covariates.

Variable	Hazard Ratio	(95% CI)
Substance use disorder	1.17	(1.11 — 1.25)
Female	0.61	(0.58 — 0.65)
Charlson co-morbidity score at baseline	1.09	(1.07 — 1.10)
Atypical Antipsychotic Use		
1 st quartile (lowest, including no use)	ref.	
2 nd quartile	1.03	(0.94 — 1.11)
3 rd quartile	1.02	(0.94 — 1.11)
4 th quartile (highest)	1.12	(1.04 — 1.21)
Race/ethnicity		
Non-Hispanic white	ref.	
Non-Hispanic black	1.29	(1.20 — 1.38)
Hispanic	0.87	(0.80 — 0.94)
Asian	0.59	(0.53 — 0.67)
Other	1.11	(1.02 — 1.21)

χ^2 likelihood ratio for inclusion of covariates = 1049.1, $p < .0001$.

Appendix: Sensitivity Analysis of Confounding due to Smoking

California collects Medi-Cal claims information chiefly for accounting purposes and processing of reimbursements to providers. Health data on smoking prevalence among persons with SMI are often missing. Such missing data may therefore underestimate the “true” prevalence of smoking in our population. Lack of information on smoking may bias the estimate of the relation between SUD and CVD mortality among persons with SMI.

To address potential confounding bias due to smoking, we used the “confounding risk ratio” approach recommended by Breslow and Day (27) and implemented previously by researchers that examined persons with SMI (6). This approach estimates the extent to which an unmeasured confounder could affect results. The confounding risk ratio equation appears below:

$$\omega = \frac{(RR_c Q_1 + (1 - Q_1))}{RR_c Q_0 + (1 - Q_0)} \quad (1)$$

Where:

RR_c = Risk ratio for confounder

Q_1 = confounder prevalence among user group

Q_0 = confounder prevalence among nonuser group

We estimated each of these values based on previous literature. In the equation above, RR_c reflects the relative risk of CVD death due to smoking. Several reports find that smokers show a two-fold elevated risk of CVD death as compared with non-smokers. Q_1 represents persons with both SMI and SUD. The maximum estimated prevalence of smoking among this group is 70% (29). Among Q_0 , the persons with SMI but no SUD, the maximum estimated prevalence of smoking is 58% (28). Substitution of these values into the equation yields the following result:

$$\begin{aligned} \omega &= \frac{(2.0(0.70) + (1 - 0.70))}{2.0(0.58) + (1 - 0.58)} \\ &= 1.075 \end{aligned}$$

The confounding risk ratio of 1.075 suggests that the observed estimate between SUD and CVD death exceeds the relative hazard by 7.5% as compared to what would be calculated had we fully controlled for smoking. We refer the reader to the main text which describes why this value likely overestimates actual confounding by smoking.