Causes of death and comparative mortality in Texas public mental health clients, 2006-2008

Robert J. Reynolds, MPH¹ Emilie A. Becker, M.D.² Alan B. Shafer, PhD³

¹University of Texas Health Science Center at Houston ²Corresponding author Texas Medicaid Chip Mental Health Director Texas Health and Human Services Commission Austin, Texas ³Texas Department of State Health Services

ABSTRACT

Seriously mentally ill patients are known to have rates of mortality much greater than those of the general population. Prior research in Texas has shown inpatient Public Mental Health Clients (PMHCs) treated in in-patient settings were subject to greatly increased mortality, but little is known about the mortality of PMHCs in an outpatient setting in Texas.

For this study outpatient service records for PMHCs treated in Texas were combined with death data from the Texas Department of State Health Services for 2006-2008. Frequencies of causes of death, age-adjusted death rates, standardized mortality ratios, and life expectancies were calculated from these data.

The most frequent causes of death were external causes, followed by circulatory disease, and then neoplasms. Examination of the outcomes suggests that substance abuse plays a major role in the mortality of PMHCs in Texas in the form of drug overdoses, tobacco-related cancers, and alcoholic liver disease. Prevention efforts should therefore aim at integrating mental health services, substance abuse services, and careful medical and pharmacological monitoring, including medication monitoring to prevent suicides and accidental overdoses.

KEYWORDS

Mortality, Texas, public mental health, psychiatrically ill, mentally ill

INTRODUCTION

A consistent consequence of mental illness is increased mortality. A number of studies have established that people with serious mental illness die (on average) at younger ages than the general population.¹⁻³ Though the magnitude of excess risk of deaths due to specific causes have varied by age group, time, and place, seriously mentally ill patients have remained at greater risk of death from a variety of causes. Recent research indicates that this may be especially true for public mental health clients (PMHCs) – the seriously mentally ill treated at public mental health facilities.¹⁻³

Comparative mortality of PMHCs in eight US states between 1997 and 2000 was examined in a recent study conducted by the National Association of State Mental Health Program Directors using age-adjusted death rates (AADR) and standardized mortality ratios (SMRs).⁴ The AADR ranged from a low of 979.4 deaths per 100,000 person-years to a high of 3,385 deaths per 100,000 person-years, and were in every case substantially greater than the AADRs for the general populations in the corresponding states and years.³ Similarly, the all-cause standardized mortality ratios (SMR) were elevated in every state and every year, with point estimates falling between 1.2 and 4.9.³

Mortality risk was particularly high for patients in Texas, where in 1997 and 1998 the AADR and SMR for PMHC inpatients were the largest in the study.³ However, the 1999 Texas AADR was the absolute *smallest* of any in the study; in fact, the SMR dropped more than three-fold between 1998 and 1999.³ The reason for the abrupt reduction has remained unexplained; no subsequent research has been published using data from Texas, and no studies to date have examined the mortality of PMHCs treated in outpatient facilities at the state level for Texas.

Here we examine the mortality experience of PMHC in Texas using outpatient data for the years 2006 to 2008. The frequencies of major causes of death in the population are examined and PMHCs were compared to the Texas general population using AADRs, SMRs, and life expectancies (LEs).

METHODS

Mortality rates from all patients treated in Department of State Health Services (DSHS)-funded outpatient mental health clinics were compared to mortality rates from the Centers for Disease Control and Prevention (CDC) for the Texas general population for the individual years 2006, 2007, and 2008.

Mental health services are offered by the Texas DSHS through a network of 38 Local Mental Health Authorities (LMHAs), which serve the indigent or otherwise uninsured population in the 254 counties of Texas.⁵ Service records were obtained for all patients aged 15 years and older treated at these clinics between January 1, 2006 and December 31, 2008. This age range is required for formal diagnosis, and is consistent with recent work on life expectancy in the mentally ill.^{1,6,7}

The date of entry into the study was either January 1, 2006 or the date of first treatment in the period, whichever came latest. Patients were followed in the study until death or December 31, 2008, whichever came sooner, but need not have been treated by the LMHAs in the year of death. Patients qualified as a PMHC in the cohort by having at least one visit at an LMHA clinic in the study period.

To identify the PMHCs who died during the study period, the LMHA patient service records were matched with DSHS vital records from the Texas Center for Vital Statistics. Patients were matched on first letter of first name, the first four characters of the last name, date of birth, gender, and social security number. Any patients without a matching mortality record were assumed to have survived to the close of the study on December 31, 2008 and their follow-up was terminated on that date. This approach is considered to be conservative because any PMHCs who died outside of Texas will not be captured in the dataset, thus underestimating the true mortality of PMHCs in Texas. As such the results here may be considered as a best estimate, but possibly an underestimate. We used the primary cause of death from the vital records to classify deaths into causal categories.

AADRs for PMHCs were calculated using the Year 2000 US population distribution from the CDC as the standard population.⁸ This distribution is the fraction of the US

population that was in each age stratum in the year 2000. We chose the Year 2000 US population as the reference because it is widely used in contemporary epidemiological research and provides an equal basis for comparison with the AADR previously reported for Texas and elsewhere.^{3,7}

General population mortality rates for the State of Texas were downloaded from the Wide-Ranging Online Data for Epidemiologic Research (WONDER) database provided by the CDC.⁹ This database has all-cause and causespecific mortality rates for US states, territories, and public health regions, and allows for stratification on gender, race, ethnicity, and age. All statistical analyses were conducted using SAS V9.2 for Windows¹⁰ and Microsoft Excel 2007.¹¹

The first step in calculating AADRs for each year was to compute age-specific mortality rates by dividing the number of deaths observed in age- and period-specific categories by the person-years of life lived in those categories.^{8,12} The age-specific mortality rates were multiplied by a corresponding age-specific weight, which was the proportion of the standard population represented by that age category. Finally, the weighted age-specific mortality rates were summed within each year and multiplied by 100,000, yielding the AADR per 100,000 person-years for each year.^{8,12}

PMHCs were also compared with the Texas general population using SMRs. In order to be considered standardized, mortality ratios must be adjusted for age at a minimum, and when possible, are typically adjusted for other covariates of interest, such as gender, race, and location (e.g. nation or state).¹² Here we computed SMRs based on age, gender, race, and calendar year. Expected numbers of deaths are calculated by multiplying the strata-specific general population mortality rates by the observed person-years for those respective strata in the study population. The SMR is the ratio of the observed number of deaths to the expected. Here an SMR greater than 1.0 represents increased mortality risk for the PMHCs, and an SMR less than 1.0 represents decreased mortality risk for the PMHCs. Confidence intervals around the SMR point estimates were calculated by assuming that the observed count of deaths derived from a Poisson distribution.12

Life expectancy is defined as the average number of remaining years of life at a given age. Period life expectancies for both the Texas general population and the PMHCs were computed at various decennial ages in each study calendar year using a composite set of mortality rates taken to be a weighted average of the race-specific mortality rates in each calendar year. The mortality rates in the Texas general population were identically weighted so that both groups were standardized to the racial distribution of the study population in each year.

After preliminary review by the Institutional Review Board (IRB) of DSHS, the study protocol was ruled as exempt from full review and approved.

RESULTS

The final dataset contained information on 248,549 patients, who contributed 424,000 person-years of observation time over the three years of study (2006-2008). The mean age of the study subjects at cohort entry was 36.7 years (sd=14.6), the mean age of survivors at the end of the study period (December 31, 2008) was 38.1 years (sd=14.5 years), and the mean age at death for all three years was 49.5 (sd=13.7) years. The cohort was 44.6% male, the majority of whom were white non-Hispanics. Table 1 provides the full details of the demographic and actuarial characteristics of the study cohort.

The study included 4,486 deaths of PMHC patients. Table 2 gives the frequencies of the most common causes of death for PMHCs, and also lists the corresponding frequencies for the general population. The most common categories of death were external causes (unintentional and intentional injuries) (30.0%), circulatory diseases (25.1%), and neoplasms (12.6%). Digestive and respiratory diseases were the largest remaining categories with 5.2% and 6.6% of the total deaths respectively. The single most common sub-

category was accidental deaths (within the larger category of external causes of death), which alone accounted for 18.2% of the overall PMHC deaths. Ischemic heart disease (a subordinate of circulatory disease) was the second most frequent sub-category and accounted for 12.4% of the deaths, followed by suicide (sub-category of external causes) at 8.6%.

Figure 1 shows the all-cause AADR for the Texas general population and for PMHCs. AADR were greater for PMHCs in each of the three years and at a maximum in 2006. The AADR changed little between 2006 and 2007 dropping by only 34.7 deaths per 100,000 person-years, but then declined markedly in 2008, decreasing by 197.4 deaths per 100,000 person-years, nearly 15%. The overall three-year AADR was 1233.7 deaths per 100,000 person-years, while the AADR for the Texas general population was 777.9 deaths per 100,000 person-years over the same period.

Figure 2 displays the SMRs for the most common causes of death and for all causes of death combined in each of the three years. The all-cause SMR was 3.11 in 2006, was 3.00 in 2007, and then declined to 2.68 in 2008. The SMR for cancer and circulatory diseases had similar patterns: nearly uniform risk in the first two years and a decline in risk in the third.

The SMR for external causes of death as a group was the highest of any during the study period, though it declined from 6.93 in 2006 to 5.28 in 2007, and finally to 4.82 in 2008. The SMRs for digestive and respiratory diseases showed relative stability over the period with moderate variation.

Table 1. Demographic and	actuarial characte	eristics of the stud	luqoq v	ation bv	selection v	vear.
·			/			

Characteristic	2006	2007	2008	Total
Patients entering, n (% of total)	104,800 (42.2)	60,465 (24.3)	83,284 (35.3)	248,549 (100.0)
Person-years, n (% of total)	81,735 (19.3)	135,644 (32.0)	206,621 (48.7)	424,000 (100.0)
Deaths, n (% of total)	1,052 (23.5)	1,553 (34.6)	1,881 (41.9)	4,486 (100.0)
Males, n (% in period)	45,322 (43.3)	27,693 (45.8)	38,019 (45.7)	111,034 (44.6)
Race, n (% in period)				
Black, non-Hispanic	20,654 (19.7)	13,093 (21.7)	20,402 (24.5)	54,149 (21.8)
Hispanic black or white	26,419 (25.2)	15,264 (25.2)	20,032 (24.1)	61,715 (24.8)
White, non-Hispanic	54,541 (52.0)	30,236 (50.0)	40,065 (48.1)	124,842 (50.2)
Other	3,186 (3.0)	1,872 (3.1)	2,785 (3.3)	7,843 (3.2)
Substance abuse, n (% in period)	58,568 (55.9)	33,443 (55.3)	37,621 (45.2)	129,632 (52.2)
Age, mean (sd)				
At study entry	39.0 (14.6)	34.5 (14.1)	35.3 (14.1)	36.7 (14.4)
At death	49.0 (13.5)	49.7 (13.8)	49.7 (13.7)	49.5 (13.7)
At end of study (survivors)*				38.1 (14.5)
*Age for survivors calculated at end of study only				

	PMHC Population				Texas General Population*			
Cause of Death (ICD-10)	Females	Males	Total	% Total	Females	Males	Total	
All causes (Aoo-U89)	2,194	2,298	4,486	100.0	233,254	238,653	471,907	
Neoplasms (Coo-D48)	322	244	566	12.6	50,595	57,163	107,758	
Respiratory	117	83	200	4.5	12,425	17,244	29,669	
Digestive	61	78	139	3.1	11,080	15,412	26,492	
Breast	46	3	49	1.1	7,823	70	7,893	
Female reproductive	38	0	38	0.8	5,206	0	5,206	
Diseases of the circulatory	578	548	1126	25.1	78,624	75,9 ⁸ 5	154,609	
Ischemic heart disease	274	284	558	12.4	34,049	41,857	75,906	
Hypertensive disease	91	71	162	3.6	6,245	4,779	11,024	
Cerebrovascular	62	51	113	2.5	17,057	11,573	28,630	
Diseases of the respiratory	166	128	294	6.6	22,505	21,264	43,769	
system (Joo-J99)	0	6				6		
	89	56	145	3.2	10,771	10,416	21,187	
Pneumonia	25	25	50	1.1	5,467	4,462	9,929	
Emphysema	10	12	22	0.5	1,103	1,333	2,436	
Diseases of the digestive system (Koo-K93)	99	133	232	5.2	8,708	10,329	19,037	
Cirrhosis	29	38	67	1.5	1,875	2,940	4,815	
Alcoholic liver disease	15	34	49	1.1	123	2,095	2,218	
Hepatic failure NOS	10	6	16	0.4	359	495	854	
External causes (Vo1-Y98)	565	813	1346	30.0	11,811	26,996	38,807	
Accidents	353	477	816	18.2	8,528	16,400	24,928	
Suicide	149	240	388	8.6	1,459	5,766	7,225	
Assault	31	68	93	2.1	839	3,203	4,042	
Undetermined intent	27	22	49	1.1	164	244	408	
All other causes	333	331	664	14.8	61,011	46,916	107,927	

Table 2. Frequency of select causes of death for PMHCs and the Texas general population, 2006-2008.

*Texas general population from CDC Wonder database

Figure 1. Age-adjusted death rates for Texas PMHCs and the Texas general population, 2006-2008



Life expectancies are presented in Table 3. Just as in the general population, males had lower life expectancies

than women among PMHCs. The greatest absolute reductions in life expectancy in each year were found in the youngest ages and among males. Life expectancies for female PMHCs improved in each age stratum in each calendar year while those of males were relatively stable. General population life expectancies were essentially unchanged for both men and women over the study period. As a result, differences in life expectancies between PMHCs and the general population decreased over time.

DISCUSSION

Strengths and Limitations

The main strength of this study is that it draws upon a large population of PMHCs over three years. This large dataset provides precise and reliable estimates of mortality in a high-risk population and it allows us to provide cause-specific SMRs. These in turn allow us to





Table 3. Life expectancies (additional remaining ye	ars)
for PMHCs and the Texas general population.	

		Females			Males		
Year	Age	PMHCs	TX GP	Diff*	PMHCs	TX GP	Diff*
2006	20	48.6	60.2	-11.6	40.4	55.6	-15.2
	30	40.8	50.6	-9.8	34.4	46.3	-11.9
	40	33.3	41.1	-7.8	28.6	37.2	-8.6
	50	26.7	32.1	-5.4	23.7	28.7	-5.0
	60	20.3	23.7	-3.4	19.1	21.0	-1.9
2007	20	50.2	60.3	-10.1	41.8	55.4	-13.6
	30	41.6	50.6	-9.0	34.3	46.2	-11.9
	40	33.9	41.2	-7.3	27.3	37.1	-9.8
	50	27.3	32.1	-4.8	21.4	29.6	-8.2
	60	21.3	23.7	-2.4	16.6	21.0	-4.4
2008	20	53.2	59.8	-6.6	44.6	55.2	-10.6
	30	44.5	50.1	-5.6	36.4	46.0	-9.6
	40	36.5	40.7	-4.2	29.2	36.9	-7.7
	50	29.4	31.6	-2.2	22.7	28.3	-5.6
	60	23.0	23.1	-0.1	17.0	20.6	-3.6

*Difference in LEs calculated by subtracting TX general population from PMHCs

explore the source of mortality risk experienced by PMHCs in Texas in a detailed way.

However, a limitation of the study is the inability to stratify on psychiatric or substance abuse diagnoses. While few question that the DSHS patients are correctly diagnosed as having serious mental illness, the specific diagnoses assigned may only loosely fit the underlying disorders. The available indicator for substance abuse from the patient service record lacks any detail on the type of substance abuse, is not regularly updated, and is therefore considered similarly unreliable. The inability to stratify on mental health and substance abuse diagnoses means that this study is also limited in its ability to generalize beyond the Texas PMHC population to anything more than PMHCs in general. Nevertheless, in spite of these limitations the study offers valuable insight into the mortality experience of outpatient PMHCs in Texas.

Public Health Implications and Prevention Strategies

The single greatest risk of death for PMHCs in this study was from external causes, which was both the most frequent cause of death for PMHCs listed in Table 2 and the category with the greatest SMR (Figure 2). Deaths from external causes were responsible for just over 30% of the total deaths in the study, and the three-year SMRs show that PMHCs experienced between four and seven times the number of deaths from external causes as would be expected in the general Texas population. The frequency of death for the general population in Table 2 reflects this as well: only 8.2% of the Texas general population died of external causes. Far more frequent among the general population is death due to chronic diseases such as cancer (22.8%) and circulatory disease (32.8%). Such a tradeoff is indicative of the competing risks at work in the PMHC population, which dies at systematically younger ages of external causes, instead of growing old enough to die of chronic disease.

Accidental overdose accounted for approximately 60% of the 816 accidents in the study population (not shown in Table 2), which is consistent with a study of the mentally ill in Massachusetts, where there was a significant excess of accidental overdose on psychotropic medication.² This finding is also in agreement with the broader trend of rising prescription drug overdoses throughout the US in recent years.¹⁸ However, a large portion of the accidental overdoses in these data may have been intentional; in the absence of a suicide note or clinically documented suicidal ideation, drug overdoses are likely to be ruled as accidental by County Medical Examiners (Reade Quintin, MD, personal communication, November 2011) Therefore, depending on the number of misclassified

deaths, suicide, rather than accidents, may actually be the most frequent cause of death among PMHCs.

Current and lifetime smoking rates have been demonstrated to be substantially higher among the mentally ill compared to the general population.^{19, 20} Though data concerning smoking status were not available in the current study, a number of commonly tobacco-related diseases contributed substantially to the causes of death. Diseases commonly associated with tobacco use, such as respiratory neoplasms, certain circulatory diseases, and certain respiratory diseases collectively accounted for almost 25% of the recorded deaths for PMHCs.

The frequencies of death by chronic diseases related to alcohol abuse, such as cirrhosis, alcoholic liver disease, and general liver failure were higher among the PMHCs than in the general population (Table 2), and PMHCs also experienced increased mortality risk due to digestive diseases as expressed by the SMRs in Figure 1. This may be an indicator that alcoholism is also an issue in the PMHC population, and when considered with the frequency of tobacco-related disease, suggests that those who do not die of a drug overdose at a young age may live on only to develop chronic disease related to substance abuse later in life.

The life expectancies in Table 3 show the effect of these mortality risks on the PMHC population in Texas. In each year and at every age the mean number of remaining years is lower for these patients than for the general population. This is reflective of the burden of early mortality due to external causes of death, which take a disproportionate toll on young people, bringing the life expectancy downward. Such differences in life expectancy, when summed over hundreds of thousands of PMHCs represent enormous sums of potential life lost.

In light of the role of drugs, alcohol, and tobacco as major contributors to the mortality of the seriously mentally ill, an obvious mortality reduction strategy becomes the integration of mental health services, substance abuse services (including tobacco cessation), prescription monitoring, and general medical management. This may be particularly relevant in the context of outpatient PMHCs, who, in Texas as elsewhere, often do not have the benefit of coordinated care. Coordinating these services would allow a clinical team to work together to address all of the top causes of death in the PMHC population through adequate mental health treatment, medication monitoring and reconciliation, substance abuse treatment (including tobacco cessation), and overall medical management. A failure in any of these areas could render even the best efforts moot for the others.

CONCLUSIONS

Abuse of prescription drugs, illegal drugs, alcohol and tobacco appear to be prime contributors to the premature mortality of the seriously mentally ill and the PMHCs in Texas in particular. To meet the goal of reducing mortality among PMHCs the mental health and public health systems should focus on prevention and treatment of substance abuse, inclusive of prescription and nonprescription drugs, alcohol, and tobacco. Combining these services with appropriate mental health treatment and medical management could further reduce mortality by providing a holistic approach to treating and managing PMHCs. Without such integration existing treatment systems will continue to struggle to effectively treat PMHCs in the community.

ACKNOWLEDGEMENTS

The authors wish to acknowledge the dedicated staff of the Texas LMHAs, who provide psychiatric care for seriously mentally ill patients across the state.

This work was made possible by the Texas Department of State Health Services, Mental Health and Substance Abuse Division, and through the voluntary efforts of the authors. No grant funding was used in connection with this study.

REFERENCES

- Chang C-K, Hayes RD, Perera G, Broadbent MTM, Fernandes AC, Lee WE, et al. Life expectancy at birth for people with serious mental illness and other major disorders from a secondary mental health care case register in London. PLoS ONE. 2011;6(5):e19590. DOI: 10.1371/journal.pone.0019590. PubMed PMID: 21611123; PubMed Central PMCID: PMC3097201.
- Dembling BP, Chen DT, Vachon L. Life expectancy and causes of death in a population treated for serious mental illness. Psychiatr Serv. 1999;50(8):1036-42. PubMed PMID: 10445651.
- Colton CW, Manderscheid RW. Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states. Prev Chronic Dis. 2006;3(2):A42. PubMed PMID: <u>16539783</u>.
- Lutterman T, Ganju V, Schacht L, Shaw R, Monihan K. Sixteen State Study on Mental Health Performance Measures. 2003; DHHS Publication No. (SMA) 03-3835.
- Texas Department of State Health Services. List of Local Mental Health Authorities (LMHAs) - Mental Health and Substance Abuse (MHSA) Division. Available at: http://www.dshs.state.tx.us/mhsa/lmha-list/. Accessed May 15, 2013.
- American Psychiatric Association, American Psychiatric Association. Task Force on DSM-IV. Diagnostic and statistical manual of mental disorders: DSM-IV-TR. 4th, text revision ed. Washington, DC: American Psychiatric Association; 2000.
- Reynolds RJ, Shafer AB, Becker EA. Mortality of public mental health clients treated at the Local Mental Health Authorities of Texas. Texas Public Health Journal 2012;64(2).

- 8. Klein RJ, Schoenborn CA. Age adjustment using the 2000 projected U.S. population. Healthy People Statistical Notes, no. 20. 2001; Hyattsville, Maryland: National Center for Health Statistics.
- Centers for Disease Control and Prevention, National Center for Health Statistics. Compressed Mortality File 1999-2008. CDC WONDER On-line Database, compiled from Compressed Mortality File 1999-2008 Series 20 No. 2M, 2010. Available at: http://wonder.cdc.gov/cmf-icd10.html. Accessed May 15, 2013.
- 10. SAS Corporation. The SAS System for Windows V9.2.
- 11. Microsoft Corporation. Microsoft Access 2007.
- 12. Rosner B. Fundamentals of Biostatistics. 7th ed. Boston: Brooks/Cole, Cengage Learning; 2011.
- Greig RL, Baker A, Lewin TJ, Webster RA, Carr VJ. Long-term follow-up of people with co-existing psychiatric and substance use disorders: patterns of use and outcomes. Drug Alcohol Rev. 2006;25(3):249-58. DOI: 10.1080/09595230600657741. PubMed PMID: 16753649.
- Dumais A, Lesage AD, Alda M, Rouleau G, Dumont M, Chawky N, et al. Risk factors for suicide completion in major depression: a case-control study of impulsive and aggressive behaviors in men. Am J Psychiatry. 2005;162(11):2116-24. DOI: <u>10.1176/appi.ajp.162.11.2116</u>. PubMed PMID: <u>16263852</u>.
- Dickey B, Dembling B, Azeni H, Normand S-LT. Externally caused deaths for adults with substance use and mental disorders. J Behav Health Serv Res. 2004;31(1):75-85. PubMed PMID: <u>14722482</u>.
- Eldridge D, Dawber N, Gray R. A well-being support program for patients with severe mental illness: a service evaluation. BMC Psychiatry. 2011;11:46. DOI: 10.1186/1471-244X-11-46. PubMed PMID: 21418627; PubMed Central PMCID: PMC3070634.
- 17. Santhouse A, Holloway F. Physical Health of Patients in Continuing Care. Adv Psychiatr Treat. 1999;5(6):455-462. DOI: <u>10.1192/apt.5.6.455</u>.
- Vital signs: overdoses of prescription opioid pain relievers---United States, 1999--2008. MMWR Morb Mortal Wkly Rep. 2011;60(43):1487-92. PubMed PMID: 22048730.
- Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH. Smoking and mental illness: A population-based prevalence study. JAMA. 2000;284(20):2606-10. PubMed PMID: <u>11086367</u>.
- de Leon J, Diaz FJ. A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. Schizophr Res. 2005;76(2-3):135-57. DOI: <u>10.1016/j.schres.2005.02.010</u>. PubMed PMID: <u>15949648</u>.

How to cite this article

Reynolds RJ, Becker EA, Shafer AB. Causes of death and comparative mortality in Texas public mental health clients, 2006-2008. Ment Health Clin [Internet]. 2013;3(1):28-34. Available from: <u>http://dx.doi.org/10.9740/mhc.n161217</u>