

**The association between total daily dose of chronic opioids and falls in older adults**

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## **Abstract**

Opioids pose a risk of medication-related adverse side effects, including falls. The aim of this report was to explore the association between total daily dose of opioids (daily Morphine Milligram Equivalents or MME) and other health related features and fall status among older patients ( $\geq 65$  years old). The data was received from UNC-CH Eshelman School of Pharmacy research group. Data visualization and analysis including t-test, Chi-Squared test, and logistic regression were implemented to explore the relationships. Features including Age, Gender, and health condition indicators (Psychiatric, COPD, Cancer) have statistically significant impact on the fall status. In particular, patients with older age and health conditions are more likely to have a fall. Female patients are more likely to fall than male patients. The MME distributions between not-fall and fall groups were not significantly different. The fall rate (the percentage of people in a group that had a fall) binned as a function of  $\log_{10}$  (MME) showed a v - shape trend, a decrease in the low MME region and an increase in the high MME region.

## **Introduction**

Falls are the leading cause of fatal and nonfatal injuries in older adults.<sup>1</sup> Drug use is one of the most important factors to lead to falls and fall-related injuries. Opioids are a class of drugs, which are risk medications related to falls.

The class of medication called opioid, includes methadone, hydromorphone, oxycodone and so on. These opioids, which have different relative strength, are converted to Morphine Milligram Equivalent (MME), which is the value of milligrams of morphine an opioid dose is equal to. Generally, total daily MME is used as total daily dose of opioids.

This is a retrospective cohort study. In this study, patients took at least one of the opioids for at least 6 weeks. We used several statistical methods to explore the association between the chance of fall and the features based on the data.

## **Data Description**

The data were obtained from electronic health records starting in September 2018. They were collected on older adult patients in four primary care outpatient clinics in the UNC Health Care System. The dataset contains 12 features measured on 762 subjects. After excluding the records with missing value, we received a dataset with 590 observations. Among the 12 features, MME

and Age are continuous numeric data and the other features are categorical. Among the categorical features, patient race has 6 types, the remaining 9 features are binary. A brief summary of the dataset including data type and basic statistics is listed in Table 1.

Table 1. A brief summary of the features in the dataset

Features	Data type	Range	Mean	Std.
MME	Continuous	0.542 - 817.992	26.557	52.226
Age	Continuous	65 - 99	75.063	7.295
Acute Pain Indicator	Categorical	0/1	0.980	NA
Benzo Indicator	Categorical	0/1	0.185	NA
Cancer Indicator	Categorical	0/1	0.275	NA
COPD Indicator	Categorical	0/1	0.186	NA
CVD Indicator	Categorical	0/1	0.956	NA
Fall Status	Categorical	0/1	0.351	NA
Gender	Categorical	F/M	0.647 (F)	NA
Psychiatric Indicator	Categorical	0/1	0.578	NA
Sleep Apnea Indicator	Categorical	0/1	0.190	NA
Patient Race	Categorical	1/2/3/4/5/6	0.007/0.005/0.131 /0.002/0.002/0.854	NA

Note: (a) Patient race: 1 - American Indian or Alaska Native; 2 - Asian; 3 - Black or African American; 4 - Other Race; 5 - Patient Refused; 6 - White or Caucasian

(b) For patient race, the means were the proportions of each category.

(c) For the binary features (0/1), the means were the proportions of category 1.

## Results

### 1. Univariate analysis

#### 1.1 MME distribution

Distribution is a function that summarize a population of a sample space. The two plots on the left in Figure 1 were standard histogram, on the right were the smoothed version of called kernel density estimation. The two plots on the top revealed that the MME distribution was skewed to the

left. The log transformation is widely used to address skewed data<sup>2</sup>. Typically, most data analytic methods work well when the input data is normally distributed. Input data that is not approximately normally distributed will result an effective statistical analysis. After deploying log transformation with 10 as the base,  $\log_{10}(\text{MME})$  is approximately normally distributed, as shown in Figure 1 at the bottom. Hence, in the following analysis,  $\log_{10}(\text{MME})$  was used, instead of the original MME data.

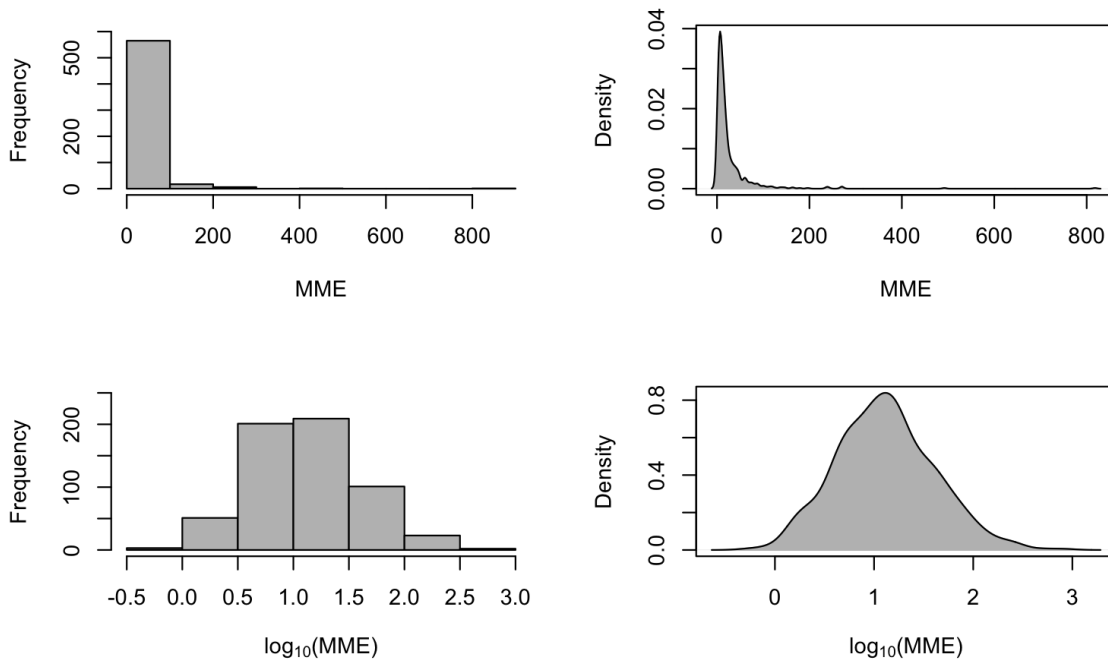


Figure 1. Histogram and Kernel Density estimation of MME and  $\log_{10}(\text{MME})$

*This shows log transformation will lead to effective statistical analysis.*

### 1.2 Age distribution

The distribution of patient age was shown in Figure 2. The count become smaller with increasing age, which makes sense for the population of older adults. There is no need to transform this variable.

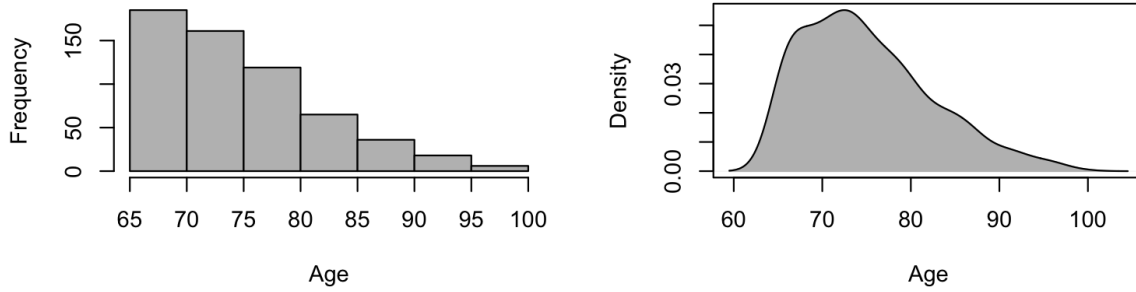


Figure 2. Histogram and Kernel Density estimation of Age

*There is no need to do transformation for age.*

### 1.3 $\log_{10}(\text{MME})$ distribution in groups of not-fall and fall

In this section, the data were split into the not-fall and the fall groups based on the record of fall status. In Figure 3, The  $\log_{10}(\text{MME})$  distributions were estimated for these two groups. Box plots visually show the distribution of numerical data and skewness by mean of displaying the data quantiles and medians. We created the boxplot for each group. As shown in Figure 3, the medians (the bold line in the middle of box), the 25 percentiles (the bottom line of the box) and 75 percentiles (the top line of the box) are close between the not-fall and fall groups by visual check. A t-test of  $\log_{10}(\text{MME})$  in these two groups returned a  $p$ -value of 0.76, much larger than 0.05. Hence, the distributions of  $\log_{10}(\text{MME})$  were similar between the not-fall and fall groups.

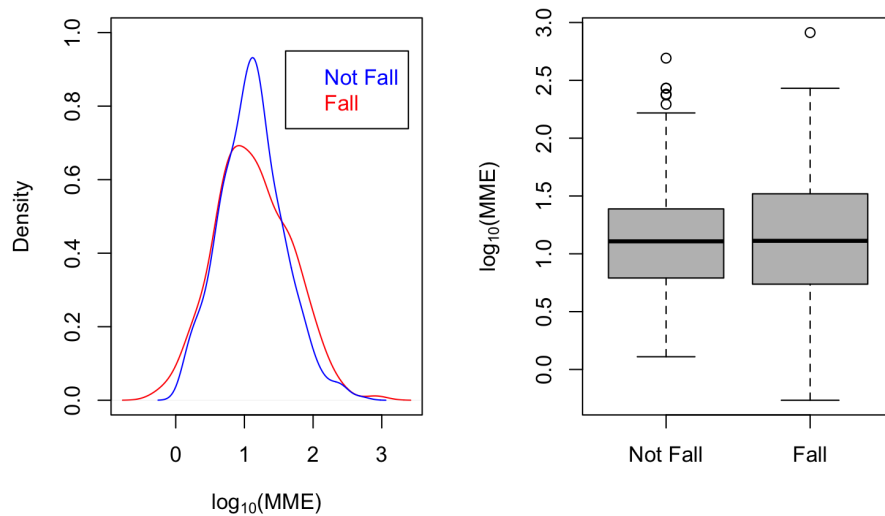


Figure 3. Kernel density estimation and boxplots of  $\log_{10}(\text{MME})$  in groups of not-fall and fall

*The distributions of  $\log_{10}(\text{MME})$  were similar between the not-fall and fall groups*

#### 1.4 Age distribution in groups of not-fall and fall

We examined the age distribution and boxplot of the not-fall and fall group. As shown in Figure 4 on the left, the age in fall group was slightly higher than that in the not-fall group by visual check. A t-test of age in these two groups returned a  $p$ -value of 0.065, which is close to the typical threshold of 0.05, indicating relatively significant differences in age distribution between not-fall and fall group.

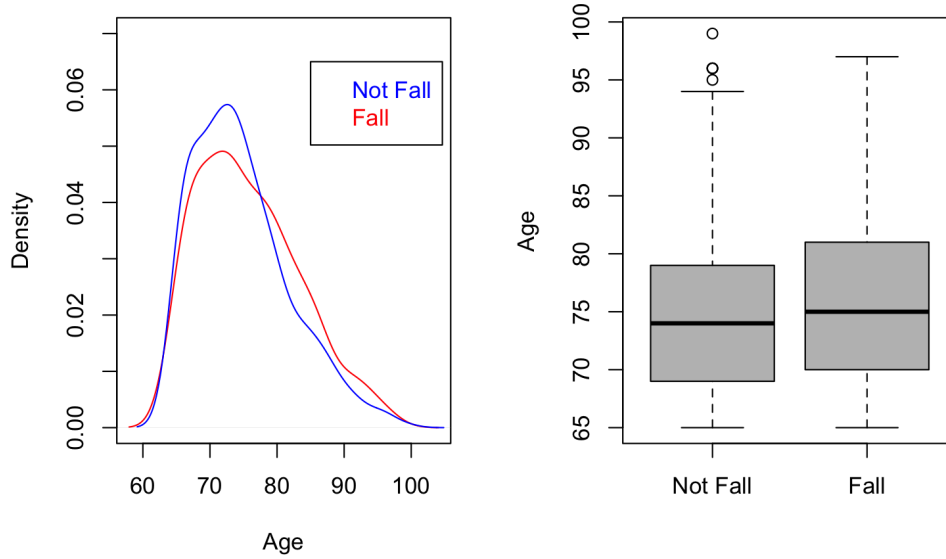


Figure 4. Age distribution and boxplot in groups of not-fall and fall

*The age in fall group was relatively higher than that in the not-fall group*

## 2. Bivariate analysis

In this section, bivariate analysis was implemented to explore the association between the fall status and the features.

### 2.1 Fall status and the continuous features ( $\log_{10}(\text{MME})$ and age)

To further explore the distributions, we made bar plots showing the fall rate (the percentage of people in the MME group that had a fall) for two continuous features -  $\log_{10}(\text{MME})$  and age. In Figure 5, we divided the sample into 10 equally distributed groups using percentile of MME and explored fall rate as a function of MME. It seems that in the lower MME groups (under 50 percentiles), the fall rate decreased with the increase of MME. On the other hand, in the higher MME groups, the fall rate increased with the increase of MME.

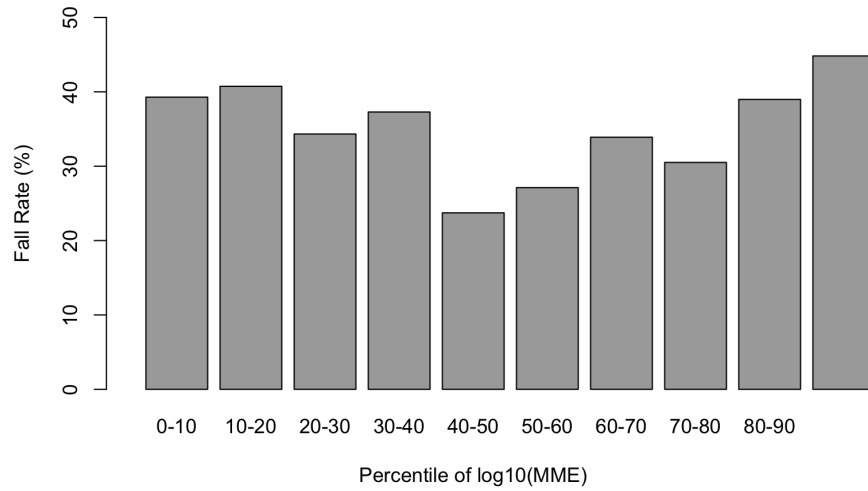


Figure 5. Plots of the fall rate binned as a function of  $\log_{10}(\text{MME})$

*In the lower MME groups (under 50 percentiles), the fall rate decreased with the increase of MME. In the higher MME groups, the fall rate increased with the increase of MME.*

Figure 6 studied fall rate as a function of age. The number on each bar are the count of people in that age group. There is an apparent trend that the fall rate increased steadily with the increase of age, which is in line with our common sense. For the age group 95 to 97, the fall rate decreased. A possible reason could be that the group size is too small.

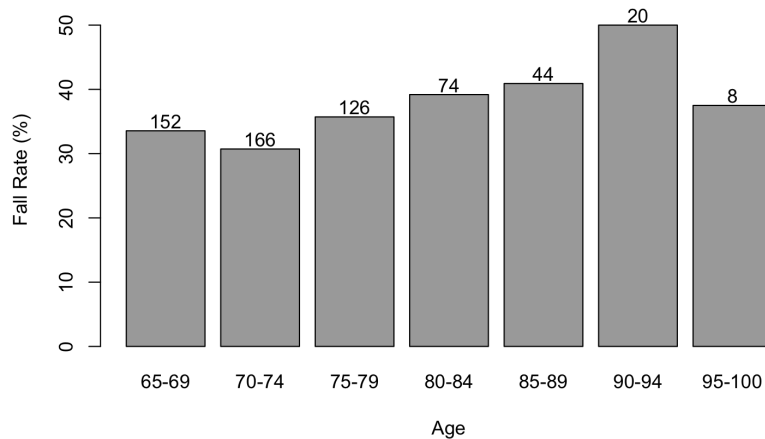


Figure 6. Plots of the fall rate binned as a function of patient age

*The fall rate increased steadily with the increase of age, except for the 95-100 age group, which has a small sample size.*

In addition, we examined the scatter plot of  $\log_{10}(\text{MME})$  and age for the not-fall and fall groups in Figure 7. The red points represent the patients who had a fall, the blue ones are the patients who did not fall.

Based on the data visualization below, the relationship between MME and fall rate in older adults was not apparent which indicates no systematic relationship between age and MME prescription.

The red points and blue points did not fall apart. In another word, there was no apparent visual difference for not-fall and fall groups.

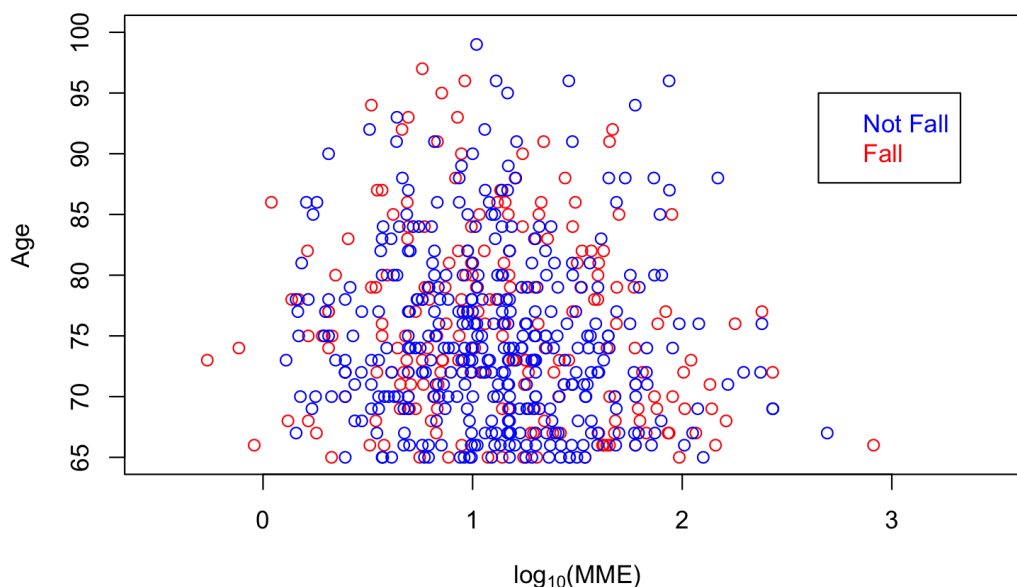


Figure 7. Scatter plot for  $\log_{10}(\text{MME})$  and age.

*There is no systematic relationship between age and MME prescription. And there was no apparent visual difference for the not-fall and fall group.*

## 2.2 Fall status and the categorical features (gender, race, and health indicators)

The Chi-Square test is applicable to situations comparing experimental frequencies and theoretical frequencies based on a hypothesis.

We obtained the contingency table between the fall status and each categorical feature and tested whether there is a difference of fall status between/among different gender, race, and health conditions.



As shown in Table 2, the  $p$ -value of Chi-Square test of Psychiatric Indicator (0.001), COPD Indicator (0.002), Gender (0.015), and Cancer Indicator (0.024) are below the threshold of 0.05. We conclude that the fall status was statistically different between Psychiatric/COPD/Cancer condition or different gender.

In particular, 27.209 % older patients had a fall in the subgroup without Psychiatric health condition, while 40.762 % had a fall in subgroup with Psychiatric condition. 32.083 % older patients had a fall in the subgroup without COPD condition, 48.182 % had a fall in the subgroup with COPD condition. 32.243 % older patients had a fall in the subgroup without Cancer, 42.593 % had a fall in the subgroup with Cancer. So, the patients with Psychiatric, COPD or Cancer condition are more likely to fall. And the female patients among the older patients are more likely to fall.

There were 98% and 95.6% of patients with Acute Pain and CVD problems, respectively. 85.4% of patients were in the race group of White or Caucasian (Table 1). The sample sizes for the minor groups were small, which were extremely unbalanced compared to the sample sizes in the dominant groups. It is not enough to reliably run the Chi-Square test in this situation. Hence, Chi-Square test was not applied to the contingency tables for Acute Pain Indicator, CVD Indicator, and Race Indicator.

Table 2. Chi-Square test for the categorical features

Features	Feature Value	Count of Not Fall	Count of Fall	<i>p</i> -value of Chi-Square test
Psychiatric Indicator	0	181	68	0.001
	1	202	139	
COPD Indicator	0	326	154	0.002
	1	57	53	
Gender	Female	234	148	0.015
	Male	149	59	
Cancer Indicator	0	290	138	0.024
	1	93	69	
Sleep Apnea Indicator	0	318	160	0.113
	1	65	47	
Benzo Indicator	0	318	163	0.243
	1	65	44	
Acute Pain Indicator <sup>a</sup>	0	8	4	/
	1	375	203	
CVD Indicator <sup>a</sup>	0	22	4	/
	1	361	203	
Race Indicator <sup>a</sup>	1/2/3/4/5/6	/	/	/

<sup>a</sup> Sample sizes were extremely unbalanced among the subgroups.

### 2.3 $\log_{10}$ (MME) between not-fall and fall in subgroups

In Section 2.2, we found that the binary features including Psychiatric Indicator, COPD Indicator, Gender, and Cancer Indicator have significant impact on the fall status. In this section, we excluded the influence from these features and compared  $\log_{10}$  (MME) between the groups of not-fall and fall. The data were split into subgroups based on each of the four significant features above Psychiatric condition, COPD condition, Cancer condition and Gender.

As shown in Figures 8-11, the distributions of  $\log_{10}$  (MME) between the groups of not-fall and fall were similar for psychiatric condition, COPD condition, Cancer condition, and different gender.

As shown in Table 3, the t-test results also indicated the means of  $\log_{10}(\text{MME})$  were not statistically different between the groups of not-fall and fall as the  $p$ -values were much larger than 0.05 (Table 3).

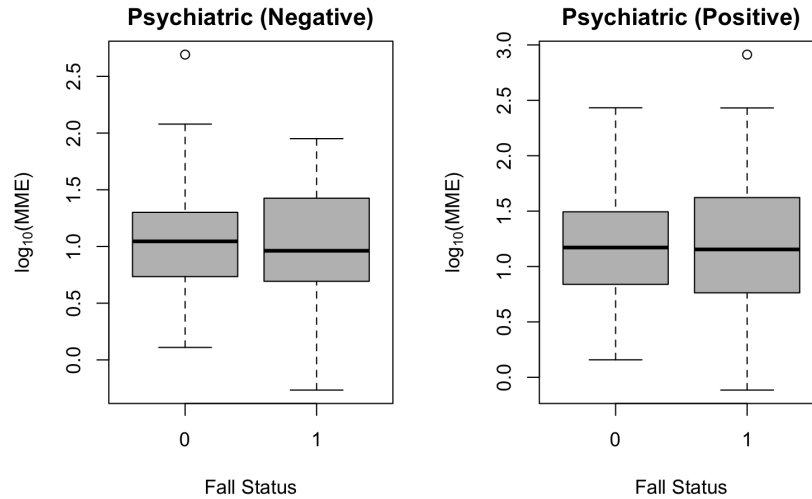


Figure 8. Boxplots of  $\log_{10}(\text{MME})$  in groups of not-fall and fall for patients without and with Psychiatric condition

*The distributions of  $\log_{10}(\text{MME})$  between the groups of not-fall and fall were similar for different psychiatric condition.*

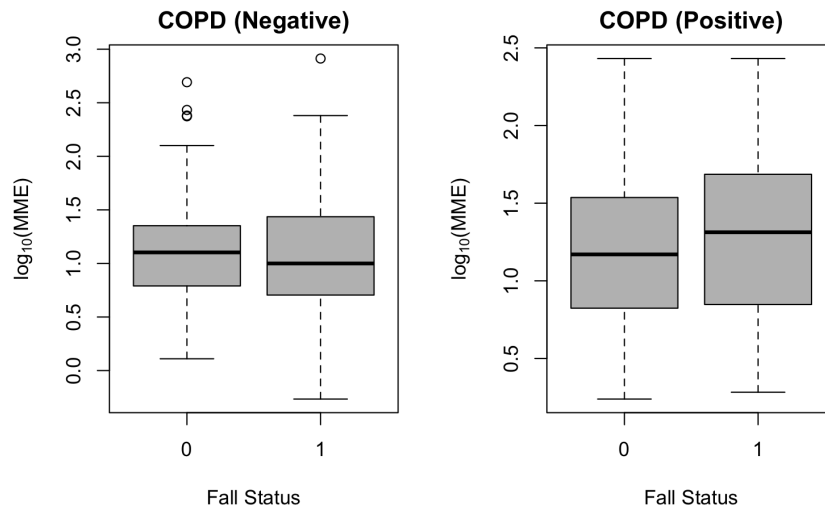


Figure 9. Boxplots of  $\log_{10}(\text{MME})$  in groups of not-fall and fall for patients without and with COPD condition

*The distributions of  $\log_{10}(\text{MME})$  between the groups of not-fall and fall were similar for different COPD condition.*

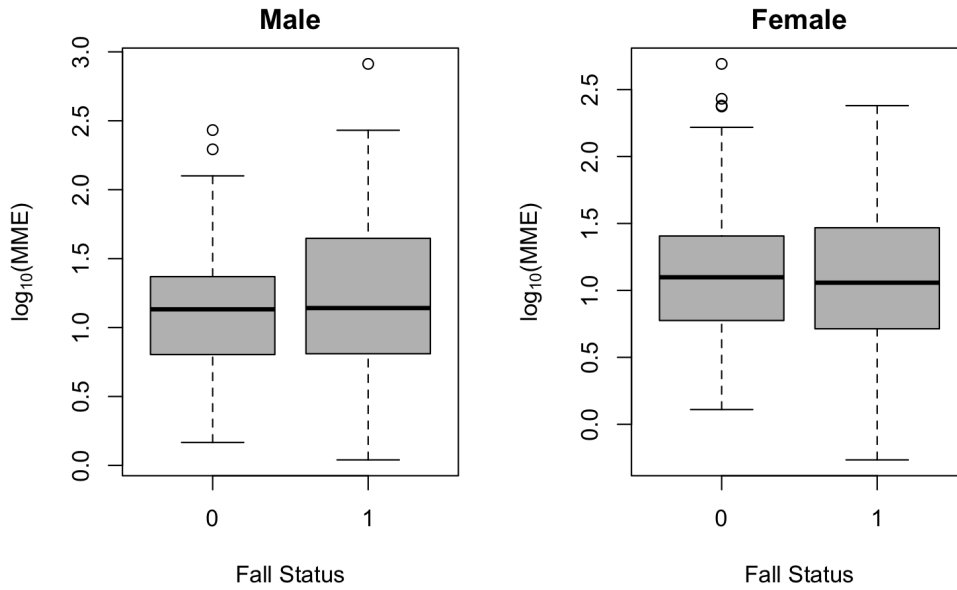


Figure 10. Boxplots of  $\log_{10}(\text{MME})$  in groups of not-fall and fall for male and female  
*The distributions of  $\log_{10}(\text{MME})$  between the groups of not-fall and fall were similar for different gender*

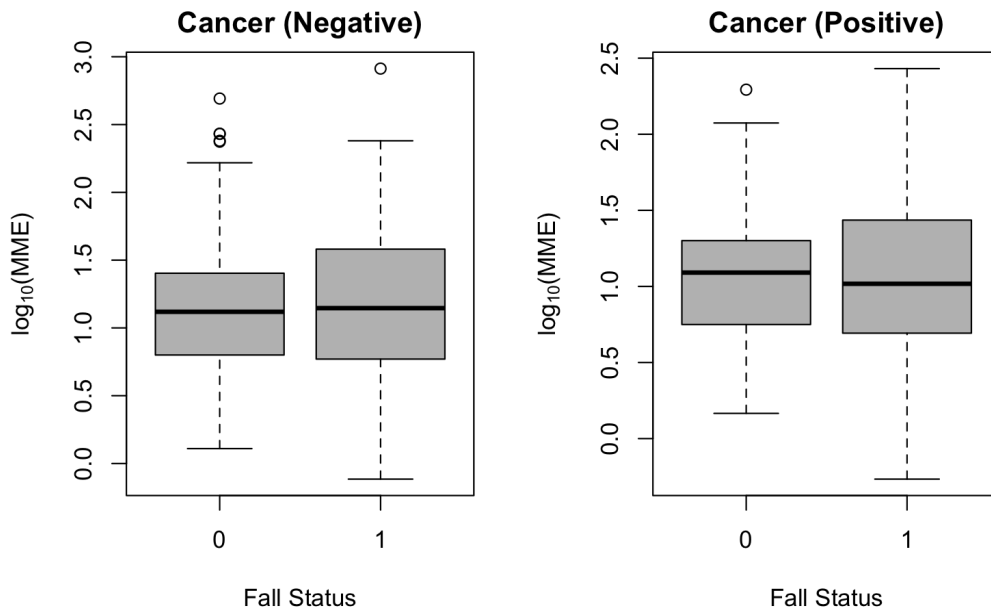


Figure 11. Boxplots of  $\log_{10}(\text{MME})$  in groups of not-fall and fall for patients without and with  
 Cancer condition  
*The distributions of  $\log_{10}(\text{MME})$  between the groups of not-fall and fall were similar for different cancer condition.*

Table 3. t-test results of  $\log_{10}$  (MME) between the groups of not-fall and fall

<b>Features</b>	<b>Feature value</b>	<b>Mean <math>\log_{10}</math> (MME) in not-fall group</b>	<b>Mean <math>\log_{10}</math> (MME) in fall group</b>	<b><i>p</i>-value of t-test</b>
Psychiatric Condition Indicator	Negative	1.015	1.041	0.696
	Positive	1.179	1.174	0.937
COPD Indicator	Negative	1.057	1.091	0.489
	Positive	1.323	1.224	0.330
Gender	Male	1.227	1.114	0.176
	Female	1.084	1.109	0.643
Cancer Indicator	Negative	1.147	1.125	0.677
	Positive	1.080	1.067	0.874

### 3. Logistic Regression

#### 3.1 Logistic regression with all features

Logistic regression is the go-to method for binary classification problems, which is a machine learning technique in the field of statistics. We used Logistic Regression to explore the association between the fall status in older adults and the features, by using the features as parameters and the fall status (0 – not-fall; 1 – fall) as the response.

We added a new feature, which is the square of  $\log_{10}(\text{MME})$ . The model was trained using all the features. The coefficients for the train model were listed in Table 4.

The  $p$ -values for Psychiatric Indicator,  $\log_{10}(\text{MME})^2$ , Age,  $\log_{10}(\text{MME})$ , Gender, Cancer Indicator, COPD Indicator, Sleep Apnea Indicator were smallest and under the threshold of 0.05. Hence, we conclude that these features were mostly related to the fall status.

The  $p$ -values for Patient Race, Benzo Indicator, Acute Pain Indicator, and CVD Indicator were above 0.05, showing these features were not important to predict the fall status in this model. This was consistent with the findings in section 2.2, in which the Chi-Square test indicated that these features were not significantly related with the fall status (see Table 2).

Table 4. Coefficients of the Logistic regression model using all the features

Feature	Estimate	Std. Error	z value	Pr(> z )
Intercept	-3.520	1.438	-2.448	0.014*
Psychiatric Indicator	0.578	0.198	2.924	0.003**
$\log_{10}(\text{MME})^2$	0.640	0.256	2.499	0.012*
Age	0.032	0.013	2.485	0.013*
$\log_{10}(\text{MME})$	-1.496	0.628	-2.382	0.017*
Gender	-0.471	0.198	-2.377	0.017*
Cancer Indicator	0.465	0.201	2.319	0.020*
COPD Indicator	0.511	0.227	2.250	0.024*
Sleep Apnea Indicator	0.508	0.232	2.193	0.028*
CVD Indicator	1.021	0.576	1.771	0.076.
Patient Race	0.063	0.084	0.741	0.459
Acute Pain Indicator	-0.191	0.663	-0.288	0.773
Benzo Indicator	0.049	0.234	0.209	0.834

Note:  $0.001 < p\text{-value} < 0.01$  ‘\*\*’;  $0.01 < p\text{-value} < 0.05$  ‘\*’;  $0.05 < p\text{-value} < 0.10$  ‘.’

### 3.2 Logistic regression with selected features

We dropped the features with  $p$ -value larger than 0.05, which were Benzo Indicator, Acute Pain Indicator, Patient Race, and CVD, got the updated model. The coefficients of the new model with fewer features were listed in Table 5.

The features Psychiatric Indicator and Age showed the lowest  $p$ -values (0.002, 0.008), indicating strongest impact on the fall status. The signs of the feature coefficients made sense and agreed with intuition. The coefficient of gender was negative since female (=1) has a larger fall rate than male (=2) (fall rate of female VS male is 38% vs 28%). The other features including age and the health conditions had positive coefficients, which indicated patients who were older or had health conditions had a larger chance to fall.

Table 5. Coefficients of the Logistic regression model using selected features

Feature	Estimate	Std. Error	z value	Pr(> z )
Intercept	-2.578	1.094	-2.356	0.019*
Psychiatric Indicator	0.608	0.193	3.153	0.002**
Age	0.034	0.013	2.646	0.008**
COPD Indicator	0.555	0.226	2.460	0.014*
$\log_{10}(\text{MME})^2$	0.610	0.253	2.407	0.016*
Cancer Indicator	0.480	0.200	2.405	0.016*
$\log_{10}(\text{MME})$	-1.436	0.622	-2.308	0.021*
Patient Gender	-0.451	0.197	-2.291	0.022*
Sleep Apnea Indicator	0.519	0.231	2.249	0.025*

### 3.3 Logistic regression with selected features for subgroup age smaller than 80

In the following logistic regression, a subset of the data was used to train the model to exclude the influence from Patient Age. Table 6 showed the coefficient estimation of the logistic model trained on data of patient age less than 80.

The  $p$ -value of patient age was 0.174, showing age is not an important feature in predicting the fall status within this subgroup. In this subset (age <80), some features such as COPD Indicator,  $\log_{10}(\text{MME})^2$ ,  $\log_{10}(\text{MME})$ , Gender became more important to predict the fall status, compared to the previous two models trained with data containing all ages (65 < age < 99). In particular, the

COPD indicator had a much smaller  $p$ -value of 0.0037 in this subgroup, relative to the  $p$ -value of the previous two models which were above 0.01. It suggests that, within the subgroup of age ranges from 65 to 80, the feature COPD Indicator become more important to predict fall status in the logistic model.

Table 6. Coefficients of the Logistic regression model using data of patient age <80 (n=444)

Feature	Estimate	Std. Error	z value	Pr(> z )
Intercept	-2.413	2.016	-1.197	0.231
COPD Indicator	0.766	0.264	2.900	0.0037**
$\log_{10}(\text{MME})^2$	0.798	0.279	2.856	0.0043**
$\log_{10}(\text{MME})$	-1.862	0.697	-2.672	0.008**
Patient Gender	-0.612	0.234	-2.616	0.009**
Psychiatric Indicator	0.596	0.238	2.503	0.012*
Cancer Indicator	0.597	0.244	2.449	0.014*
Sleep Apnea Indicator	0.584	0.256	2.286	0.022*
Age	0.036	0.026	1.360	0.174

#### 4. Exploration of the threshold of MME for fall status

We tried to explore the threshold of MME using contingency tables in this section. We separated the data based on a threshold of MME (percentile of MME) into two groups, lower MME group and higher MME group, then compared  $p$ -values of contingency (one way is fall status, the other way is the MME) test between not-fall and fall group and check whether there is a difference in MME between these two groups, as shown in Figure 12.

Percentile of MME ranges from 0.1 to 0.9, at a step of 0.05. Above the percentile of 0.6, the  $p$ -value decreased, which indicates that the fall rate difference between the two MME groups became larger.

Using an MME threshold of 34.364 (according to 0.80 percentile) to split the data into two groups, the  $p$ -value of Chi-Squared is 0.081. Using an MME threshold of 43.155 (according to 0.85 percentile) to split the data into two groups, the Chi-Squared test shows significant difference in fall rate between the two groups, with a  $p$ -value of 0.025. Even though the  $p$ -value were smaller than the usual threshold of 0.05, it was likely not strong evidence. Since we were doing multiple



comparison here, other features including age, gender, some health conditions were more related to the fall status other than MME in the above analysis in section 1 and 2.

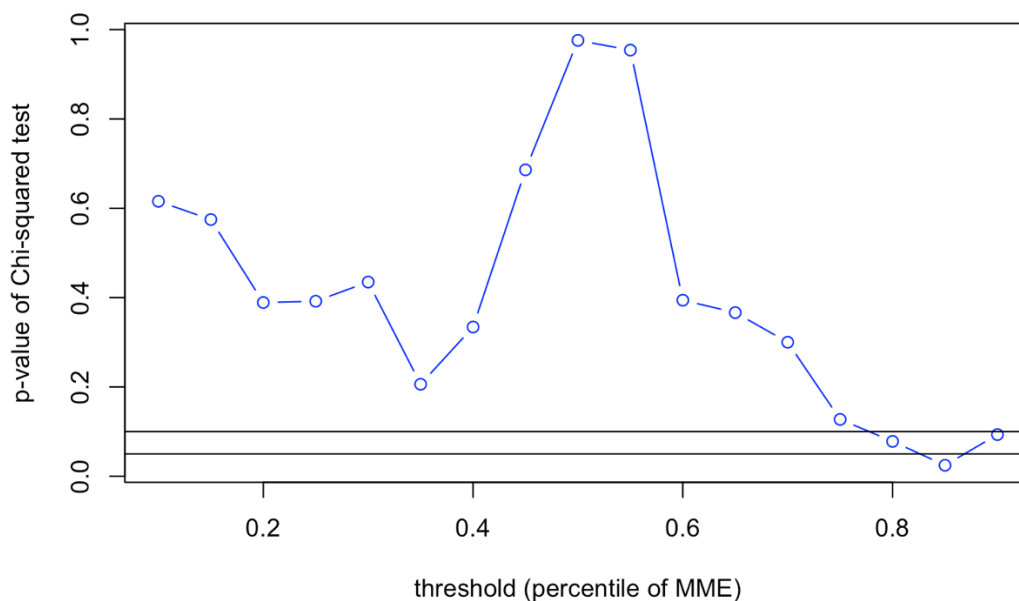


Figure 12. The  $p$ -value of Chi-Square test using different percentile of MME as the threshold. The  $p$ -value at percentile of 0.85 (43.155) was under 0.05. However, we could not draw firm conclusion. Since we were doing multiple comparison here.

## Discussion

We conclude that fall rate increases with the increase of age. Patients with health conditions such as psychiatric diseases, COPD condition, Cancer have larger chance to fall.

As for the threshold of MME, the fall rate decreased for smaller MME and increased for larger MME. And the distribution of MME in not-fall and fall group are similar with each other. CDC's report shows that dosage at or above 50 MME/day increase risks for overdose, by at least twice as a fact of the risk below 20 MME/day. We may keep collecting data and check these subgroups to explore the association between MME and fall in the future.

## References

1. Cuevas-Trisan R. Balance Problems and Fall Risks in the Elderly. *Clin Geriatr Med*. 2019;35(2):173-183. doi:10.1016/j.cger.2019.01.008
2. Changyong F, Hongyue W, Naiji L etc., Log-transformation and its implications for data science: Shanghai Arch Psychiatry. 2014 Apr; 26(2): 105-109. doi: 10.3969/j.issn.1002-0829.2014.02.009
3. R studio was used for this analysis. R libraries of openxlsx, dplyr, glmnet, ROCR, caTools were used.