Reconsidering High Intensity Zones: Its Role in Intervertebral Disk Degeneration and Low Back Pain

Journal: European Spine Journal

Authors: Stone Sima, Xiaolong Chen*, Kyle Sheldrick, Jeff Kuan, Ashish D. Diwan

***Corresponding author:** Xiaolong Chen

Spine Labs, St George and Sutherland Clinical School, University of New South Wales, New South Wales, Australia

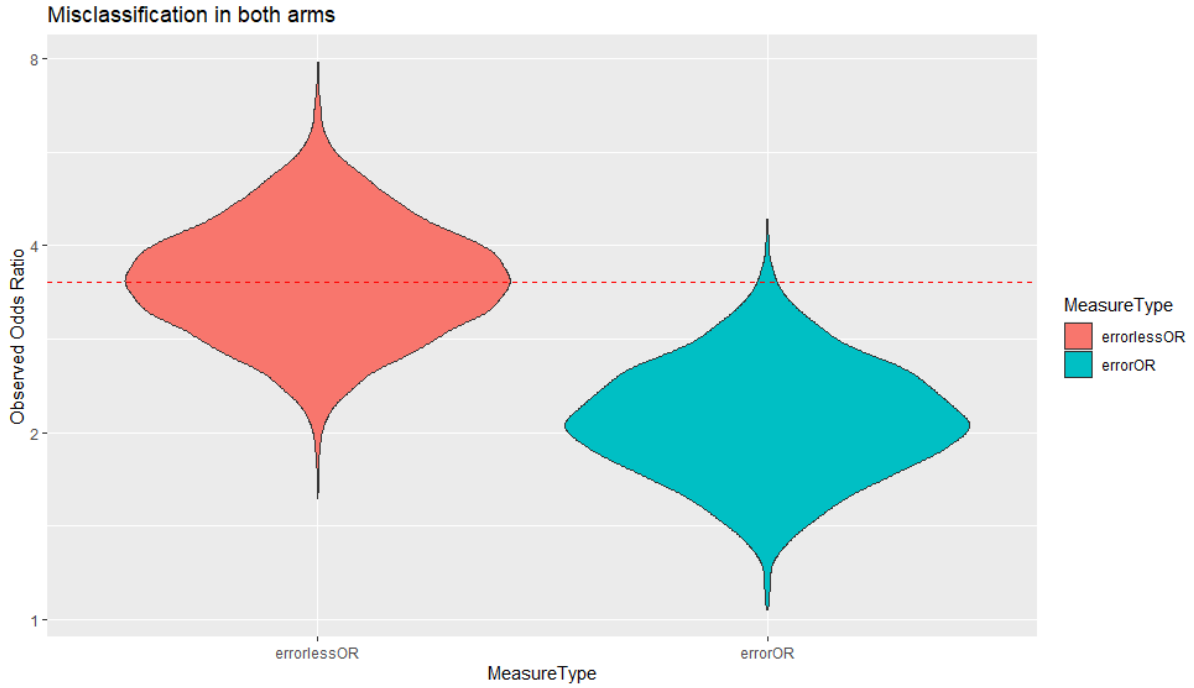
Email Address: xiaolong.chen1@unsw.edu.au

Electronic Supplementary Material 1

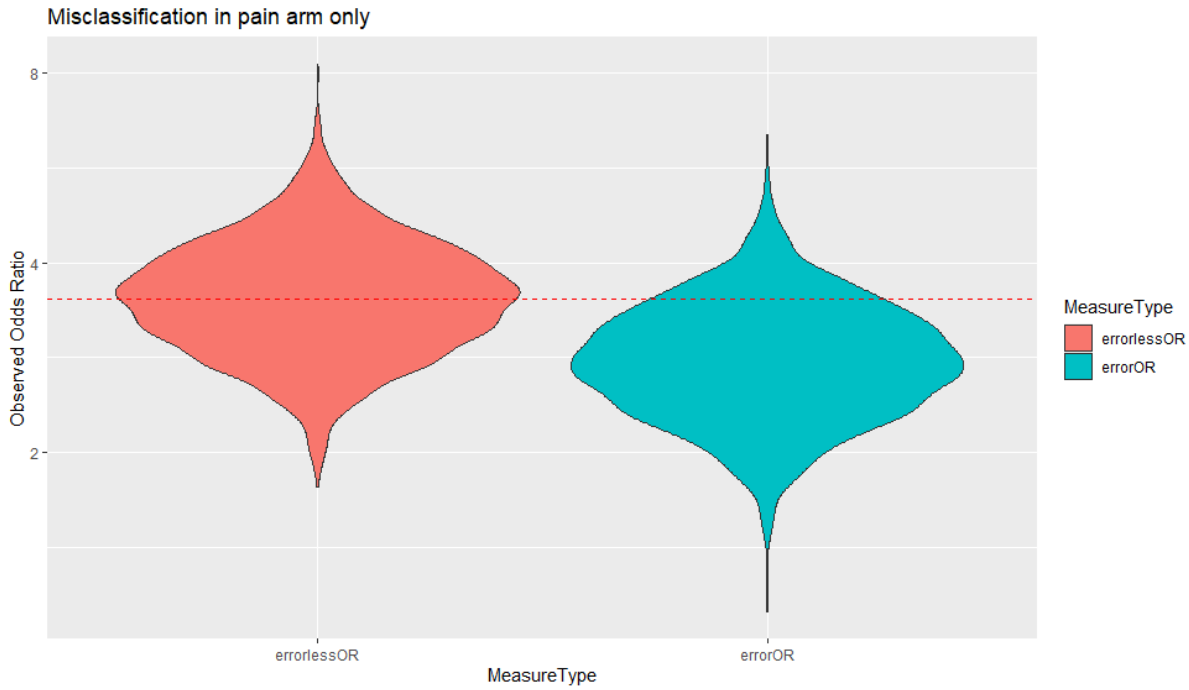
Simulation demonstrating the effect of classification error in pain status.

This is a simulation of 5000 studies of 400 patients with a 50% chance of having pain (with a 60% chance of HIZ) and 50% chance of having no pain (with a 30% chance of HIZ), for a true underlying OR of 3.5. (Recall that OR will be substantially larger than RR for non-rare outcomes).

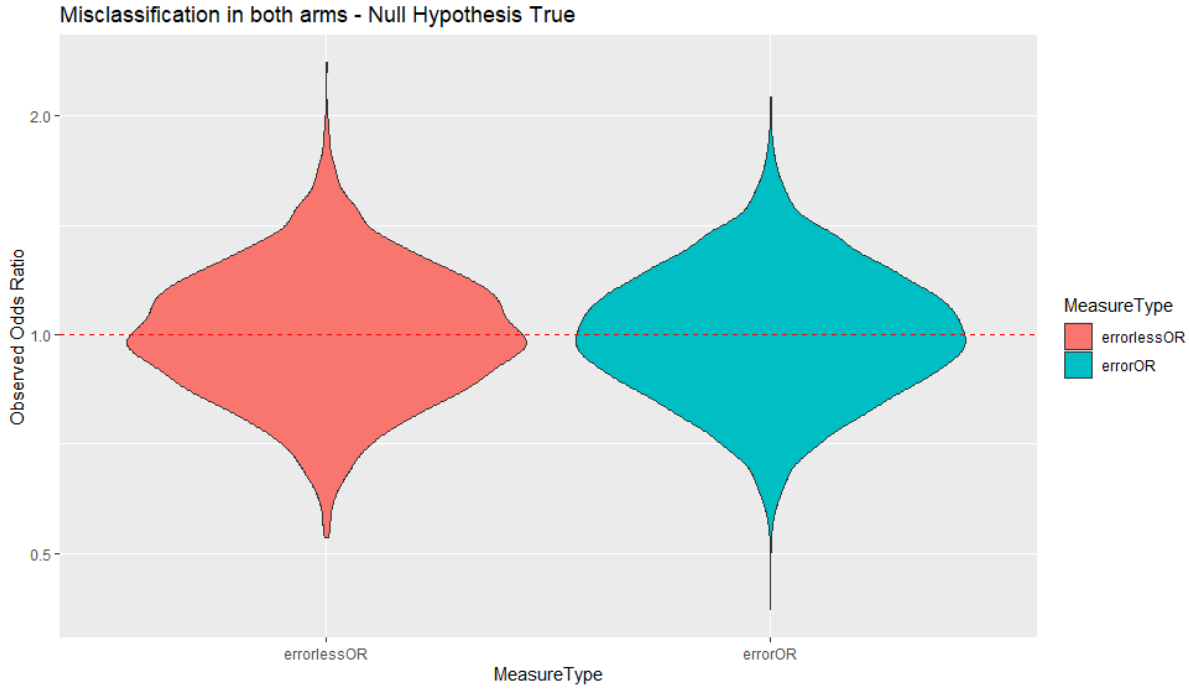
If we simulate patients with pain having a 20% chance of being misclassified as no pain (and vice versa) we can see there is a substantial bias towards the null, with the observed ORs centring on ~2.1 instead of the correct ~3.5 which is what was observed with no classification error.



Likewise, if we simulate such a classification error only in patients who genuinely have pain (i.e. false negatives but no false positives), we again see a substantial but smaller bias towards the null with the observed ORs centring on ~2.8 instead of the correct ~3.5 seen with no classification error.



Finally if the null hypothesis is true, classification error does not bias the results towards an effect (in either direction).



In short: any classification error would only result in a weakening of the observed association, not a spurious association. That is the underlying association is likely stronger than what we are reporting, and we have added a sentence to the discussion drawing this to the attention of readers.

The R code for the simulation study demonstrating the effect of classification error in pain status is written below:

Misclassification of Pain Code

```
#step 0, load the packages

library(car)
library(epitools)
library(ggplot2)
library(tidyr)
library(dplyr)

#Step 1, Set seed makes the RNG start at the same place
set.seed(1)

#Step 2, decide how many times to run
loops <- 5000

#Step 3, decide how many patients
nPatients <- 400

# Step 4, make a vector for every outcome you want to save from the
 study
errorlessOR = numeric(loops)
errorOR = numeric(loops)

#step 5 start a "for" loop, everything in this will be repeated
 "loops" times
for (i in 1:loops) {

  #Step 6, simulate the measured pain status, and presence of HIZ
 for each patient

  pid=seq(1, by=1, len=nPatients) #create consecutive pids
  truepain=rbinom(nPatients, 1, 0.5) # this randomly assigns each
 patient to have or not have pain with a 1:1 ratio regardless of
 what came before or after
  measuredpain = numeric(nPatients)
  HIZ = numeric(nPatients)

  for (j in 1:nPatients){

    if(truepain[j]==0){
      measuredpain[j] = rbinom(1, 1, 0.2) #this introduces a 20%
 error rate in pain classification, change to zero for no error in
 this group
```

```
      HIZ [j] = rbinom(1, 1, 0.3) #allocates HIZ with a 30% chance
in pain free participants
    }

    if(truepain[j]==1){
      measuredpain[j] = rbinom(1, 1, 0.8)  #this introduces a 20%
error rate in pain classification
      HIZ [j] = rbinom(1, 1, 0.6) #allocates HIZ with a 60% chance
in participants with pain
    }

  }

  noerror = oddsratio(table(truepain,HIZ))
  witherror = oddsratio(table(measuredpain,HIZ))

  errorlessOR[i] = noerror$measure[2]
  errorOR[i] = witherror$measure[2]


}

data = data.frame(errorlessOR,errorOR)
datalong = gather(data, key="MeasureType", value="Val")
ggplot(datalong, aes(x=MeasureType, y=Val, fill=MeasureType)) +
  geom_violin() +
  geom_hline(yintercept=3.5, linetype="dashed", color = "red") +
  scale_y_continuous(trans='log2')+
  ggtitle("Misclassification in both arms")+
  ylab("Observed Odds Ratio")


quantile(errorlessOR)
quantile(errorOR)
```

If Null Hypothesis is True Code

```
#step 0, load the packages

library(car)
library(epitools)
library(ggplot2)
library(tidyr)
library(dplyr)

#Step 1, Set seed makes the RNG start at the same place
set.seed(1)

#Step 2, decide how many times to run
loops <- 5000

#Step 3, decide how many patients
nPatients <- 400

# Step 4, make a vector for every outcome you want to save from the
 study
errorlessOR = numeric(loops)
errorOR = numeric(loops)

#step 5 start a "for" loop, everything in this will be repeated
 "loops" times
for (i in 1:loops) {

  #Step 6, simulate the measured pain status, and presence of HIZ
 for each patient

  pid=seq(1, by=1, len=nPatients) #create consecutive pids
  truepain=rbinom(nPatients, 1, 0.5) # this randomly assigns each
 patient to have or not have pain with a 1:1 ratio regardless of
 what came before or after
  measuredpain = numeric(nPatients)
  HIZ = numeric(nPatients)

  for (j in 1:nPatients){

    if(truepain[j]==0){
      measuredpain[j] = rbinom(1, 1, 0.2) #this introduces a 20%
 error rate in pain classification, change to 0 for no error in this
 group
      HIZ [j] = rbinom(1, 1, 0.5) #allocates HIZ with a 30% chance
 in pain free participants
    }
```

```
    if(truepain[j]==1){
      measuredpain[j] = rbinom(1, 1, 0.8)  #this introduces a 20%
 error rate in pain classification
      HIZ [j] = rbinom(1, 1, 0.5) #allocates HIZ with a 60% chance
 in participants with pain
    }

  }

  noerror = oddsratio(table(truepain,HIZ))
  witherror = oddsratio(table(measuredpain,HIZ))

  errorlessOR[i] = noerror$measure[2]
  errorOR[i] = witherror$measure[2]


}

data = data.frame(errorlessOR,errorOR)
datalong = gather(data, key="MeasureType", value="Val")
ggplot(datalong, aes(x=MeasureType, y=Val, fill=MeasureType)) +
  geom_violin() +
  geom_hline(yintercept=1, linetype="dashed", color = "red") +
  scale_y_continuous(trans='log2')+
  ggtitle("Misclassification in both arms - Null Hypothesis True")+
  ylab("Observed Odds Ratio")


quantile(errorlessOR)
quantile(errorOR)
```