

FDA/M-CERSI Workshop, White Oak 2015

Data linkage to obtain information on driving conditions in a study evaluating exposure to ADHD medications and motor-vehicle accidents

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# Background

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- Effect of drugs on driving performance and related injury is long-standing topic in pharmacoepidemiology / drug safety research
- Claims or medical records capture only injuries due to accidents
  - ▣ Low sensitivity; potential for differential misclassification
  - ▣ Validity of E codes not formally addressed
- Driving-related accidents are classic example where patient susceptibility is critical
  - ▣ No driver's license or no driving is highly protective of accidents
  - ▣ Driving in low traffic areas affects risk

# Background: Data sources

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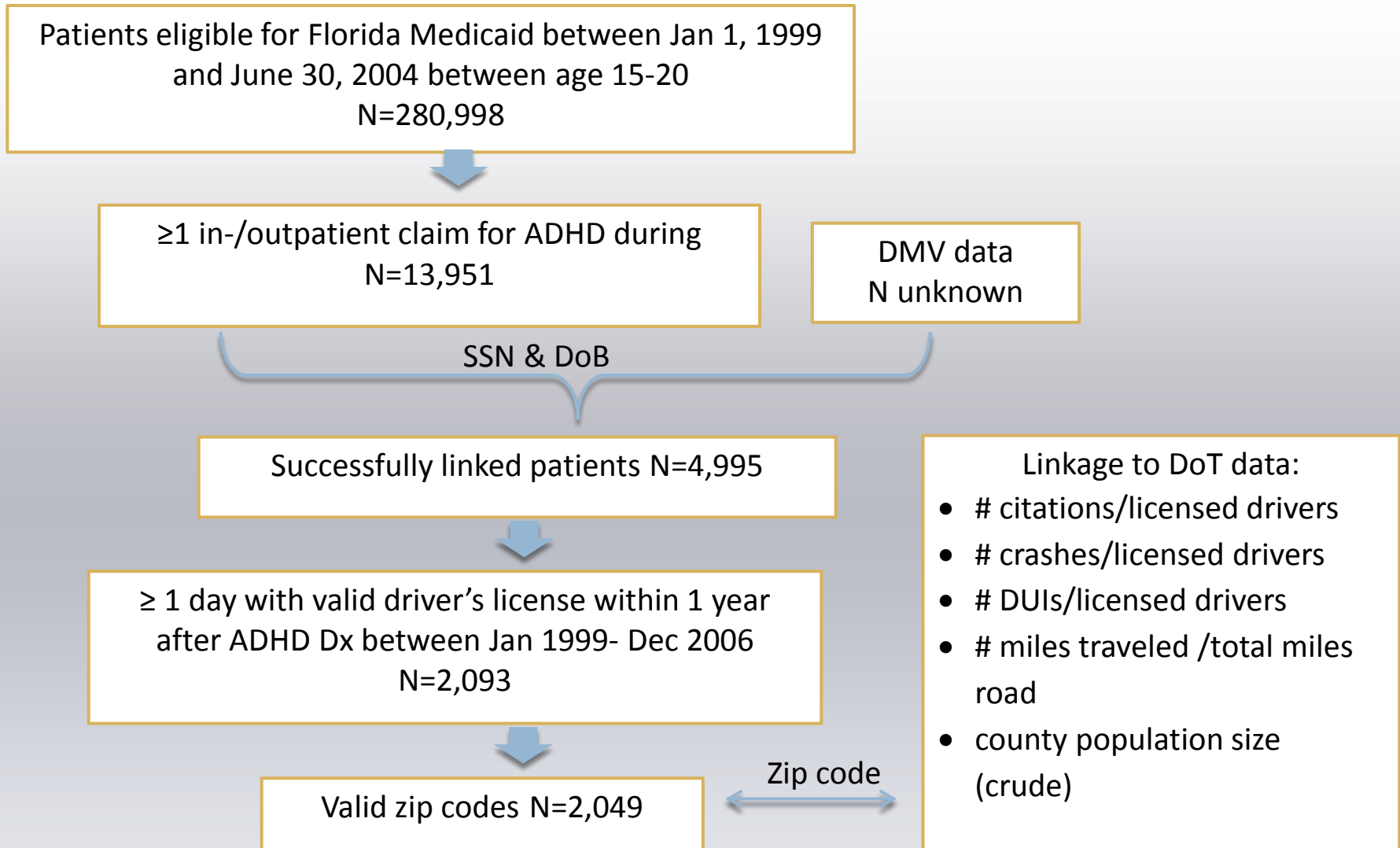
- Systematic review of benzodiazepines/accidents: 66 studies with primary focus on traffic accidents (Smink, CMS Drugs 2010)
  - Study population
    - General population
    - General driving population
    - Accident-involved persons w/wo injury
    - Persons hospitalized for injury
    - Responsible/non-responsibility accident involved drivers
  - Exposure
    - Toxicology
    - Prescription data
    - Questionnaire

# Application: Effectiveness of ADHD treatment on driving performance

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- Several studies have suggested ADHD effect
  - ▣ Increased risk taking & attention deficit
- Treatment effectiveness only studied in driving simulators
- Good application to balance cardiac safety study to further explore treatment effects
- Problem:
  - ▣ 15-20 year old patients: varying effects on driving performance and age-dependent drug exposure
  - ▣ Geographic determinants of driving outcomes and exposure

# Cohort construction



# Cohort definitions

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- Cohort entry: 15<sup>th</sup> birthday, in- or outpatient diagnosis of ADHD (ICD9-CM 314xx), issuance of driver's license,  $\geq 6$  months continuous eligibility, whichever was last (index date).
- Censoring criteria: end of Medicaid eligibility,  $>12$  months without ADHD diagnosis, driver's license expiration/suspension, 21<sup>st</sup> birthday, study endpoint, whichever came first.
- Endpoints: crashes and citations for active driving violations

# Independent variables

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- Exposure: time-varying, stimulants or atomoxetine based on days' supply + 25%
- Exposure propensity score
  - At index date: Age, driver's license learner permit status, disability, foster care, poverty, cash assistance
  - During 6 months look back: Substance use disorder, diabetes, epilepsy, ODD
  - Fixed: 2000 population size in county of residence, 2002 county-level citations / crashes / DUIs per licensed driver, total annual daily vehicular miles traveled per miles of paved road
- Time-varying: Valid driver's license >1 year, age, substance use disorder, exposure to antidepressant, anticonvulsant, antipsychotic, anxiolytic,  $\alpha$ -agonist

## Cohort characteristics (selection)

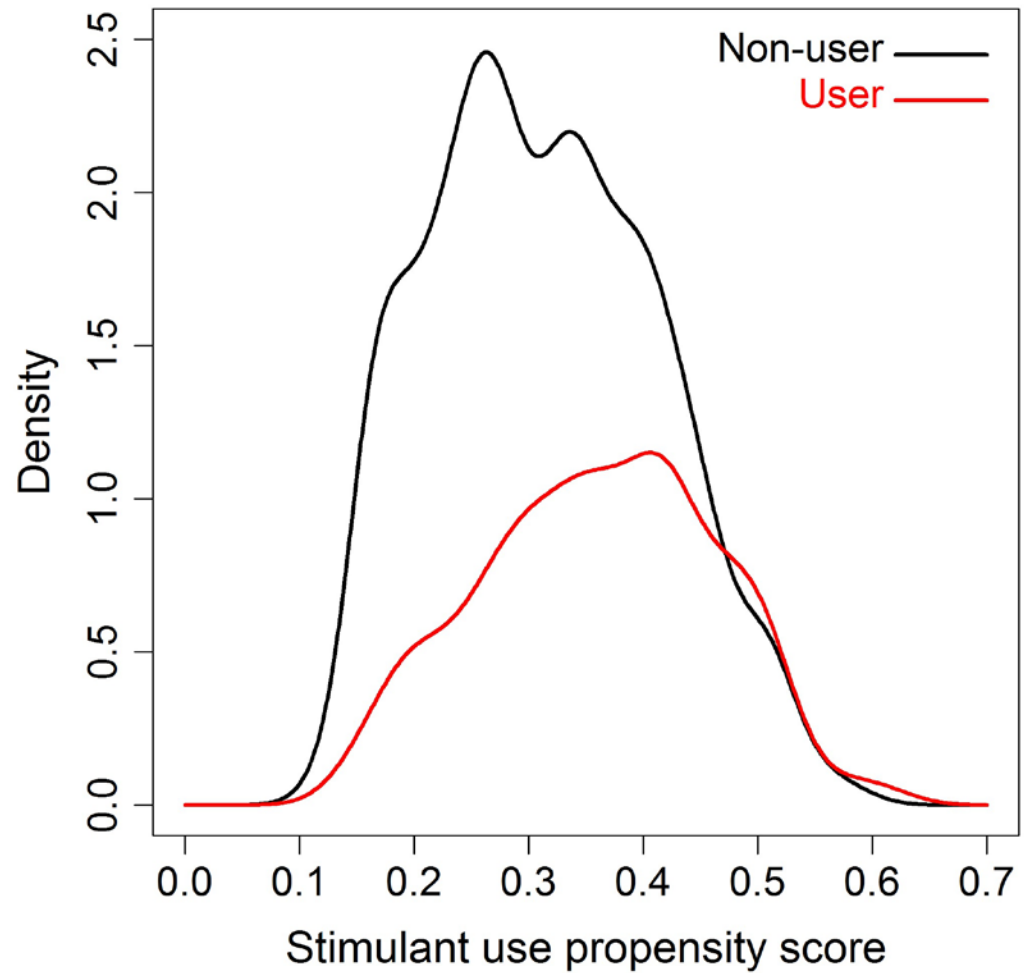
	No stimulant during follow-up (N=936)	Some stimulant during follow-up (N=1113)
Age	17.9 (SD 1.2)	17.6 (SD 1.2)
Male	723 (77.2%)	851 (76.5%)
White	542 (57.9%)	761 (68.4%)
Black	191 (20.4%)	185 (16.6%)
Hispanic	162 (17.3%)	107 (9.6%)
Foster care	178 (19.0%)	148 (13.3%)
Substance abuse	35 (3.7%)	43 (3.9%)
ODD/CD	115 (12.3%)	94 (8.5%)
Diabetes	8 (0.9%)	7 (0.6%)
Epilepsy	19 (2.0%)	20 (1.8%)
Any CNS drug	350 (37.4%)	587 (52.7%)
Antidepressants	261 (27.9%)	399 (35.9%)
Antipsychotics	136 (14.5%)	195 (17.5%)
Anticonvulsants	127 (13.6%)	147 (13.2%)
Anxiolytics	69 (7.4%)	80 (7.2%)
Alpha-agonists	36 (3.9%)	141 (12.7%)
DL learning permit	121 (12.9%)	148 (13.3%)



# County characteristics (selection)

County-level characteristics		No stimulant during follow-up (N=936)	Some stimulant during follow-up (N=1113)
2002 citations/licensed drivers:	Q1	151 (16.1%)	281 (25.3%)
	Q2	145 (15.5%)	196 (17.6%)
	Q3	221 (23.6%)	264 (23.7%)
	Q4	341 (36.4%)	299 (26.9%)
	Q5	78 (8.3%)	73 (6.6%)
2002 crashes/licensed drivers:	Q1	142 (15.2%)	190 (17.1%)
	Q2	132 (14.1%)	197 (17.7%)
	Q3	140 (15.0%)	161 (14.5%)
	Q4	142 (15.2%)	209 (18.8%)
	Q5	380 (40.6%)	356 (32.0%)
2002 miles traveled/miles road:	Q1	35 (3.74%)	57 (5.1%)
	Q2	71 (7.6%)	96 (8.6%)
	Q3	176 (18.8%)	252 (22.6%)
	Q4	191 (20.4%)	254 (22.8%)
	Q5	463 (49.5%)	454 (40.8%)
2000 county population	Q1	24 (2.6%)	47 (4.2%)
	Q2	71 (7.6%)	84 (7.6%)
	Q3	131 (14.0%)	183 (16.4%)
	Q4	184 (19.7%)	276 (24.8%)
	Q5	256 (56.2%)	523 (47.0%)

# Propensity score distributions



# Crude rates

	<b>N</b>	<b>Patient-years</b>	<b>Rate per 100 patient-years</b>
Crashes			
All Patients	67	2059.9	3.3
Unexposed	45	1319.4	3.4
Any exposure	22	740.6	3.0
Citations			
All patients	319	1909.4	16.7
Unexposed	223	1212.9	18.4
Any exposure	96	696.6	13.8

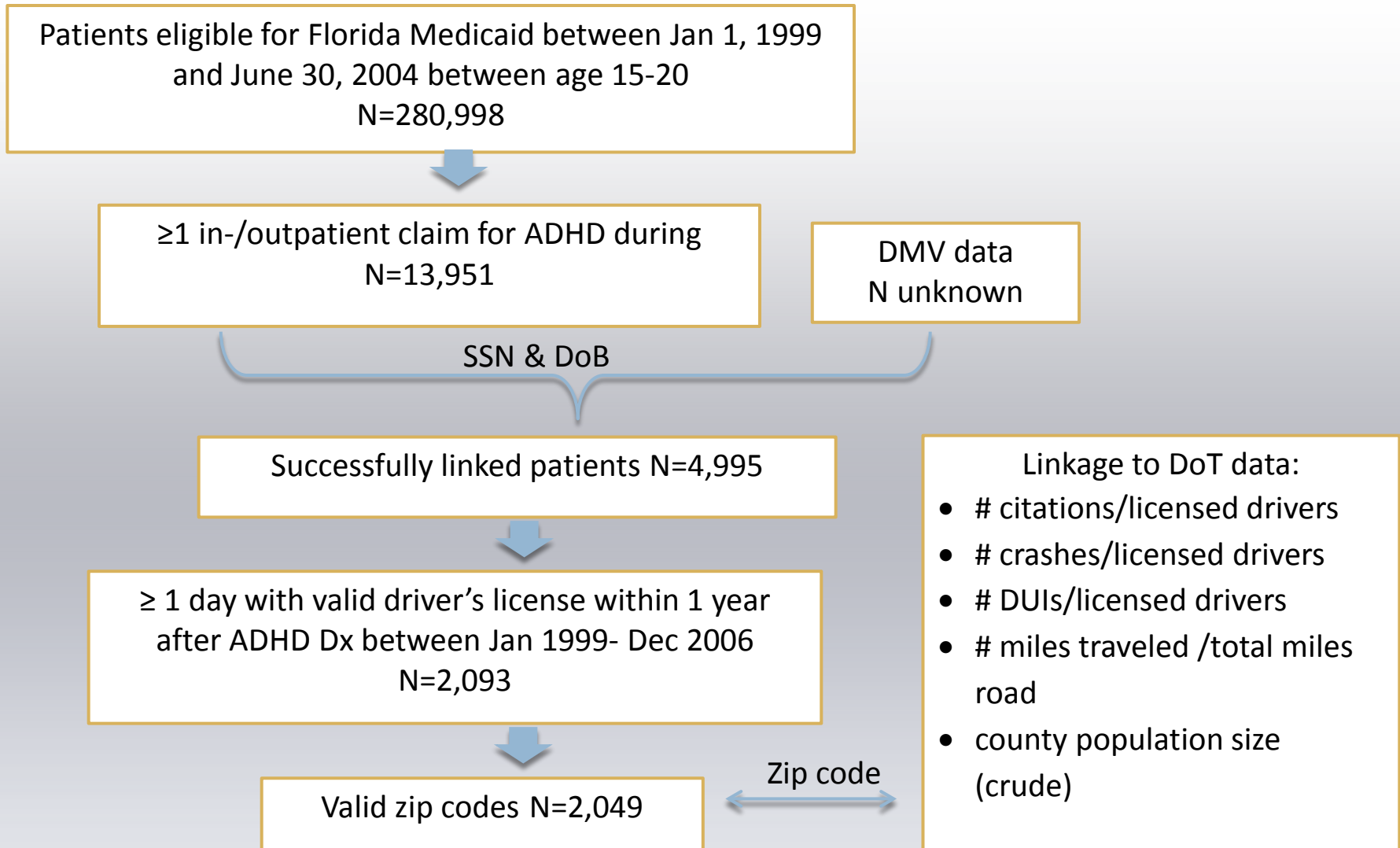
# Hazard ratios: Crashes

	<b>Crashes</b>	
	<b>Unadjusted HR</b>	<b>Adjusted HR</b>
Stimulant use	0.87 (0.52-1.45)	1.22 (0.66-1.90)
Propensity score (logit)	0.56 (0.25-0.91)	0.57 (0.35-0.94)
Substance use	2.63 (1.05-6.59)	2.67 (1.07-6.71)
Antidepressant	0.30 (0.11-0.84)	0.30 (0.11-0.85)
Antipsychotic	1.21 (0.55-2.68)	
Anticonvulsant	0.82 (0.26-2.62)	
Anxiolytic	1.92 (0.60-6.13)	
DL > 1 years	1.93 (0.98-3.78)	
Age (linear)	1.19 (0.96-1.47)	

# Hazard ratios: Citations

	Citations	
	Unadjusted HR	Adjusted HR
Stimulant use	0.75 (0.59-0.95)	0.89 (0.69-1.13)
Propensity score (logit)	0.72 (0.57-0.89)	1.04 (0.81-1.33)
Substance use	0.70 (0.31-1.57)	
Antidepressant	0.72 (0.52-0.99)	0.71 (0.51-0.99)
Antipsychotic	0.78 (0.50-1.21)	
Anticonvulsant	0.88 (0.53-1.45)	
Anxiolytic	0.90 (0.42-1.90)	
DL > 1 years	2.68 (2.01-3.57)	2.05 (1.52-2.77)
Age (linear)		
Age: 15 years	Reference	Reference
16 years	3.33 (1.31-8.48)	2.84 (1.13-7.17)
17 years	4.41 (1.95-9.98)	3.38 (1.48-7.71)
18 years	8.52 (3.63-19.97)	6.46 (2.72-15.36)
19 years	8.03 (3.40-18.98)	5.91 (2.45-14.24)
20 years	5.54 (2.13-14.39)	3.91 (1.47-10.4)

# Cohort construction



# Effect of residual confounding

Patients eligible for Florida Medicaid between Jan 1, 1999  
and June 30, 2004 between age 15-20  
N=280,998



≥1 in-/outpatient claim for ADHD during  
N=13,951

DMV data  
N unknown

SSN & DoB

To obtain citation and crash data

# Effect of residual confounding

<b>Crashes</b>	
<b>DMV link</b>	<b>No DMV link</b>
1.22 (0.66-1.90)	0.95 (0.58-1.56)
<b>Citations</b>	
<b>DMV link</b>	<b>No DMV link</b>
0.89 (0.69-1.13)	0.940 (0.74-1.19)

- Age effect increased into double digits
- AD, AP, and AC showed protective effects



# Summary

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- No evidence for ADHD treatment effectiveness, but confidence intervals were wide
- Driving variables were strongly associated with endpoints, but not exposure
- “protective effect” of other psychotropics suggests that actual driving activity remains insufficiently captured.

# Acknowledgements

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  - Jon Shuster
  - Tobias Gerhard
  - Stephan Linden



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