Duke Psychiatry & Behavioral Sciences
Duke University School of Medicine

Recent Innovations in the Assessment and Prediction of Self-Directed Violence

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MID★ATLANTIC MIRECC POST DEPLOYMENT MENTAL HEALTH

Funding & Disclosures

This work was supported by grants from the U.S. Department of Veterans Affairs (VA) Million Veteran Program (MVP) as well as the VA Office of Research and Development (ORD) Clinical Sciences Research and Development, Rehabilitation Research & Development, Health Services Research & Development, and Biomedical & Laboratory Research & Development Services. This was work was also supported by the joint VA-Department of Energy Champion program as well as the National Institute of Mental Health, the National Institute on Drug Abuse, the National Institute on Alcohol Abuse and Alcoholism, the Department of Defense, and the Federal Emergency Management Agency. Dr. Kimbrel was also supported by the Mental and Behavioral Health Service Line of the Durham VA Health Care System, the VA Mid-Atlantic Mental Illness Research, Education, and Clinical Center (MIRECC), and the Department of Psychiatry & Behavioral Sciences at the Duke University School of Medicine. The views expressed in this presentation are those of Dr. Kimbrel only and do not necessarily reflect the position or policy of the VA, Duke, the U.S. government, or any other affiliated institution.

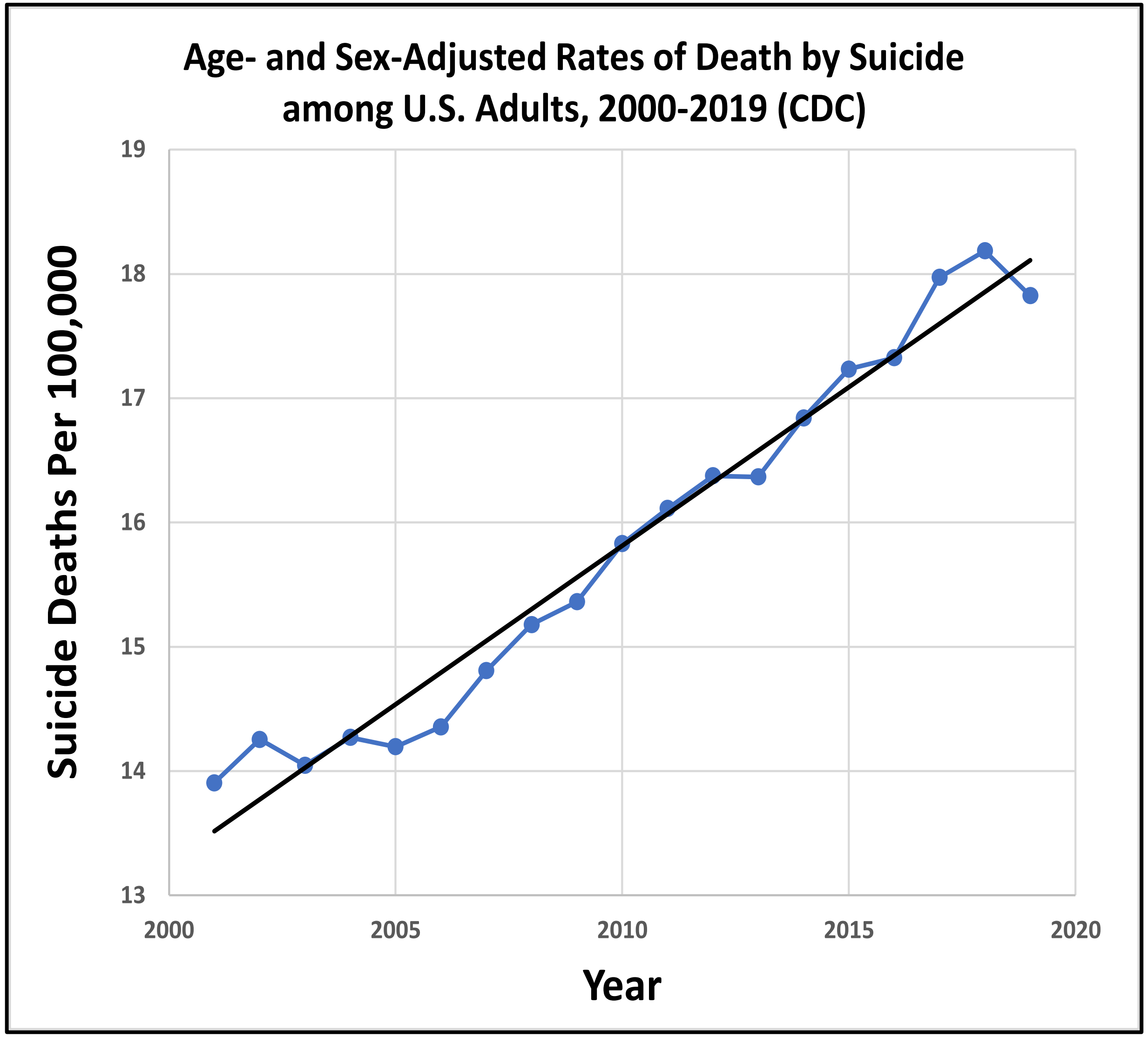
I have no conflicts of interest to disclose at this time.

Understanding the Scope of the Problem

Suicide Statistics within the U.S.

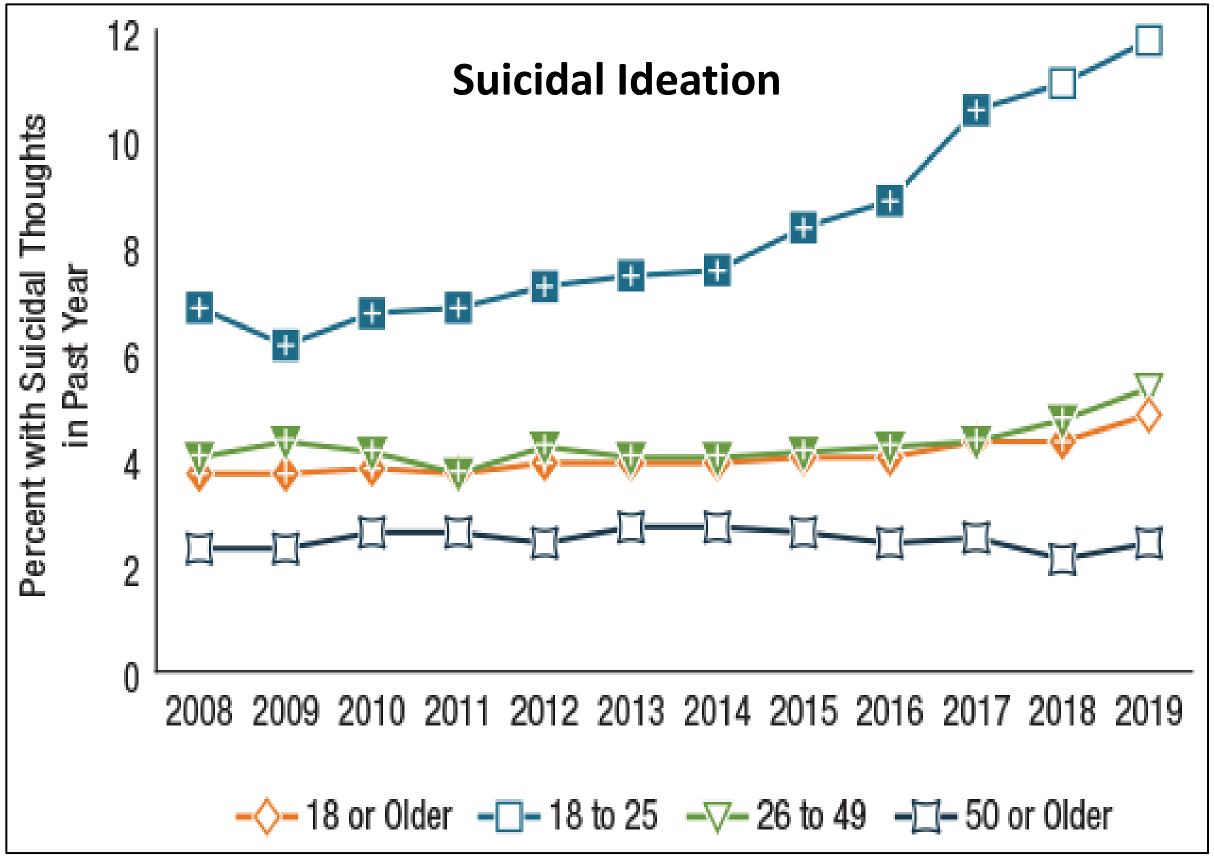
- Suicide rates have increased by 28% among U.S. adults since 2001.
- Death by suicide accounted for 45,979 deaths in 2020 alone, nearly twice the number of homicides (24,576)
- Among U.S. adults in 2020:
    - 12.2 million experienced suicidal ideation
    - 3.2 million planned a suicide attempt
    - 1.2 million attempted suicide

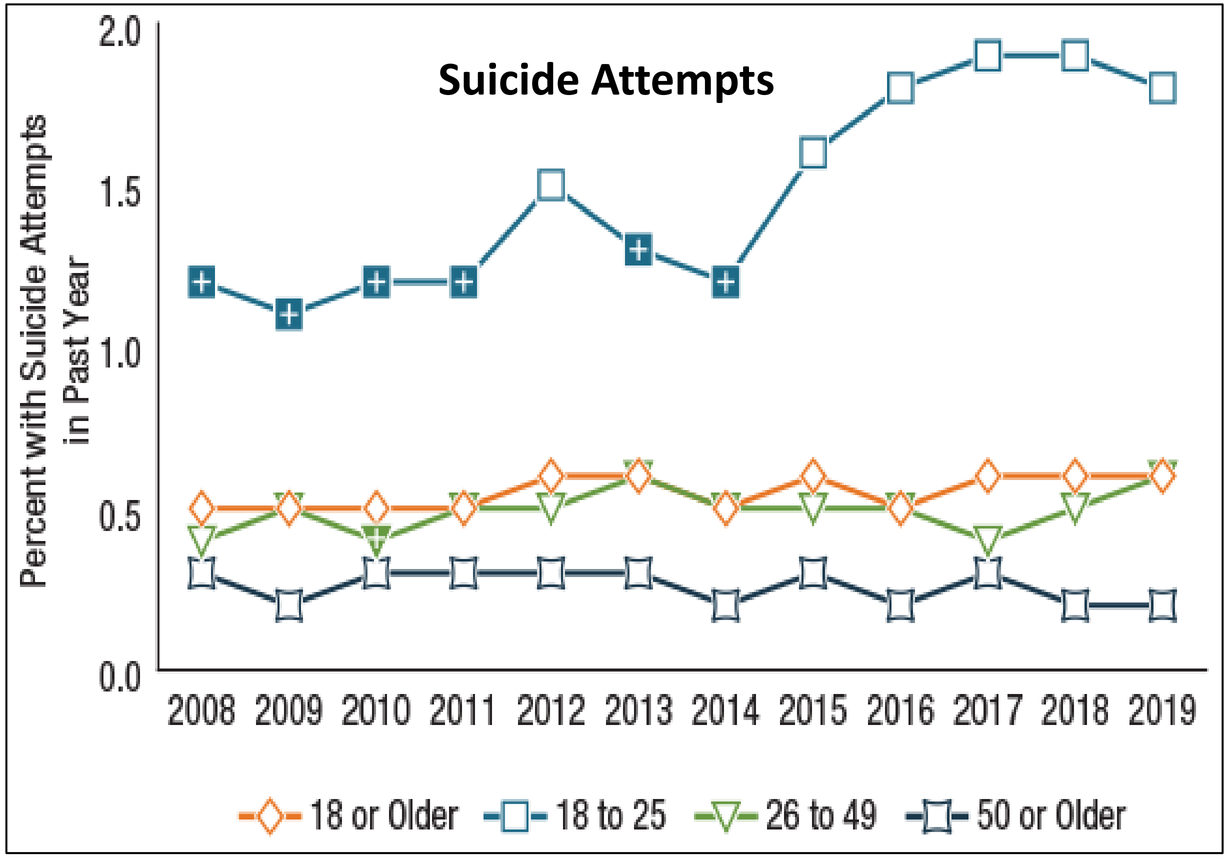
(CDC, 2022)



Suicide Statistics within the U.S.

Results from the 2019 National Survey on Drug Use and Health Suggest that Rates of Suicidal Ideation and Suicide Attempts are Increasing Rapidly Among 18-25 Year-olds

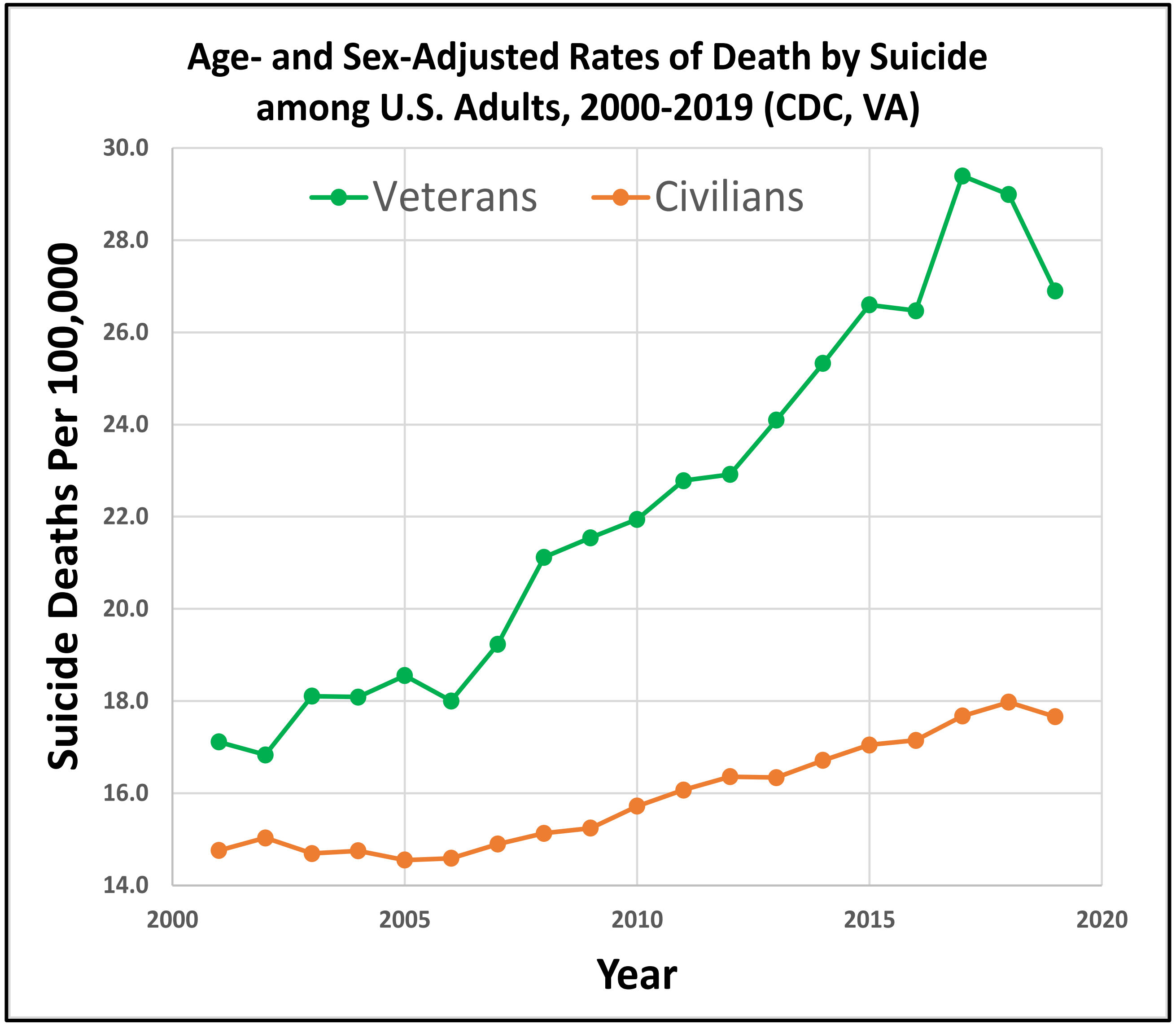




Suicide Statistics within the U.S.

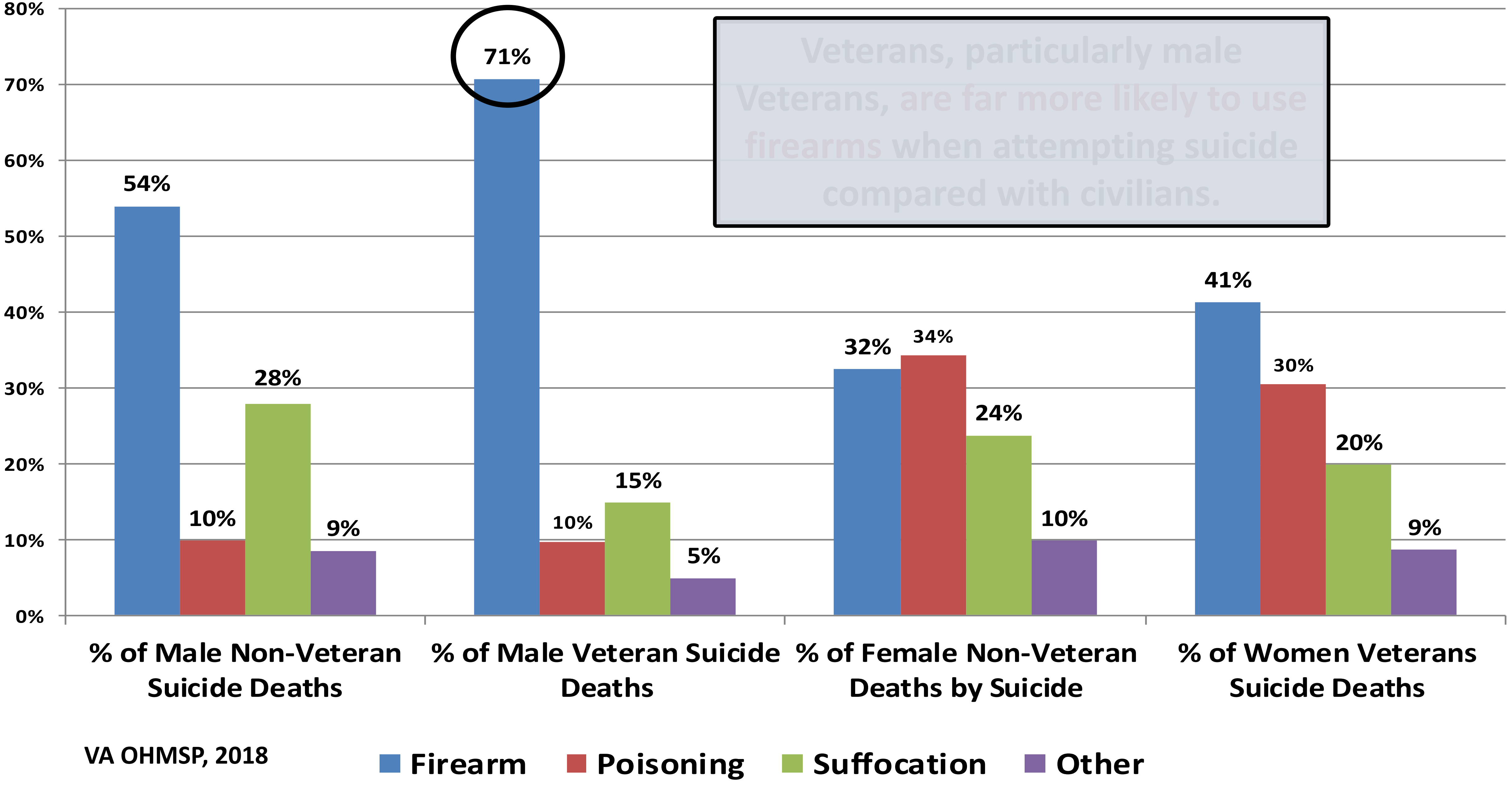
Unfortunately, much of the increase in suicide rates observed in the U.S. during the past 20 years has been due to the **dramatic increase in the suicide mortality rate among U.S. military Veterans.**

In fact, the suicide mortality rate among U.S Veterans increased by **57%** from 2001 to 2019, compared with a 20% increase among civilians.



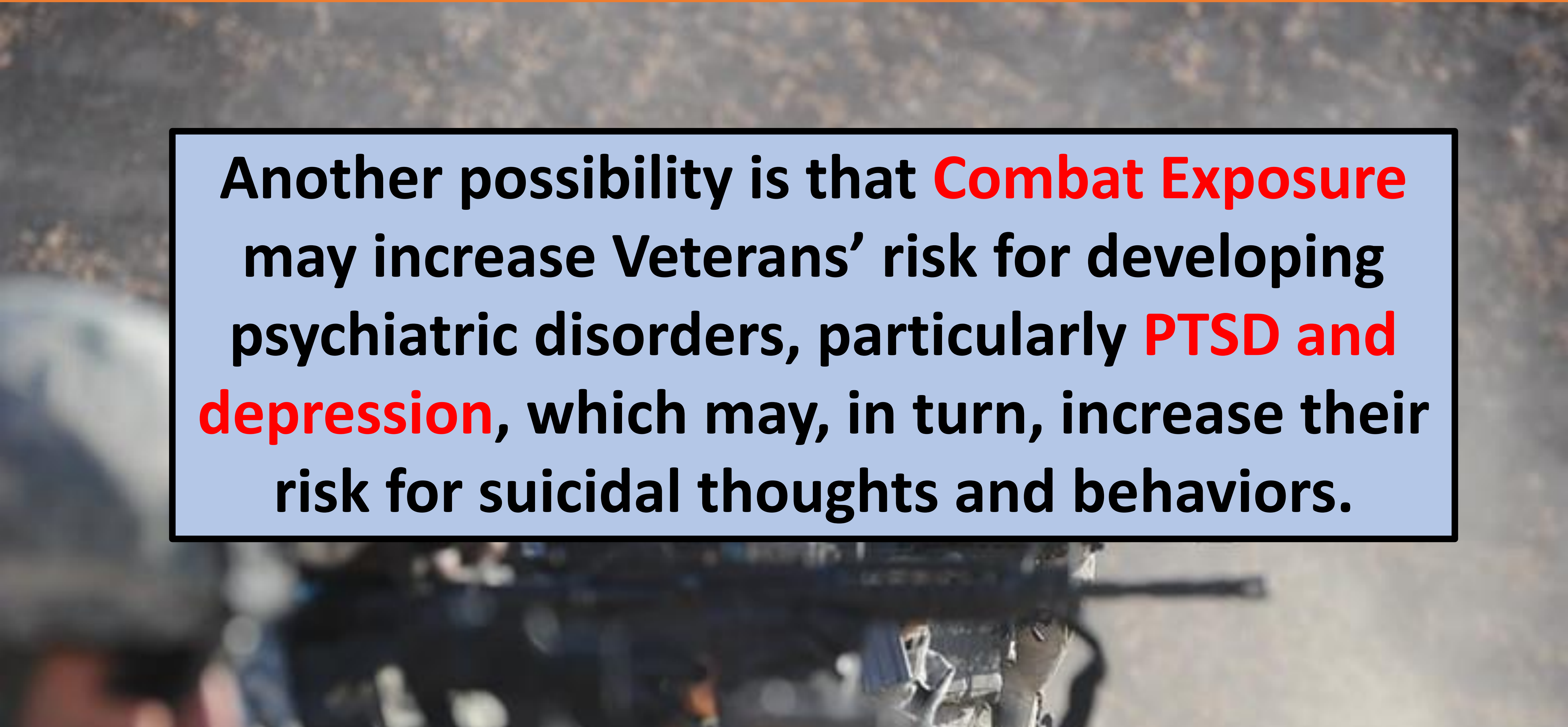
Why has the Suicide Mortality Rate Increased So Rapidly among Veterans during the Past 20 years?

Veterans and Non-Veteran Suicides by Method



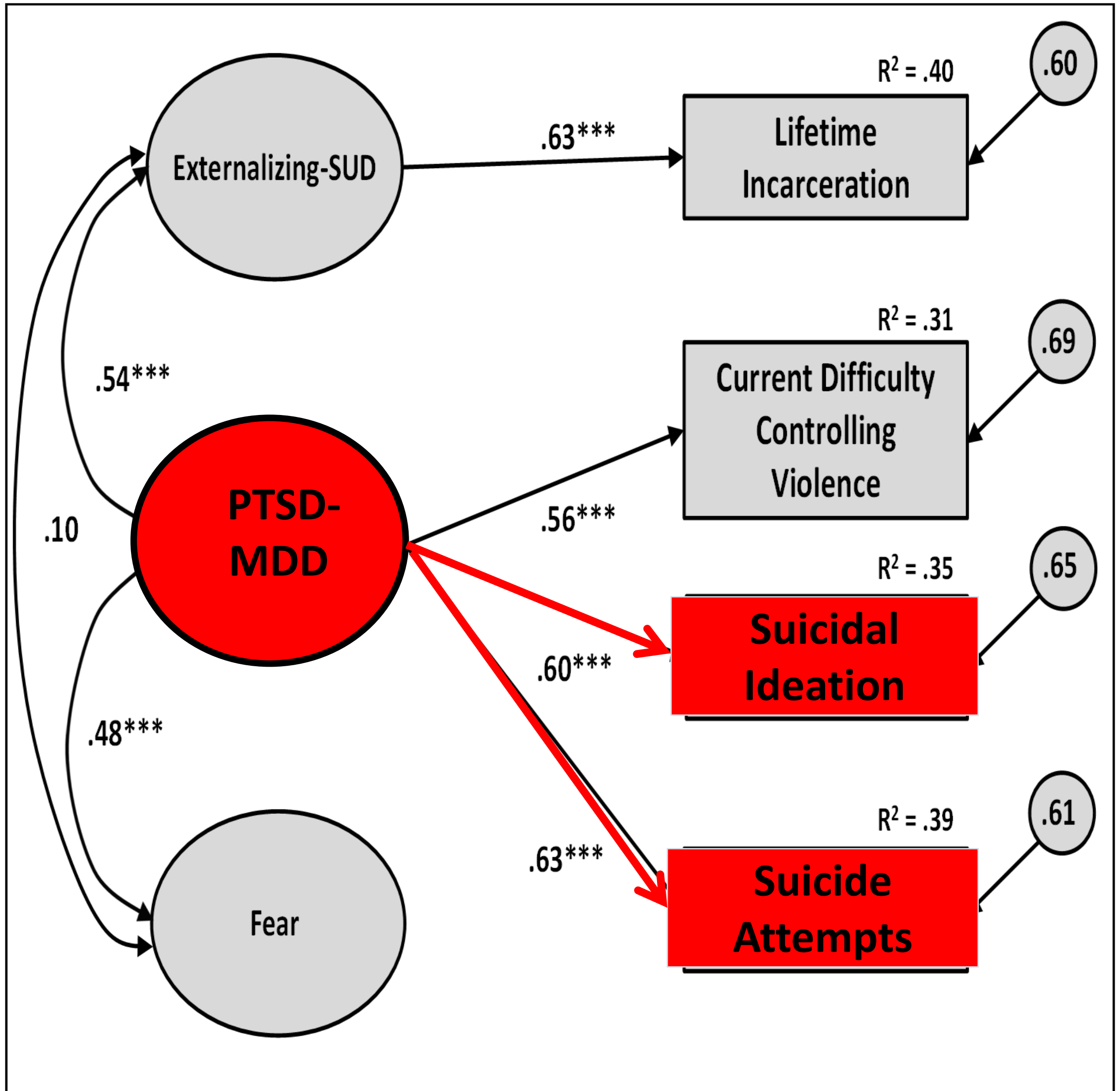
VA OHMSP, 2018

Why has the Suicide Mortality Rate Increased So Rapidly among Veterans during the Past 20 years?

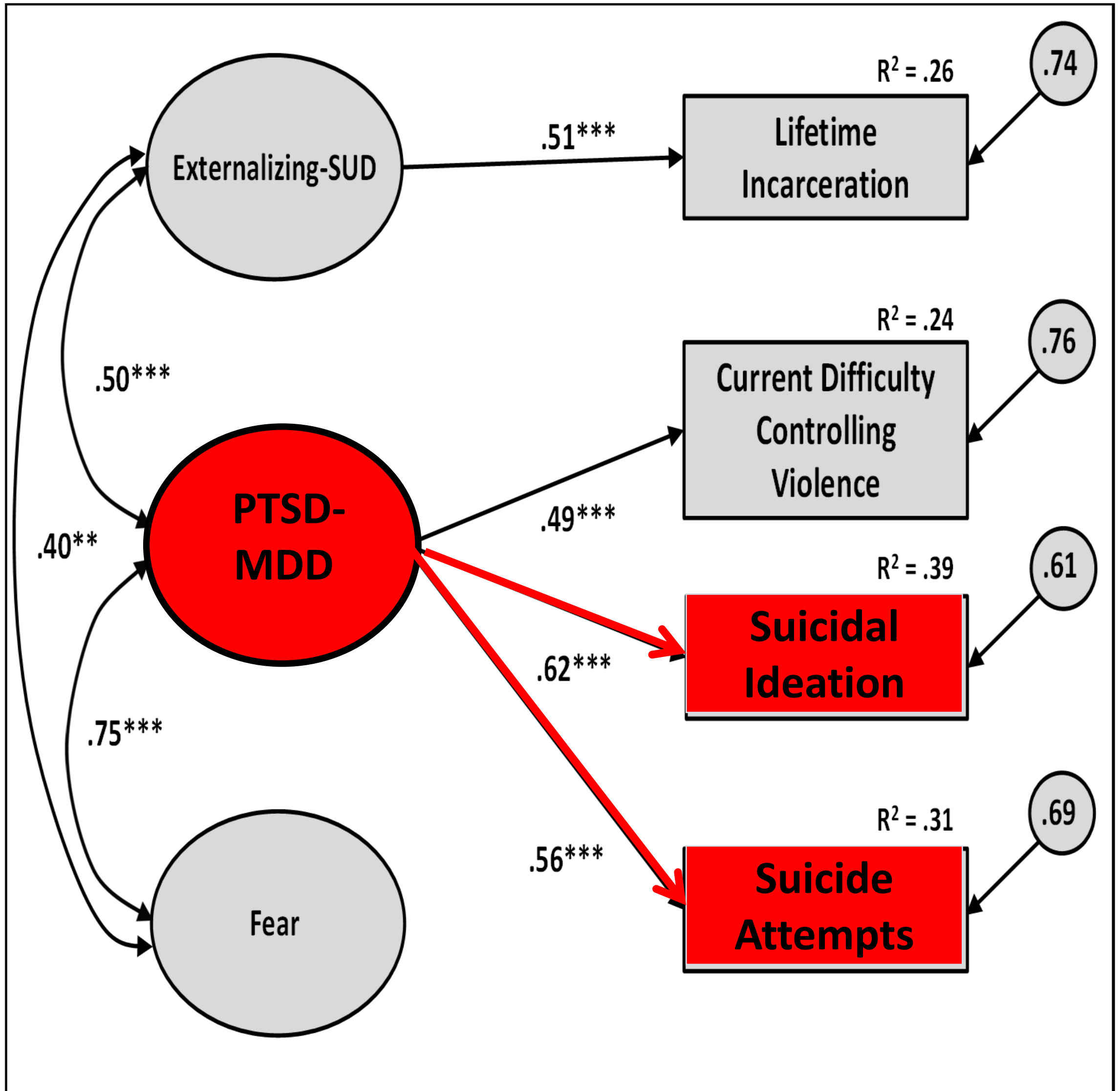


Another possibility is that Combat Exposure may increase Veterans’ risk for developing psychiatric disorders, particularly PTSD and depression, which may, in turn, increase their risk for suicidal thoughts and behaviors.

PTSD and Depression are strongly associated with suicidal ideation and attempts in Veterans



Alternative Structural Model in Sample 1 (*n* =925)



Alternative Structural Model in Sample 2 (*n* =972)

(Kimbrel, Calhoun et al., 2014)

Dillon and colleagues (2018) have shown that combat exposure appears to primarily affect risk for suicidal behavior through its effects on PTSD and Depression Symptoms

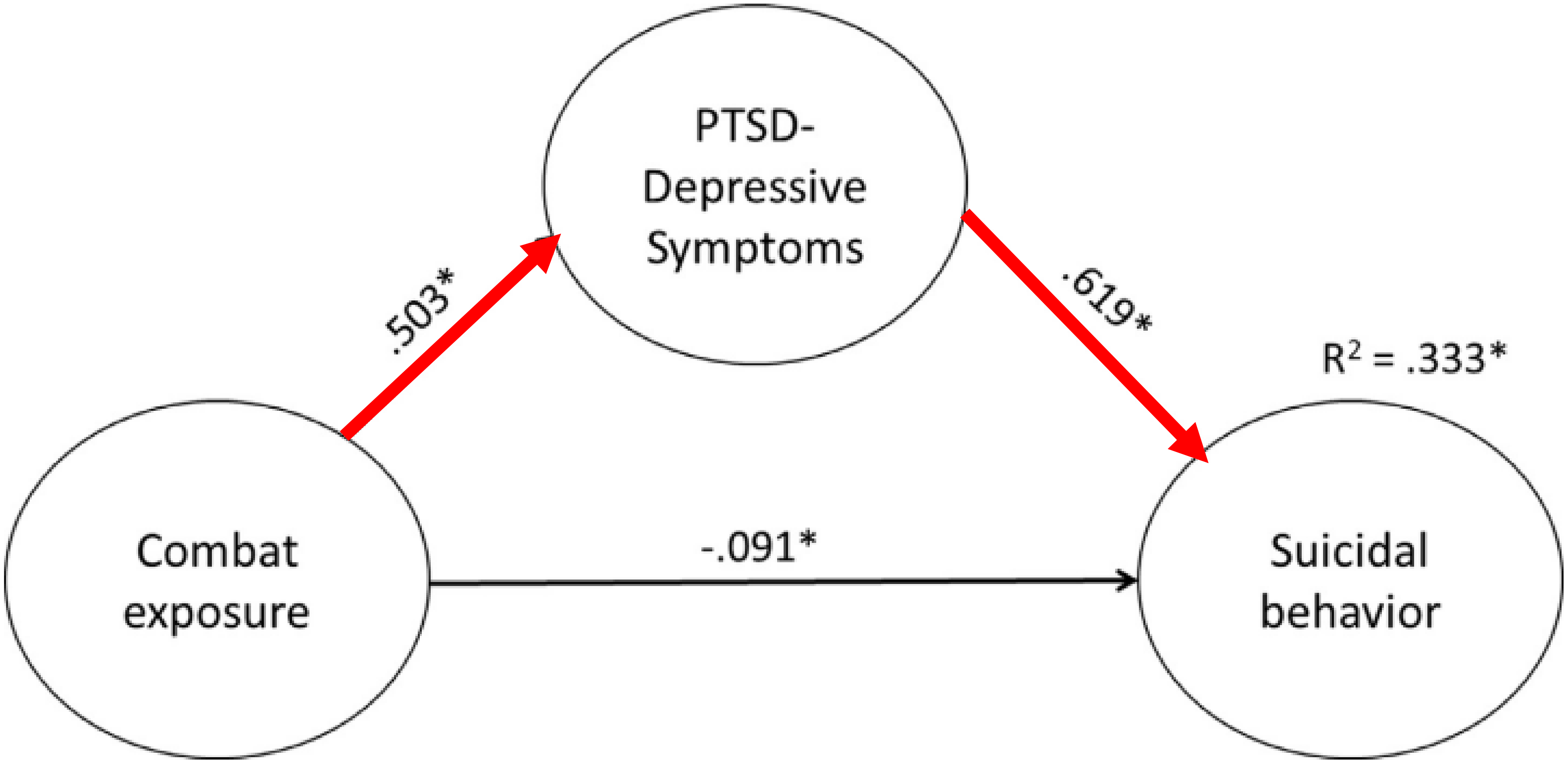
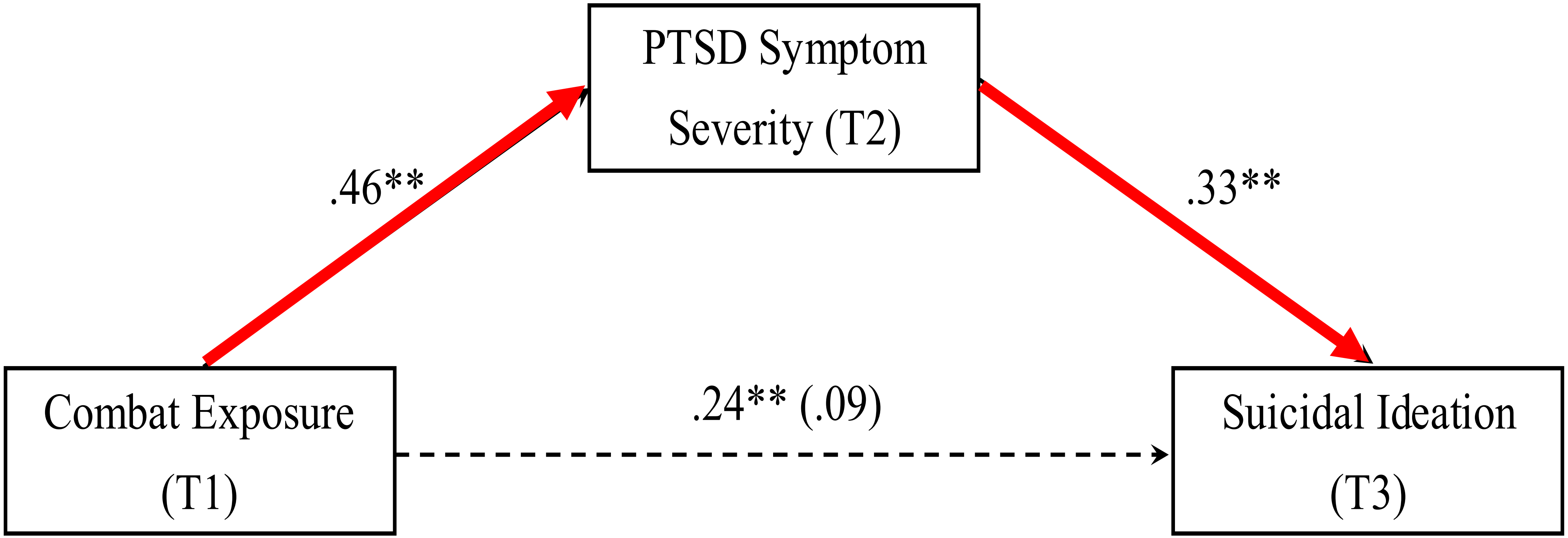
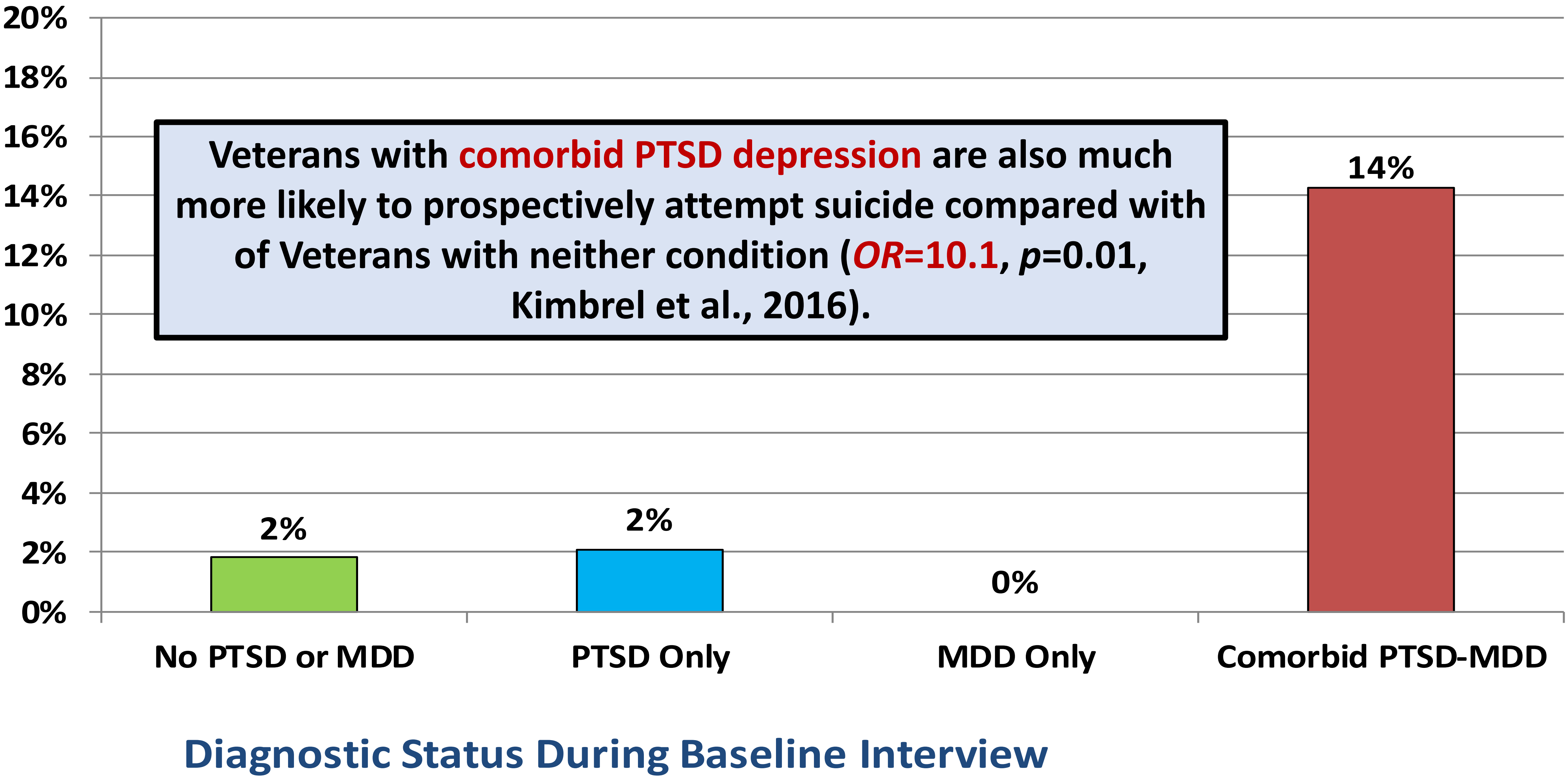


Fig. 3. Model E: Hypothesized partial mediation model with standardized beta weights.

The combat-> PTSD -> suicidal ideation model also holds when tested longitudinally over a 12-month period of time (Glenn, Dillon et al., 2020)



Rates of Prospective Suicide Attempts During the 12 Months Following Baseline Assessment (Kimbrel et al., 2016)



Other Psychiatric Disorders (e.g., Substance Use Disorders) Also Significantly Increase Risk for Suicide

Meta-Analysis of Mood Disorders, SUDs, and Suicide Based on Psychological Autopsies (Conner et al, 2019)		
Disorder	**N of studies**	**OR**
Mood disorder	18	14.34
Major depression	19	9.14
Bipolar disorder	8	3.7
Substance use disorder	20	4.09
Drug use disorder	**8**	**7.18**
Alcohol abuse	5	3.9
Alcohol dependence	8	4.4
Alcohol use disorder	11	3.68

Any Mood Disorder Remains One of the Single Best Predictors of Death by Suicide Identified to Date

Meta-Analysis of Mood Disorders, SUDs, and Suicide Based on Psychological Autopsies (Conner et al, 2019)		
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However, it is very important to note that the vast majority of Veterans with PTSD, depression, and/or a substance use disorder will never make a suicide attempt.

The Key Problem We Are Working to Address

While there are many well-established predictors of death by suicide and suicide attempts (e.g., sex, age, veteran status, PTSD, mood disorders, SUD, etc); **longitudinal prediction of future suicidal behavior using existing clinical assessment tools remains a major challenge within the field of psychiatry**.

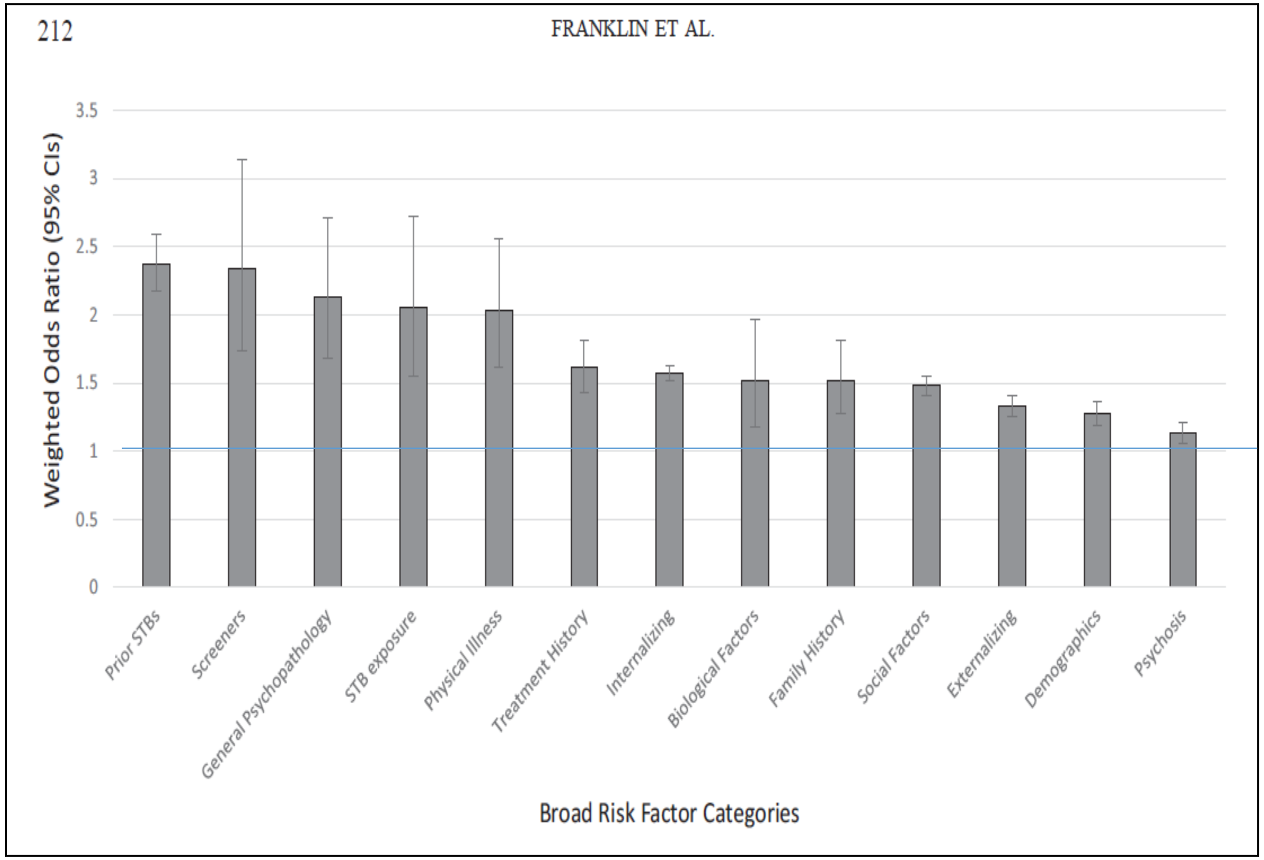
(Franklin et al., 2017; Kimbrel et al., 2021; Guiterrez et al., 2019; Runeson et al., 2017)

How Good Are Existing Longitudinal Predictors?

- Franklin and colleagues (2017) meta-analyzed the past 50 years of research on longitudinal predictors of suicidal behavior

- They concluded that prospective prediction of suicidal behavior (***including suicide risk screeners***) was only "***slightly better than chance***" at present

- Overall weighted odds ratio for longitudinal predictors of suicide attempts was **1.5**



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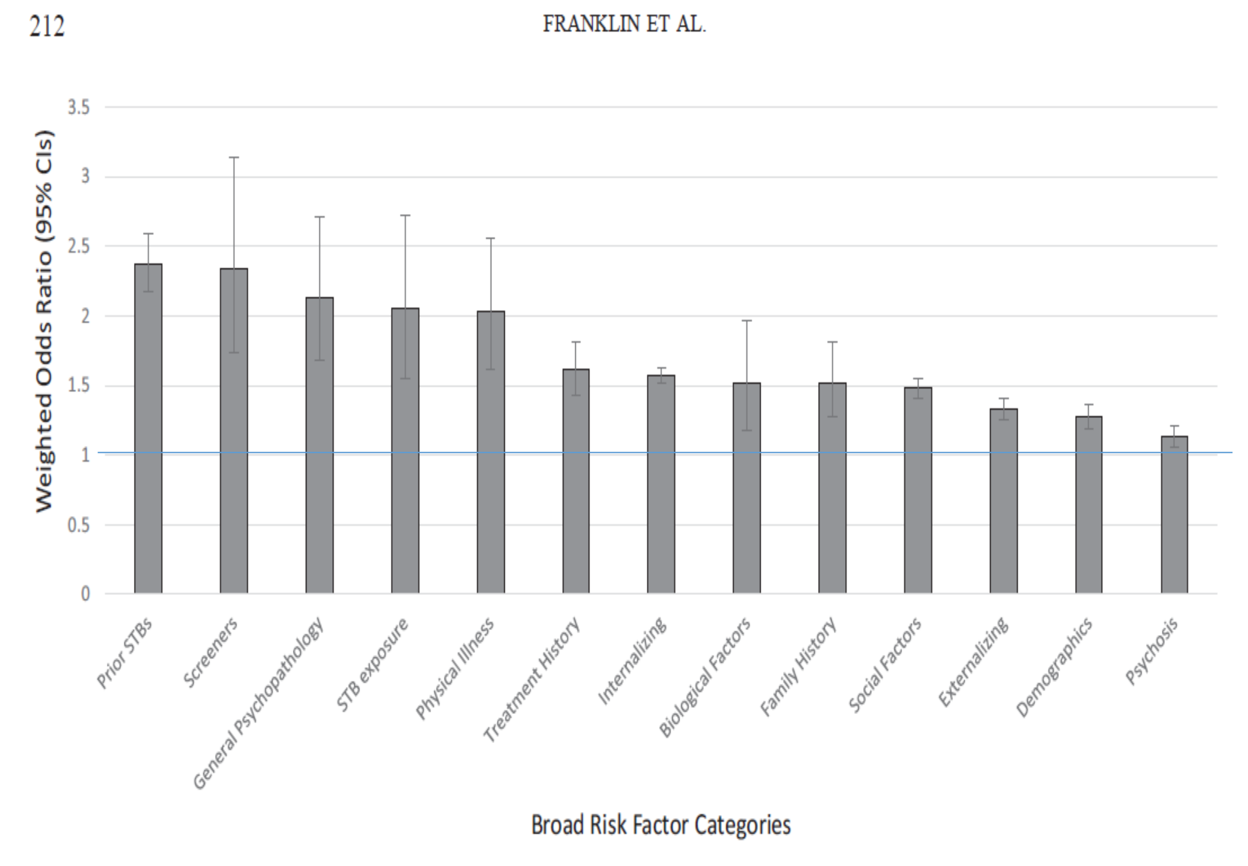
When **diagnostic accuracy** was examined, no risk factor category (***including suicide screeners***) had a weighted area under the curve (AUC) greater than 0.61 for the prediction of future suicide attempts and none greater than 0.67 for suicide deaths.



Current State of Clinical Assessments for Suicide Risk

- A 2019 study by Guiterrez et al. designed to prospectively evaluate the validity of several commonly used suicide risk instruments to predict future suicide attempts found that ***none (including the Columbia/C-SSRS) had an AUC above .67.***

- In 2017, Runeson et al. reviewed a number of frequently used suicide risk instruments including (among others) the C-SSRS, BSS, SPS, the Manchester Self-Harm Rule, and the ReACT Self-Harm Rule and concluded that there is "…***<u>no scientific support for the use of suicide risk instruments for predicting suicidal acts</u>".***

SAD PERSONS Scale

- One of the most common standardized approaches to clinical suicide risk assessment used in the world; routinely used by clinicians

- Several recent studies have found that the AUC for the SAD PERSONS Scale for prediction of future suicide attempts is not better than chance (AUC's from 0.51-0.57)

S	Male **S**ex
A	**A**ge < 20 or > 44
D	**D**epression
P	**P**revious Attempt
E	**E**thanol Abuse
R	Loss of **R**ational Thinking
S	**S**ocial Supports Lacking
O	**O**rganized Plan
N	**N**o Spouse
S	**S**ickness

Clinician Prediction of Suicide Risk

Clinician prediction of suicide risk also has very real limits.

- Woodford et al. (2019) conducted a meta-analysis analyzing clinicians' ability to accurately predict future self-harm and concluded that ***clinician estimation of future self-harm was too inaccurate to be clinically useful (AUC = .60)***

Background

There remains a pressing need for a suicide attempt risk assessment tool that is capable of helping clinicians to accurately identify individuals at risk for attempting suicide in the future.

Durham Risk Score (Kimbrel et al, 2021)

- We hypothesized that by combining a **broad array of empirically-supported risk factors into a simple-to-use risk calculator** that we could significantly enhance clinicians' ability to identify patients at risk for attempting suicide.

- Our goal was to create a **chronic suicide risk calculator** similar in nature to the well-known Framingham Risk Score and pooled cohort equations that are widely used to predict 10-year risk of cardiovascular disease.

Participants

- Development of the Durham Risk Score (DRS) involved secondary analysis of three longitudinal datasets (NESARC, VALOR, & REHAB) with 1-3 year follow-up suicide attempt data available for analysis

  - Total Sample Size: N = 35,654
    - Combined Development Cohort: N=17,630
      - (NESARC 1, NESARC 2, REHAB)
    - Combined Validation Cohort: N=18,024
      - (NESARC 3, NESARC 4, VALOR)

Analytical Approach

- Both rational and quantitative approaches were used to develop the DRS.

- ROC curves were used to identify prospective predictors that uniquely contributed to the prediction of future attempts within the context of other risk factors.

- Algorithm building analyses were conducted in the development samples in an iterative fashion until no additional variables could be identified that improved our ability to prospectively predict suicide attempts.

To be retained in the final version of the checklist, each variable needed to:

1. Have clear empirical support in the literature
2. Demonstrate a positive bivariate association with future suicide attempts in one or more of the development samples
3. Evidence incremental validity in one or more of the development samples in iterative ROC analyses; and
4. Show minimal negative impact on incremental validity in the remaining development samples in the iterative ROC analyses.

Variable Selection

- Variable selection began with a review of the literature to identify variables that had **prior empirical support.**
- We prioritized variables identified by Franklin and colleagues meta-analysis as top longitudinal predictors of suicide attempts/death by suicide.
- This meta-analysis was also used to rank broad categories of predictors.

Top 5 Longitudinal Predictors of **Suicide Attempts** Identified by Franklin et al. (2017)		
Rank	**Variable**	**wOR**
1	Prior Nonsuicidal Self-Injury	4.15
2	Prior Suicide Attempt	3.41
3	Screening Instrument	2.51
4	Personality Disorder	2.35
5	Prior Psychiatric Hospitalization	2.32
	Overall wOR (all effect sizes)	**1.51**

Top 5 Longitudinal Predictors of **Suicide Deaths** Identified by Franklin et al. (2017)		
Rank	**Variable**	**wOR**
1	Prior Psychiatric Hospitalization	3.57
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Durham Risk Score Constructs

- Hx of suicide attempt
- Hx of suicidal ideation
- Hx of nonsuicidal self-injury
- Hx of psychiatric/SUD hospitalization
- Lifetime borderline PD
- Lower SES
- Unemployed
- Less than HS education
- Lifetime mood disorder
- Current PTSD
- Extreme sleep problems
- Current SUD
- Weekly binge drinking
- Current smoker
- Perceives health as poor
- Hx of sexual abuse/assault
- Hx of physical abuse
- Hx of violence/incarceration
- LGBTQ+ status
- Female sex at birth
- Under 35 years of age

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Scoring & Interpretation are Simple

- 19 items are scored as “1” if present
- 4 items (all of which are particularly strong risk factors from the literature) are weighted more heavily and scored as “2” if present
- Clinicians then sum the items to help classify patients’ chronic risk for attempting suicide based on **risk group**

Durham Risk Score Performance

Durham Risk Score: Results

Development Cohort
(N = 17,630)

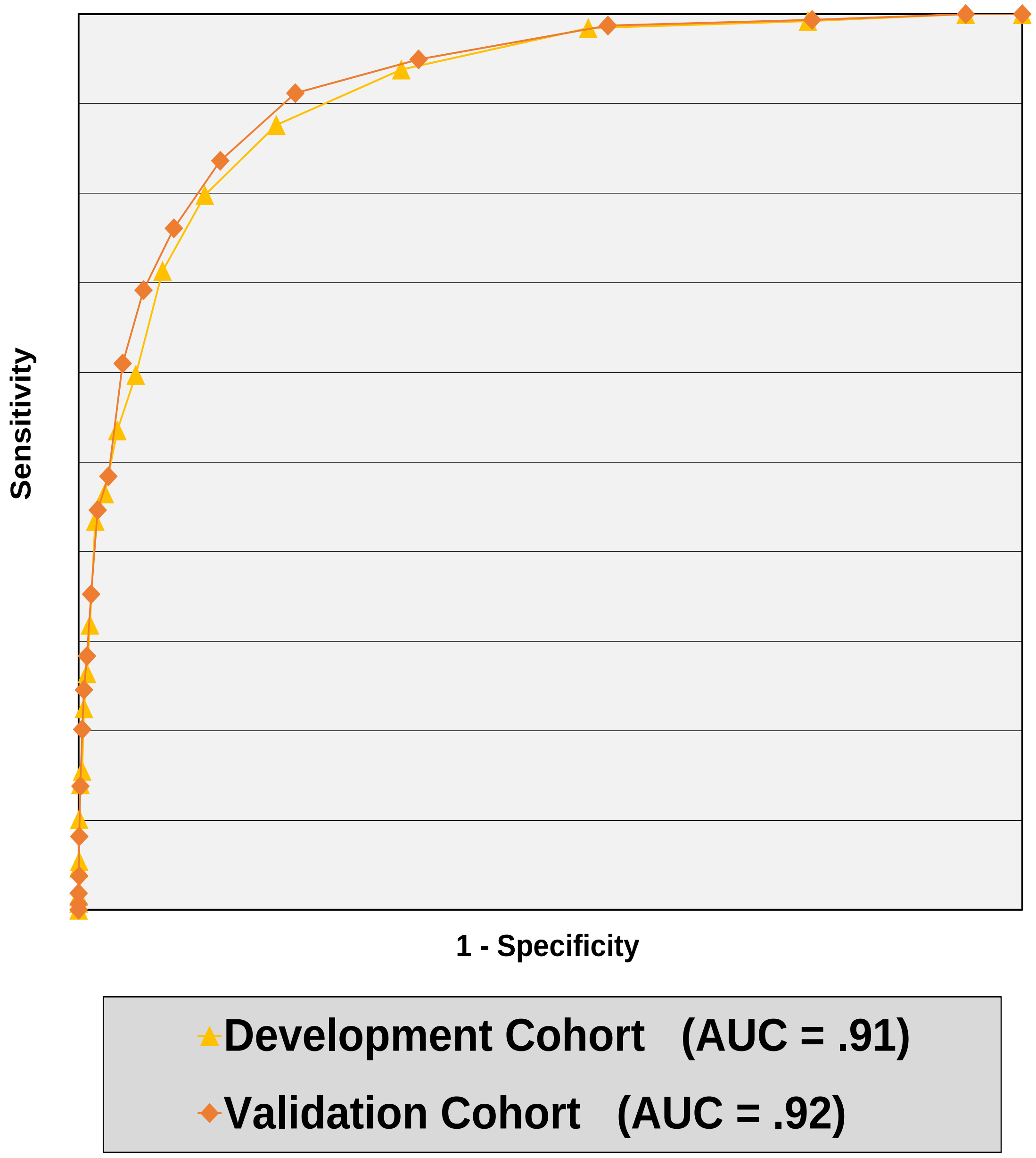
AUC = .91

Validation Cohort
(N = 18,024)

AUC = .92

Figure 1A

ROC Curves for the DSRS in the Combined Development and Validation Cohorts



Durham Risk Score: Results

Men

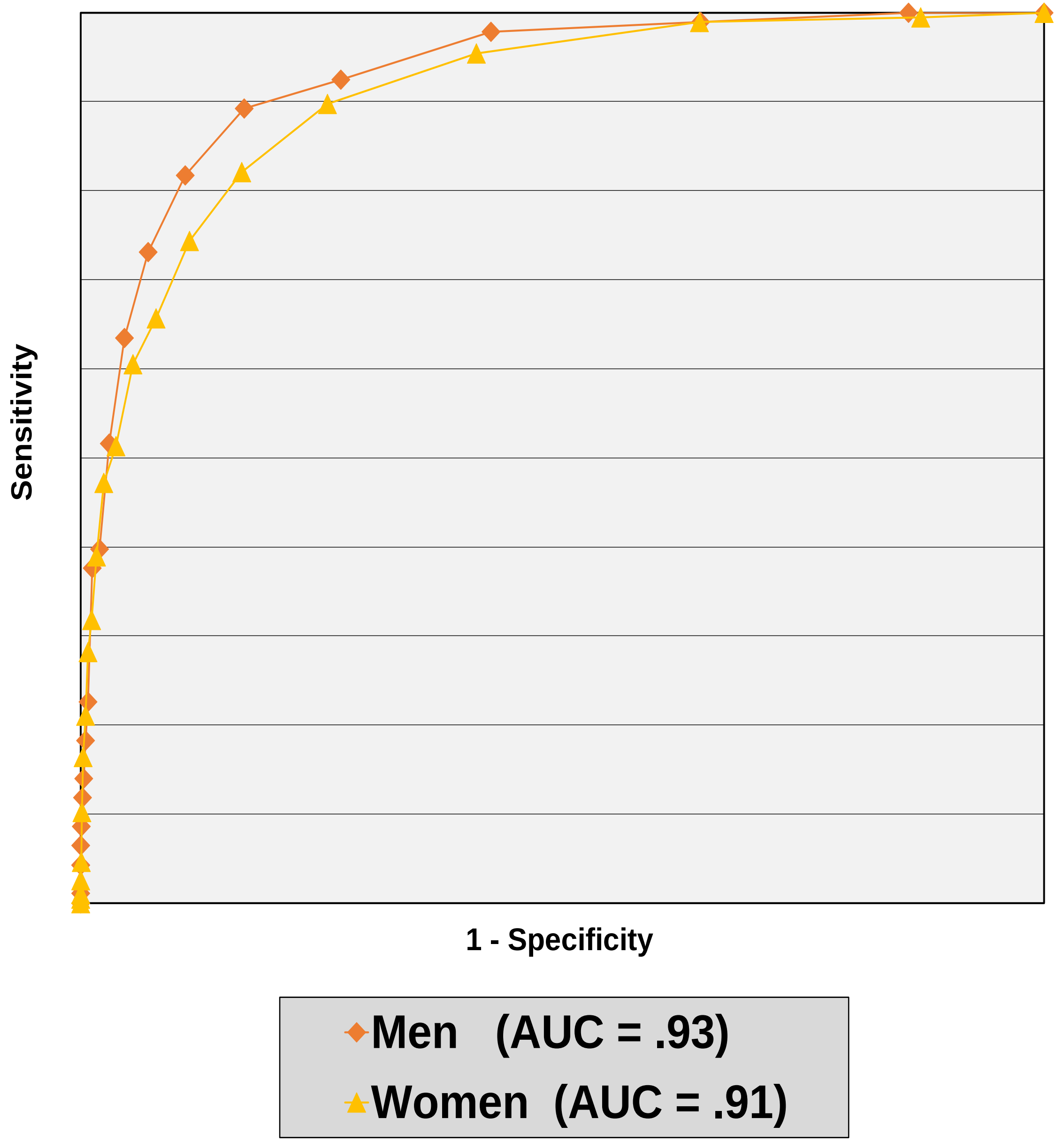
AUC = .93

Women

AUC = .91

Figure 1C

ROC Curves for the DSRS Among Male and Female Participants



Durham Risk Score: Results

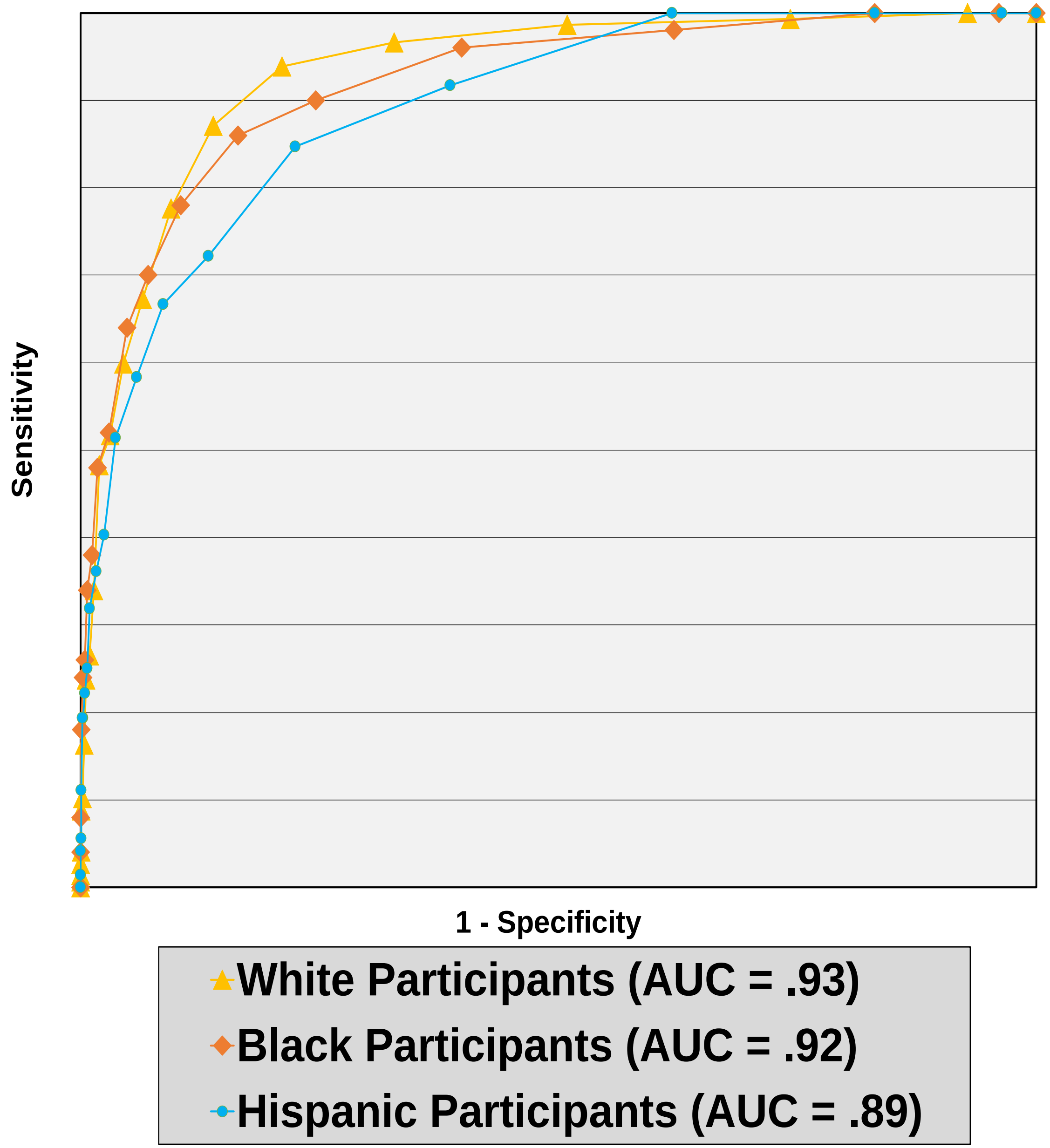
White Participants
AUC = .93

Black Participants
AUC = .92

Hispanic Participants
AUC = .89

Figure 1D

ROC Curves for the DSRS Among White, Black, and Hispanic Participants



Durham Risk Score: Results

Veteran Participants
AUC = .91

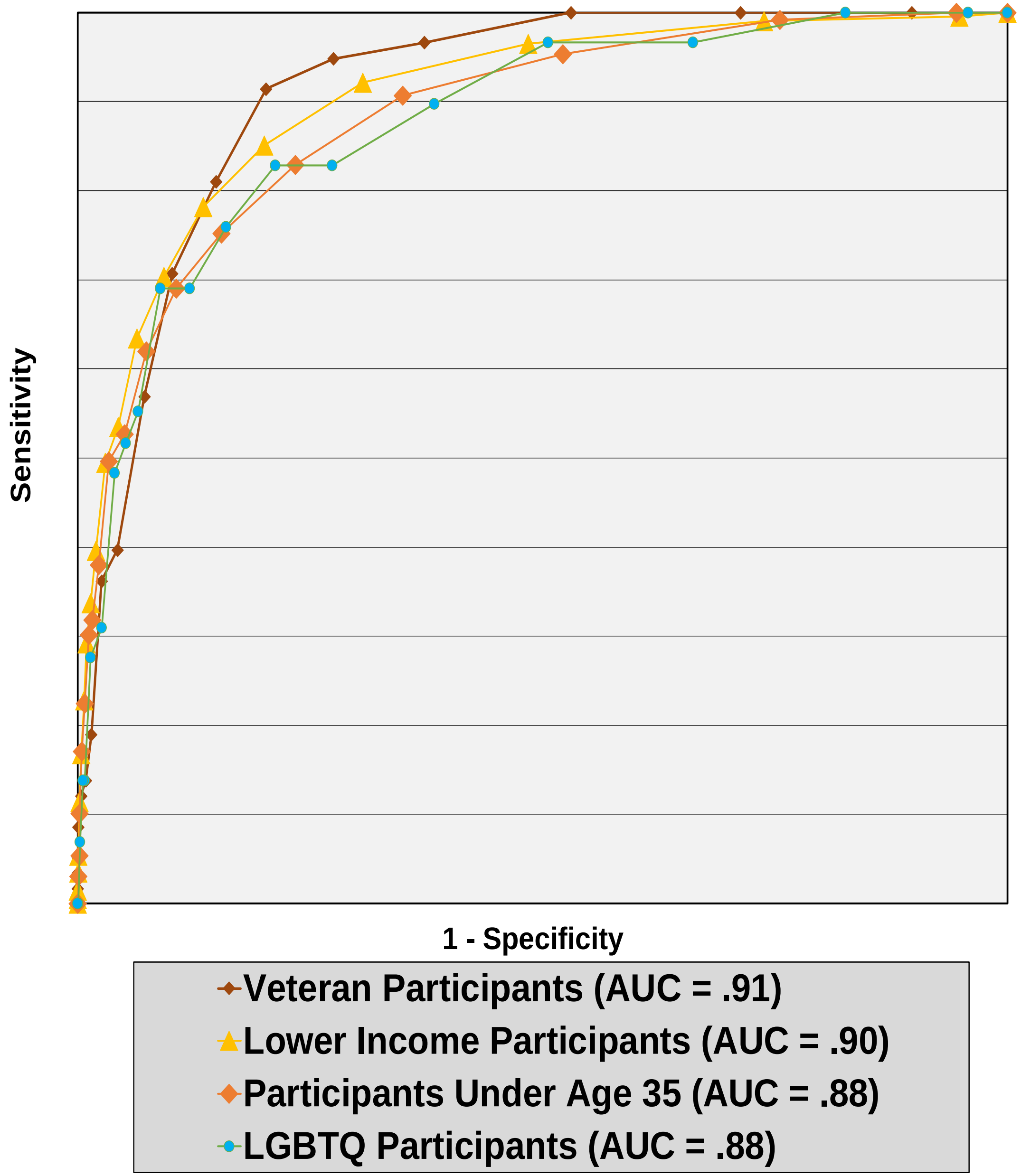
Lower Income Participants
AUC = .90

Younger Participants (<35)
AUC = .88

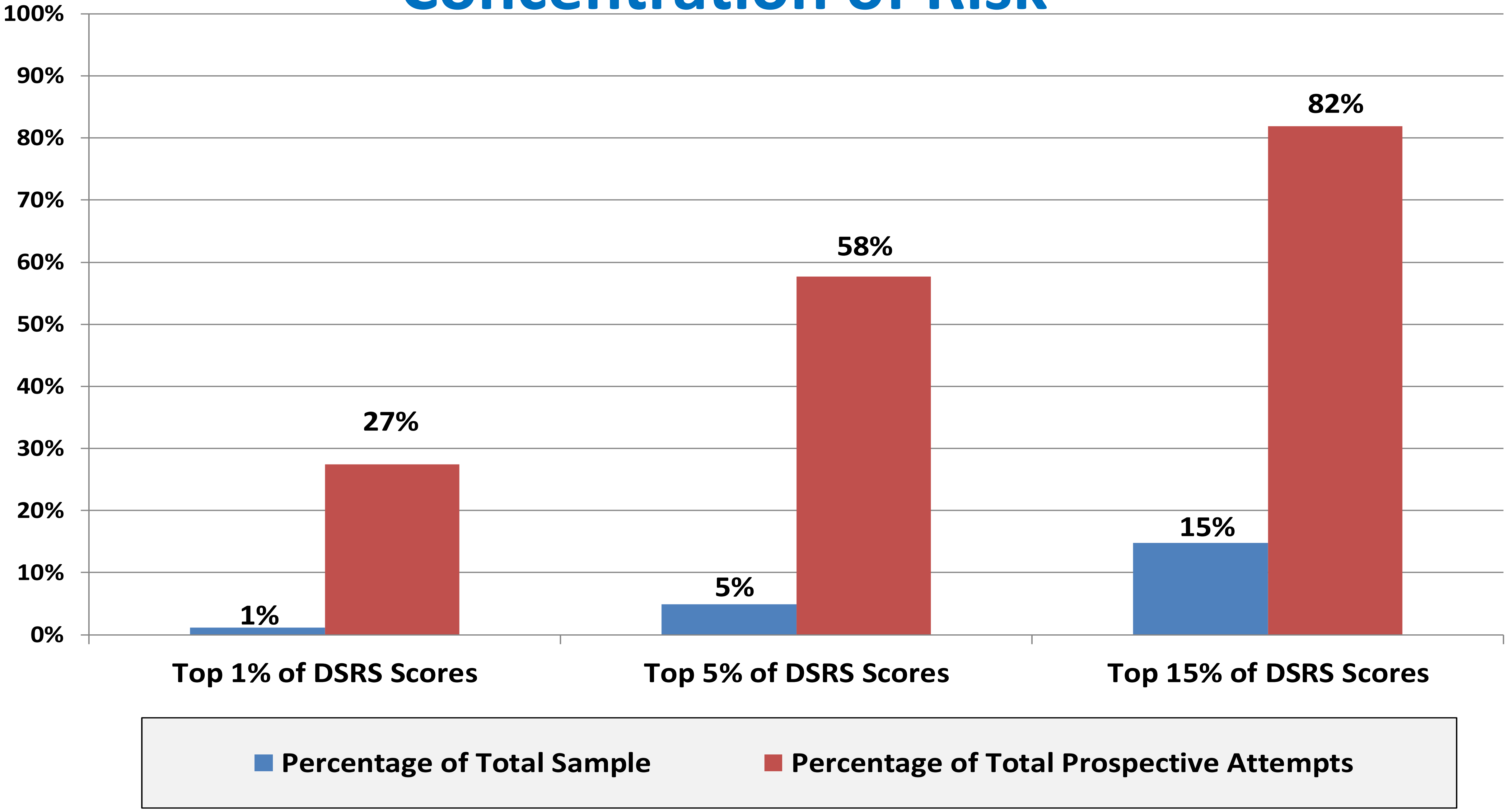
LGBTQ+ Participants
AUC = .88

Figure 1E

ROC Curves Among Veteran, Lower Income, Younger, and LGBTQ Participants



Concentration of Risk



Suicide Risk Groups Simplify Scoring & Interpretation

DSRS Total Score	Suicide Risk Group	% of Sample	Controls	Attempts	Total	Rate	Risk Ratio	Odds	Odds Ratio	Predicted Probability
0 - 2	Lowest Risk	44.6%	15,899	4	15,903	0.03%	1.0	0.0003	1.0	0.03%
3 - 5	Low Risk	40.6%	14,427	48	14,475	0.3%	13.2	0.003	13.2	0.3%
6 - 8	Moderate Risk	9.9%	3,475	70	3,545	2%	78.5	0.02	80.1	2%
9 - 11	High Risk	3.3%	1,107	69	1,176	6%	233.3	0.06	247.7	6%
12 - 14	Very High Risk	1.0%	317	45	362	12%	494.2	0.14	564.2	12%
15 - 30	Highest Risk	0.5%	141	52	193	27%	1071.2	0.37	1,465.9	27%

Suicide Risk Groups Simplify Scoring & Interpretation

DSRS Total Score	Suicide Risk Group	% of Sample	Controls	Attempts	Total	Rate	Risk Ratio	Odds	Odds Ratio	Predicted Probability
0 - 2	Lowest Risk	44.6%	15,899	4	15,903	0.03%	1.0	0.0003	1.0	0.03%
3 - 5	Low Risk	40.6%	14,427	48	14,475	0.3%	13.2	0.003	13.2	0.3%
6 - 8	Moderate Risk	9.9%	3,475	70	3,545	2%	78.5	0.02	80.1	2%
9 - 11	High Risk	3.3%	1,107	69	1,176	6%	233.3	0.06	247.7	6%
12 - 14	Very High Risk	1.0%	317	45	362	12%	494.2	0.14	564.2	12%
15 - 30	Highest Risk	0.5%	141	52	193	27%	1071.2	0.37	1,465.9	27%

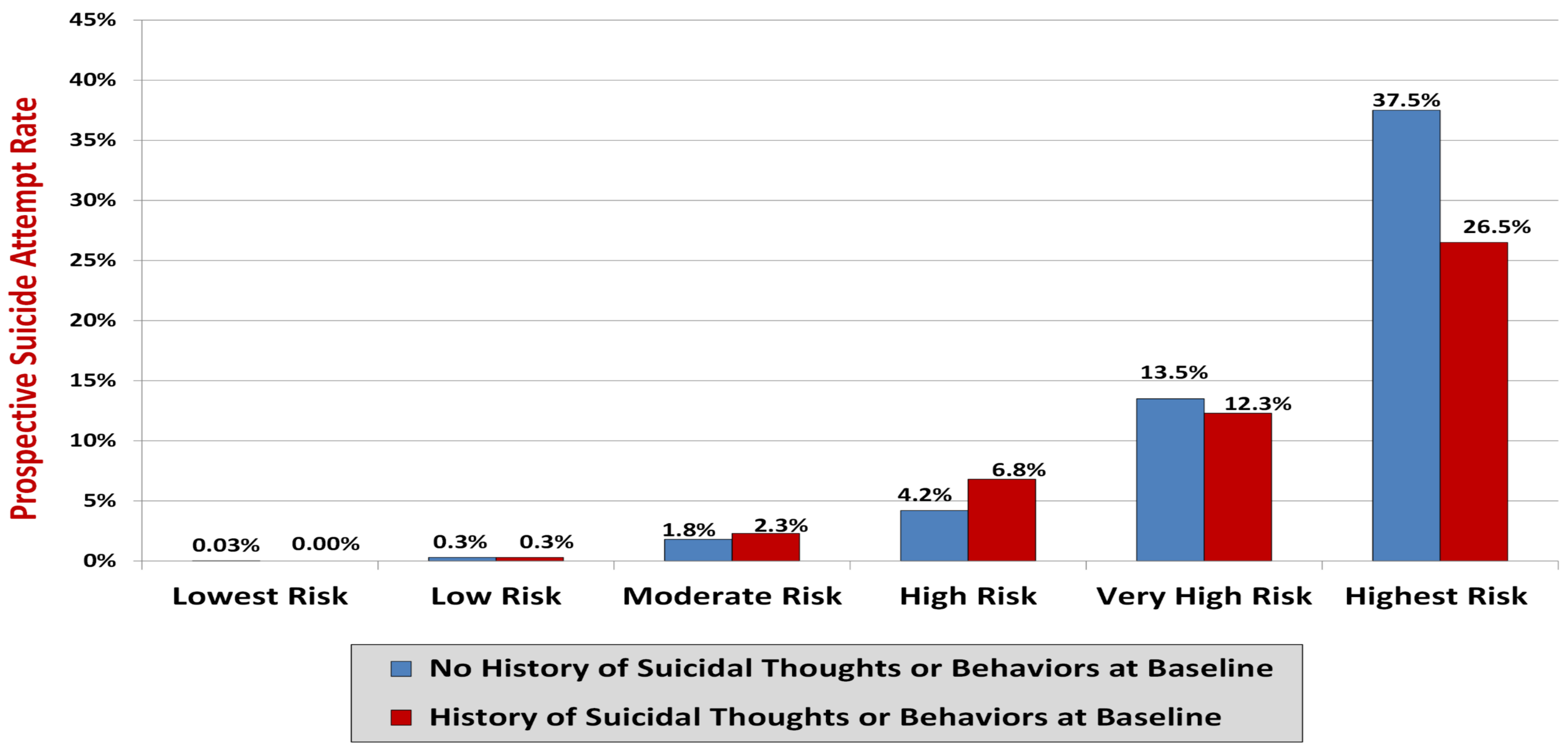
Cut Scores & Risk Groups

- Cut score 6+ (Moderate Risk Group)
  - Optimal general screening score
  - 82% sensitivity, 86% specificity, 4% PPV, 100% NPV
  - Cost-Effective to do Safety Planning

- Cut score of 9+ (High Risk Group)
  - 96% specificity, 58% sensitivity, 10% PPV of 10%, 100% NPV
  - Cost-Effective to do CBT-SP, DBT, or other intensive tx

- Cut score of 15+ (Highest Risk Group)
  - 100% specificity, 18% sensitivity, 27% PPV, 99%

Durham Suicide Risk Groups Work Equally Well for Individuals with and without a History of SITB



Durham Risk Score

- Our hope is that the DRS will substantially improve clinicians' ability to identify individuals at greatest risk for suicide.
- Systematic assessment of DRS constructs and entry into the EHR could also help to dramatically improve the quality of EHR data available for AI/ML-based algorithms, such as REACH VET

Study Limitations and Future Directions

- The primary limitation of this work is its reliance on secondary data to develop and validate the score.

- More research is needed to independently validate the DRS in prospective studies

- Additional research is also needed to identify the optimal methods to assess each of the constructs used to calculate the Durham Risk Score, particularly **nonsuicidal self-injury (NSSI)**

Top 5 Longitudinal Predictors of **Suicide Attempts** Identified by Franklin et al. (2017)		
Rank	**Variable**	**wOR**
1	Prior Nonsuicidal Self-Injury	4.15
2	Prior Suicide Attempt	3.41
3	Screening Instrument	2.51
4	Personality Disorder	2.35
5	Prior Psychiatric Hospitalization	2.32
	Overall wOR (all effect sizes)	**1.51**

Top 5 Longitudinal Predictors of **Suicide Deaths** Identified by Franklin et al. (2017)		
Rank	**Variable**	**wOR**
1	Prior Psychiatric Hospitalization	3.57
2	Prior Suicide Attempt	2.24
3	Prior Suicidal Ideation	2.22
4	Lower Socioeconomic Status	2.20
5	Stressful Life Events	2.18
	Overall wOR (all effect sizes)	**1.50**

ons and Future Directions

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validate the score.

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also needed to identify the optimal
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Nonsuicidal Self-Injury (NSSI):

Under-Assessed and Under-Treated

Nonsuicidal Self-Injury (NSSI) refers to the deliberate destruction of one's own body tissue without intent to die

(American Psychiatric Association, 2013; Klonsky, 2007)

It is estimated that around **6%** of adults in the general population have engaged in NSSI at least once during their lifetime (Klonsky, 2011).

Common NSSI behaviors include scratching, cutting, burning, or hitting oneself.

The most common functions of NSSI are to:

- **Release emotional pressure that has built up inside of you (64%)**
- **To get rid of bad feelings (60%)**
- To feel something because you were feeling numb or empty (36%)
- To punish yourself (32%)
- To communicate with someone else or to get attention (28%)
- To get out of doing something or to get away from others (8%)
- More than one of the above (67%)

(Klonsky, 2011)

Nonsuicidal Self-Injury: Under-Assessed and Under-Treated

- NSSI is the strongest predictor of future suicide attempts identified to date (Franklin et al., 2017) and is associated with significant distress and impairment (Doshi et al., 2005; Selby et al., 2012).
- Unfortunately, NSSI has historically been overlooked and under-assessed in many populations, particularly adult men and military veterans (Kimbrel et al, 2017)
- In fact, population-based studies of NSSI have consistently found no differences in the lifetime rate of NSSI between men and women (Klonsky, 2011)

Meta-Analysis of NSSI in Veterans (Gromatsky et al, in press)

"**Results revealed an average NSSI lifetime prevalence rate of 15.76% among SMVs.** Significantly higher prevalence rates were observed among studies of clinical (28.14%) versus community (11.28%) samples and those using interviews to assess NSSI (23.56%) versus self-report (13.44%) or chart review (7.84%)."

Word count: 5,373
Table count: 2
Figure count: 2
Appendix count: 2

The prevalence of nonsuicidal self-injury in military personnel: A systematic review and meta-analysis

Molly Gromatsky*, PhD,[a,b] Tate F. Halverson, PhD,[c,d] Kirsten H. Dillon, PhD,[c,e] Laura C. Wilson, PhD,[f] Stefanie T. LoSavio, PhD, ABPP,[c,e] Samantha Walsh, MLS, MA,[g] Clara Mellows,[h] Adam J. Mann, MS,[i] Marianne Goodman, MD,[a,b] Nathan A. Kimbrel, PhD[c-e,j]

[a]VISN 2 Mental Illness Research, Education and Clinical Center (MIRECC), James J. Peters Veterans Affairs Medical Center, Bronx, NY
[b]Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY
[c]Durham Veterans Affairs (VA) Health Care System, Durham, NC
[d]VA Mid-Atlantic Mental Illness Research, Education and Clinical Center, Durham, NC
[e]Department of Psychiatry and Behavioral Sciences, Duke University School of Medicine, Durham, NC
[f]Department of Psychological Science, University of Mary Washington, Fredericksburg, VA
[g]Levy Library, Icahn School of Medicine at Mount Sinai, New York, NY, USA
[h]Department of Psychology and Neuroscience, University of North Carolina at Chapel Hill, Chapel Hill, NC
[i]Department of Psychology, University of Toledo, Toledo, OH
[j]VA Health Services Research and Development Center of Innovation to Accelerate Discovery and Practice Transformation, Durham, NC

Prevalence of NSSI in the Durham VA PTSD Clinic

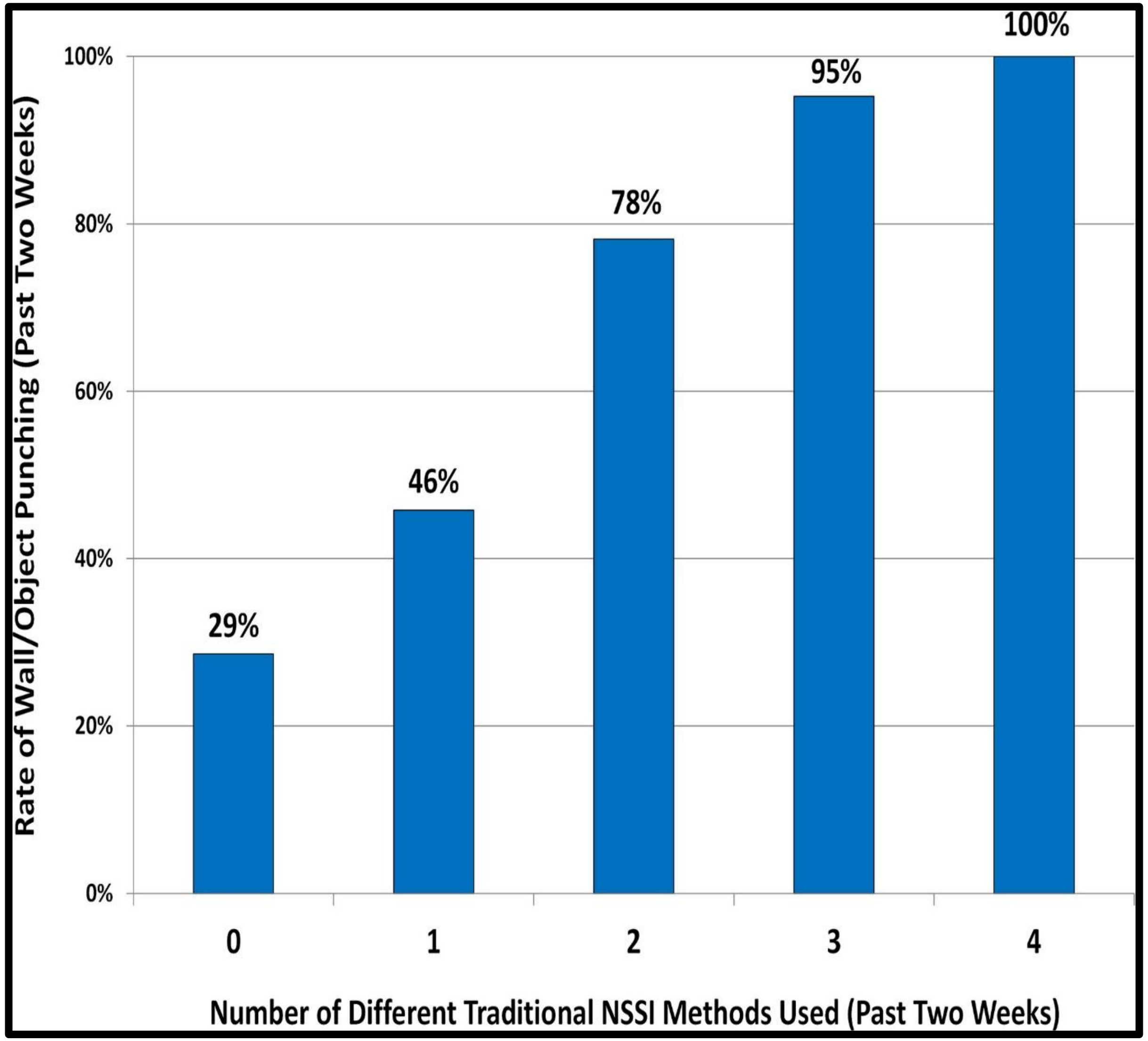
- We evaluated the prevalence of NSSI among 1,143 Veterans seeking treatment in the Durham VA PTSD Clinic, the vast majority of whom were male (~95%)

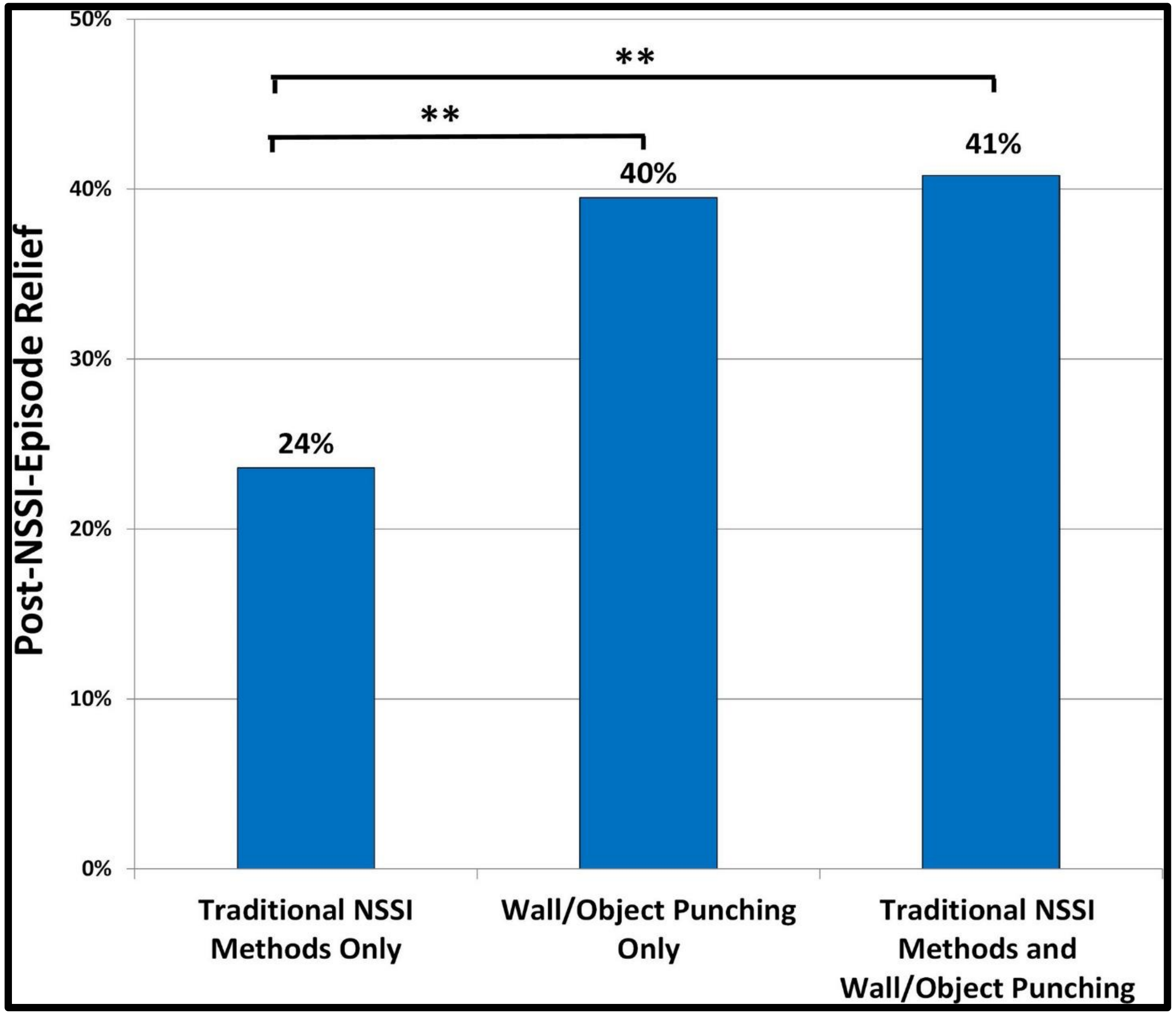
- **62%** (*n* = 705) of the Veterans reported a **lifetime history** of one or more traditional forms of NSSI (i.e., scratching, cutting, burning, or hitting oneself)

- **50%** (*n* = 570) of the Veterans reported engaging in traditional forms of NSSI during the **past two weeks**

(Kimbrel et al, 2018)

Wall/Object Punching is an Under-Recognized form of NSSI that is Especially Common among Veterans (Kimbrel et al, 2018)





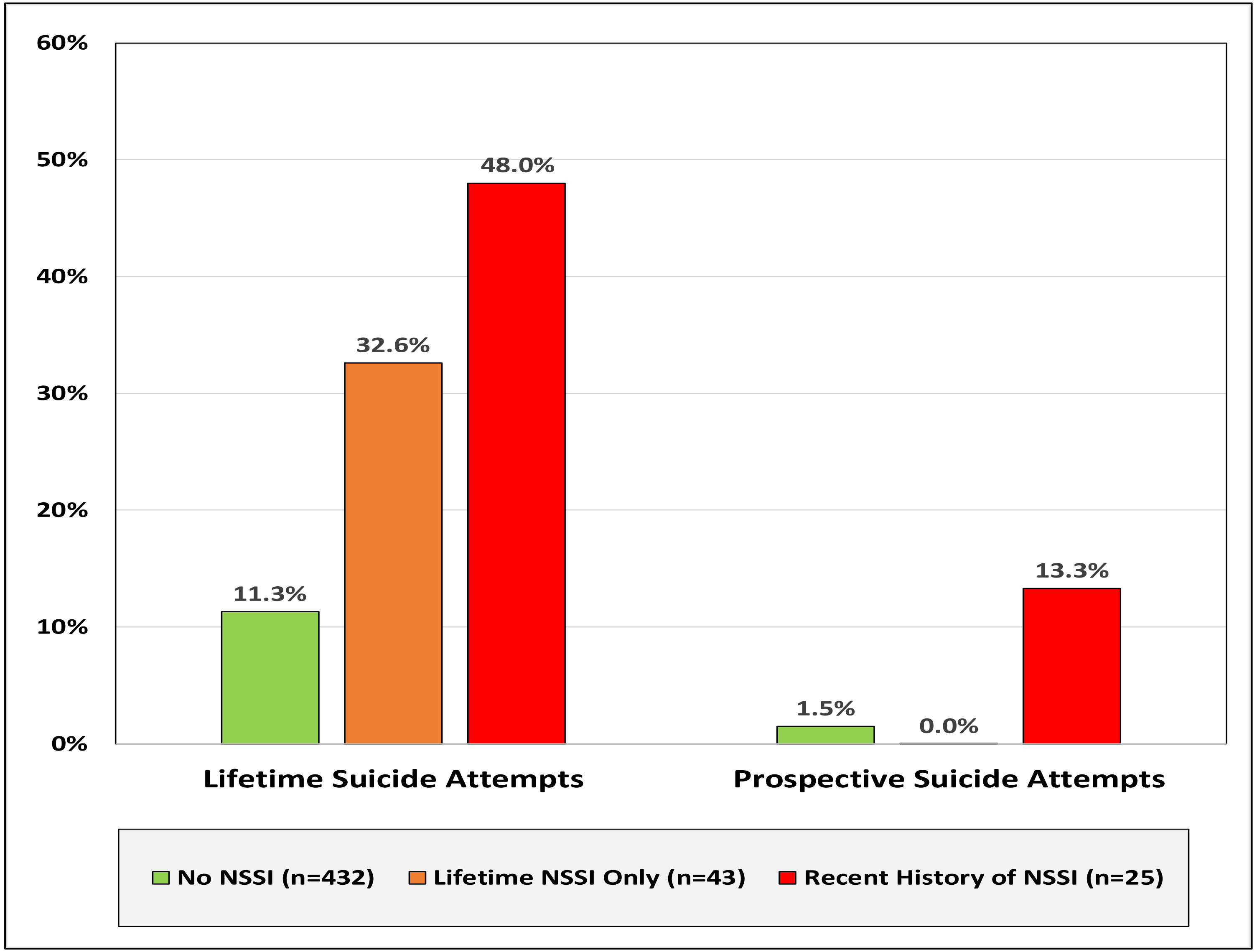
Wall/Object Punching is an Under-Recognized form of NSSI that is Especially Common among Veterans with PTSD

When wall/object punching was included in our operational definition of NSSI, the lifetime and current rates of NSSI among the 1,143 Veterans seeking treatment for PTSD at the Durham VA PTSD Clinic that we evaluated increased to **82%** and **64%,** respectively,

(Kimbrel et al, 2018)

NSSI and Suicide Attempts among Veterans

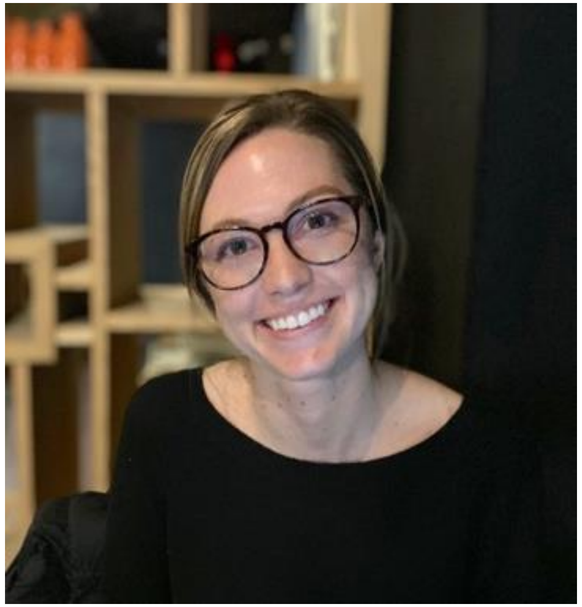
Consistent with prior research in civilians (e.g., Franklin et al, 2017), we have previously shown that a **Veterans with a history of recent NSSI are 8.9 times more likely to make a prospective suicide attempt during the next three years** compared with those with no lifetime history of NSSI (Kimbrel et al., 2019, in prep)



The Screen for Nonsuicidal Self-Injury (SNSI)

- A rapid, 10-item NSSI screening measure developed by Dr. Tate Halverson in 2021 to facilitate identification of individuals engaging in NSSI, including wall/object punching

Halverson, T.F., Patel, T.A., Mann, A.J.D., Evans, M.K., Gratz, K.L., Beckham, J.C., Calhoun, P.S., & Kimbrel, N.A. (2022). The Screen for Nonsuicidal Self-Injury (SNSI): Development and Initial Validation among Veterans with Psychiatric Disorders. *Suicide and Life-Threatening Behaviors.*



1. Have you ever intentionally cut yourself (e.g., on your wrists, legs, or torso)?	**No**	**Yes**
2. Have you ever intentionally burned yourself (e.g., with a lighter or cigarette)?	**No**	**Yes**
3. Have you ever intentionally scratched yourself to the point that you bled, or it left a mark?	**No**	**Yes**
4. Have you ever intentionally bitten your cheeks, lips, or other parts of your body to the point of bleeding or breaking the skin?	**No**	**Yes**
5. Have you ever intentionally stuck sharp objects (e.g., needles, pins, staples) into your skin?	**No**	**Yes**
6. Have you ever intentionally banged your head against walls or objects to the point of bruising or bleeding?	**No**	**Yes**
7. Have you ever intentionally punched or hit yourself to the point of bruising or bleeding?	**No**	**Yes**
8. Have you ever intentionally punched or hit walls or objects to the point of bruising or bleeding?	**No**	**Yes**
9. Have you ever intentionally prevented wounds from healing?	**No**	**Yes**
10. Have you ever done anything else to intentionally hurt or mutilate your body on purpose that resulted in tissue damage (e.g., bruising, bleeding)?	**No**	**Yes**

The Screen for Nonsuicidal Self-Injury (SNSI)

- Is very brief (10 items)
- Has been validated in Veterans
- Includes the 10 most common forms of NSSI observed in a clinical sample of Veterans with high rates of NSSI
- Has good Internal consistency (.86)
- Has a unidimensional factor structure
- Has excellent predictive validity in relation to a gold standard clinical interview concurrently and over a 1-year period of time

1. Have you ever intentionally cut yourself (e.g., on your wrists, legs, or torso)?	No	Yes
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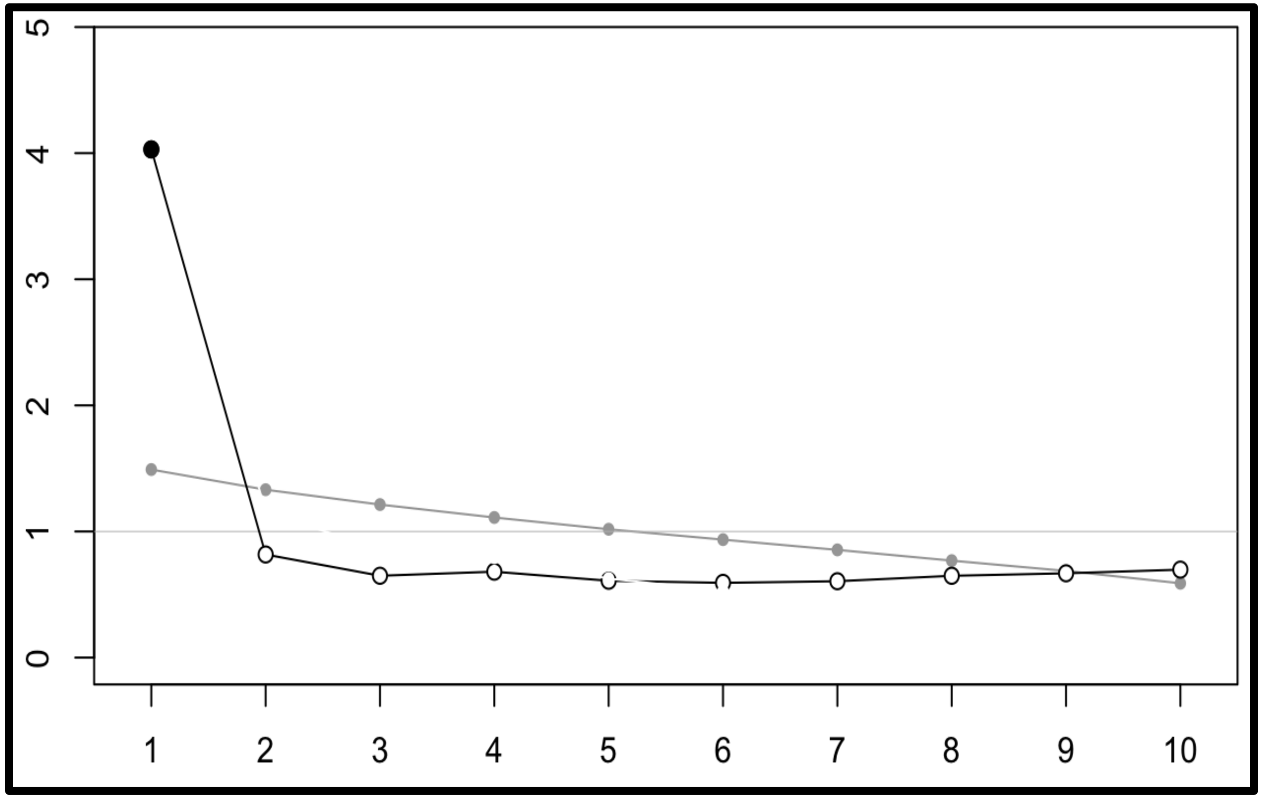
The Screen for Nonsuicidal Self-Injury (SNSI)

Parallel analysis clearly suggests that the SNSI has a unidimensional factor structure and assesses a single NSSI latent factor



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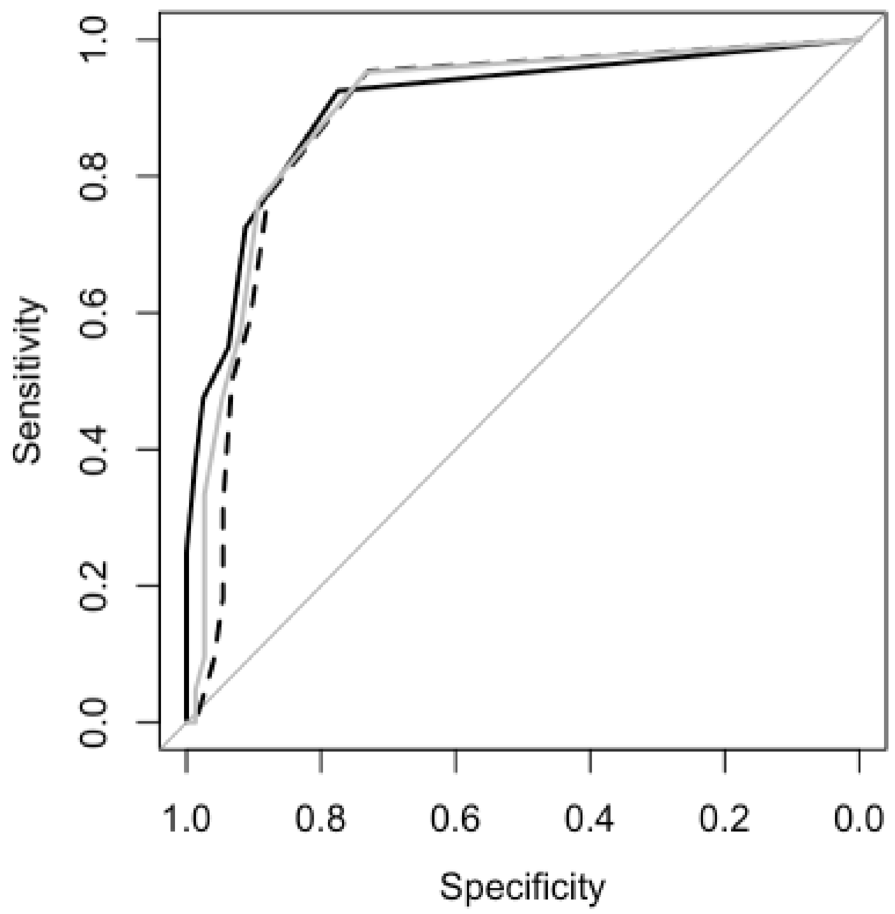
The Screen for Nonsuicidal Self-Injury (SNSI)

ROC analyses predicting NSSI Disorder (assessed via CANDI) 12 months later (AUC = .88 - .90)



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SNSI and Functional Outcomes in an Independent Sample of 1,063 Gulf War Era Veterans (Halverson et al, under review)

SNSI and Functional Outcomes in an Independent Sample of 1,063 Gulf War Era Veterans (Halverson et al, under review)

- We observed significant differences in level of functional impairment among Veterans with and without a history of current NSSI (medium to large effects sizes) which remained after covarying for a wide array of demographic factors and other forms of psychopathology

- Only 50% of veterans with current NSSI had a mental health appointment in the past year

- Fewer than 20% of Veterans with current NSSI had attended 6+ mental health appointments in the past year suggesting low engagement, but **80% of Veterans with current NSSI had attended a primary care appointment in the past year**, underscoring the potential impact of routine screening and assessment of NSSI with the SNSI

Summary

- Nonsuicidal self-injury is one of the strongest longitudinal predictors of suicide attempts identified to date.
- NSSI is common in the general population, including adult men and Veterans; however, it remains greatly under-assessed and under-treated (Kimbrel et al, 2017, 2018)
- The Screen for Nonsuicidal Self-Injury (SNSI; Halverson et al, in press) has great potential to facilitate rapid screening of individuals engaging in NSSI (including wall/object punching) and can be used in a variety of settings to identify individuals in need of further assessment and treatment.

Duke Psychiatry & Behavioral Sciences
Duke University School of Medicine

MILLION VETERAN PROGRAM

10 YEARS

Using Big Data and Precision Medicine to Assess and Manage Suicide Risk in U.S. Veterans

Nathan A. Kimbrel

Jean C. Beckham

Benjamin McMahon

David Oslin

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Co-Pis

Jean Beckham

Nate Kimbrel

Ben McMahon

Dave Oslin

Predictive Modeling/Deep Learning

Leads: Ben McMahon & Drew Levin

Natural Language Processing

Leads: Silvia Crivelli & John Pestian

Decision Support

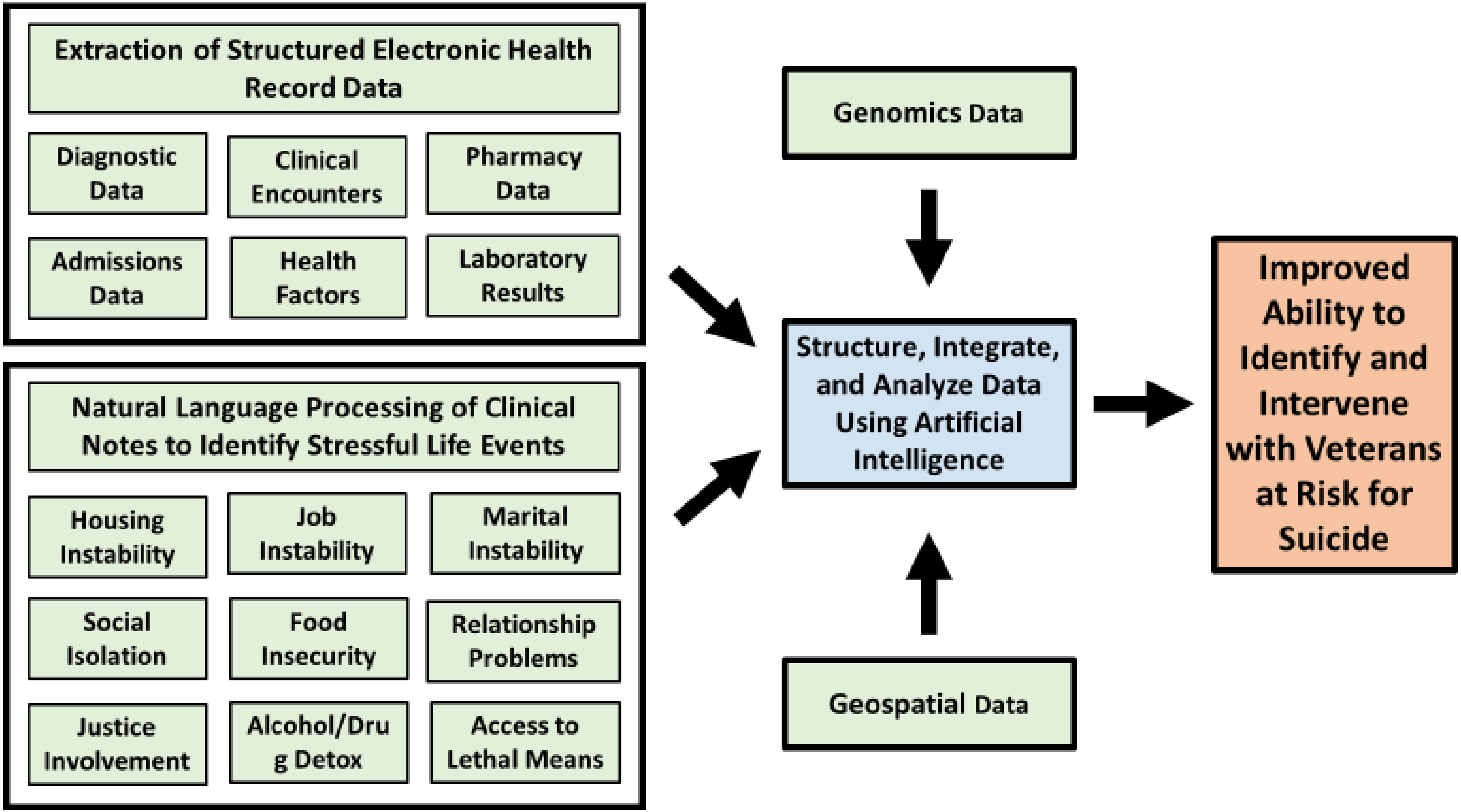
Lead: Silvia Crivelli & Dan Jacobson

Genetics

Leads: Nate Kimbrel & Jean Beckham

Primary VA and DoE Sites

Durham VAMC
Philadelphia VAMC
Los Alamos NL
Oak Ridge NL
Sandia NL
Argonne NL
Lawrence Berkeley NL
Pacific Northwest NL


Extraction of Structured Electronic Health Record Data
Diagnostic Data
Clinical Encounters
Pharmacy Data
Admissions Data
Health Factors
Laboratory Results
Natural Language Processing of Clinical Notes to Identify Stressful Life Events
Housing Instability
Job Instability
Marital Instability
Social Isolation
Food Insecurity
Relationship Problems
Justice Involvement
Alcohol/Drug Detox
Access to Lethal Means
Genomics Data
Structure, Integrate, and Analyze Data Using Artificial Intelligence
Geospatial Data
Improved Ability to Identify and Intervene with Veterans at Risk for Suicide

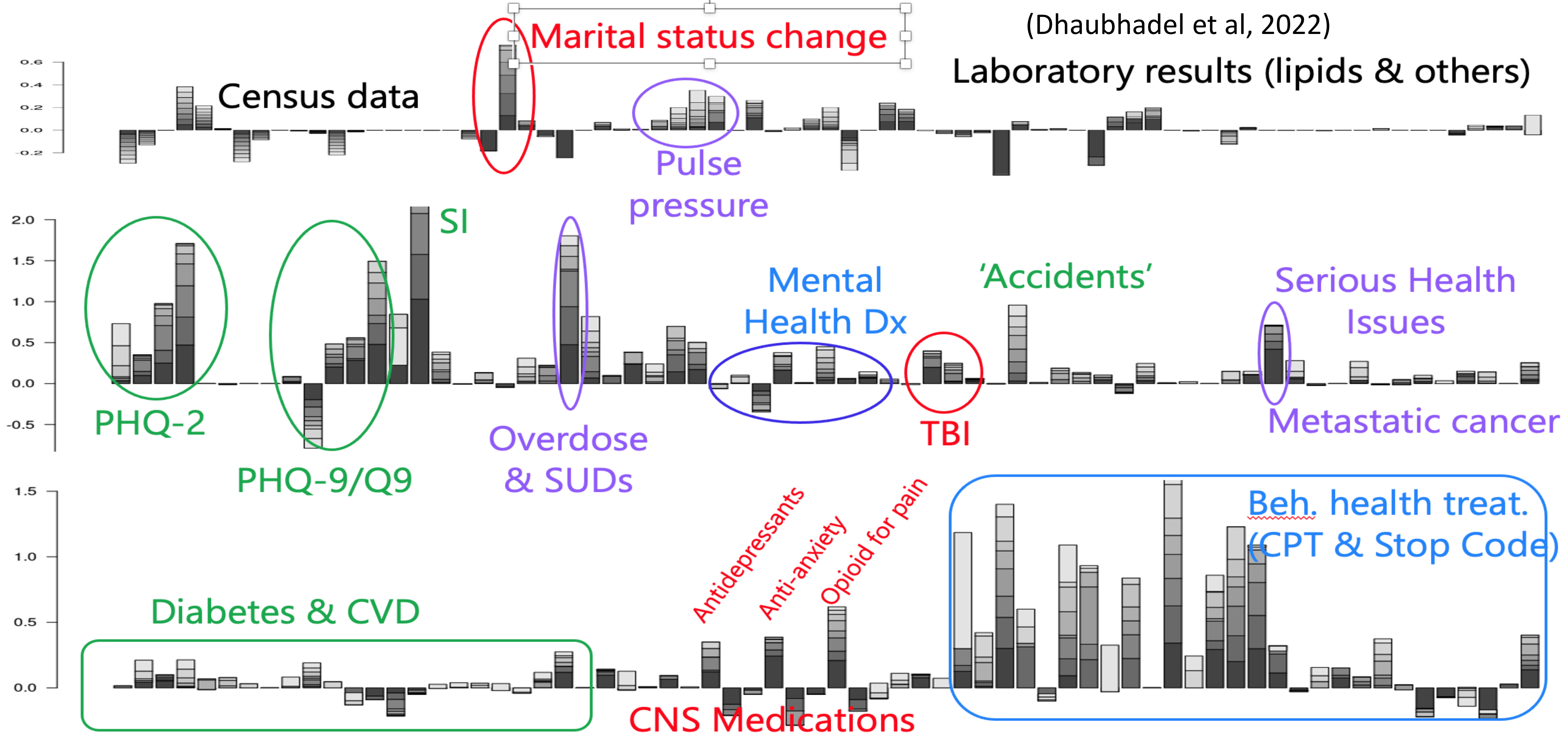
Our first task was to stage the vast quantities of structured data within the ORNL enclave so that the data can be accessed quickly and efficiently by different laboratories and across various projects and analyses.

Patients: 22 M

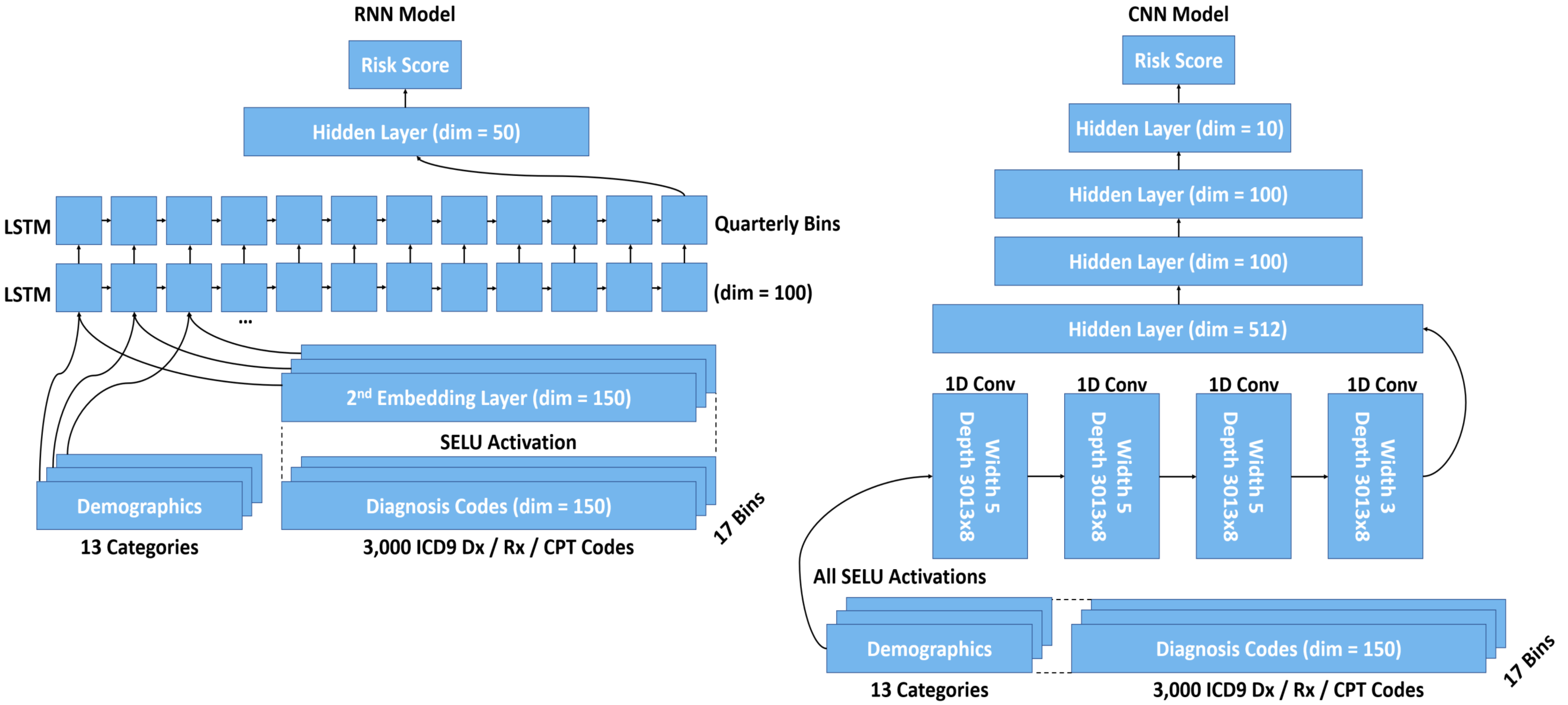
Lab Results 7.7B	Clinical Orders 4.5B	Immunizations 71 M	Appointments 1.4B
Pharmacy Fills 2.2B	Clinical Notes 3.2B	Health Factors 2.2B	Encounters 2.4 B
Radiology Proc 202 M	Vital Signs 3.3B	Consults 315 M	Admissions 17 M
		Surgeries 14 M	Oncology 1.3 M

Baseline elastic net model coefficients for predicting suicide deaths, suicide attempts, and overdose deaths

(Dhaubhadel et al, 2022)



Deep Neural Network Architecture (Martinez et al, under review)



Using Deep Neural Networks to Predict Suicide Attempts (Martinez et al, under review)

Using Deep Neural Networks to Predict Suicide Attempts (Martinez et al, under review)

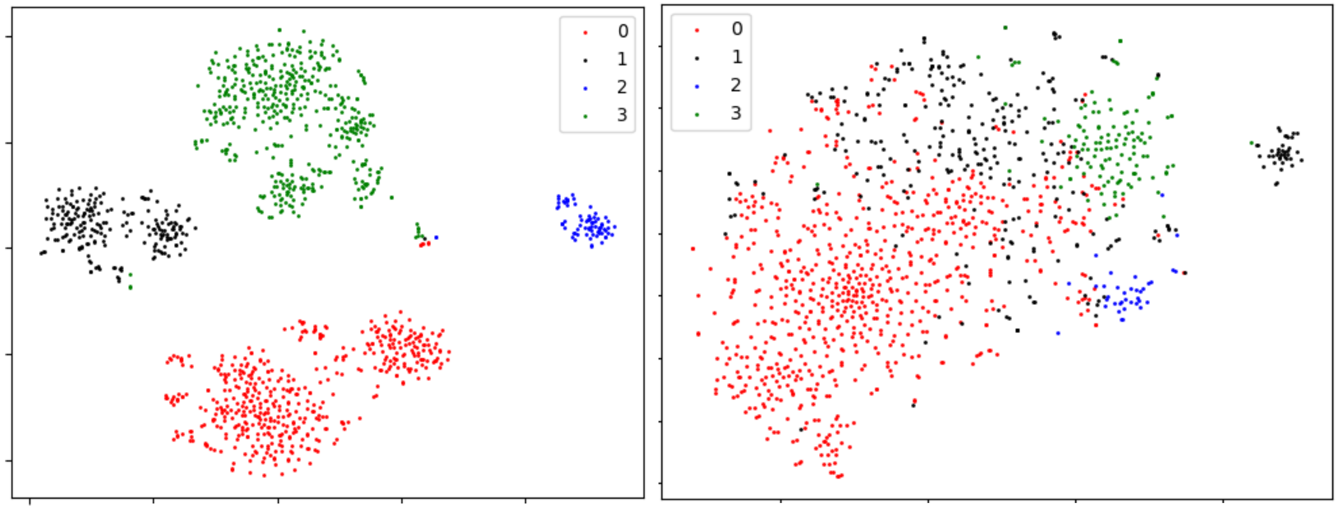
The convolutional neural network (CNN) model successfully identified the most at-risk patients (see figure).

Notably, among the 122 patients who scored in the top 0.01% risk tier by the model, *all but one attempted suicide during the study period*.

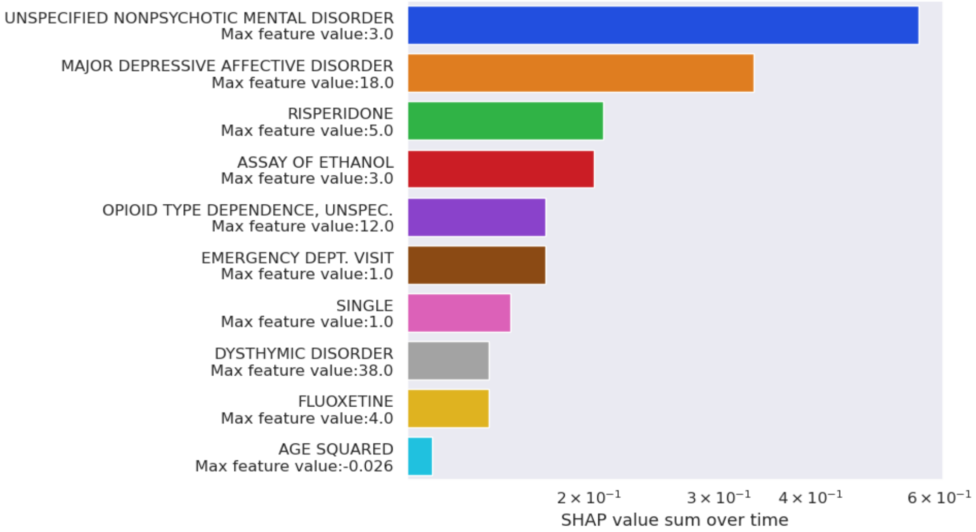
Explainable AI: Explanations provide insight into individual risk scores and subgroups of interest

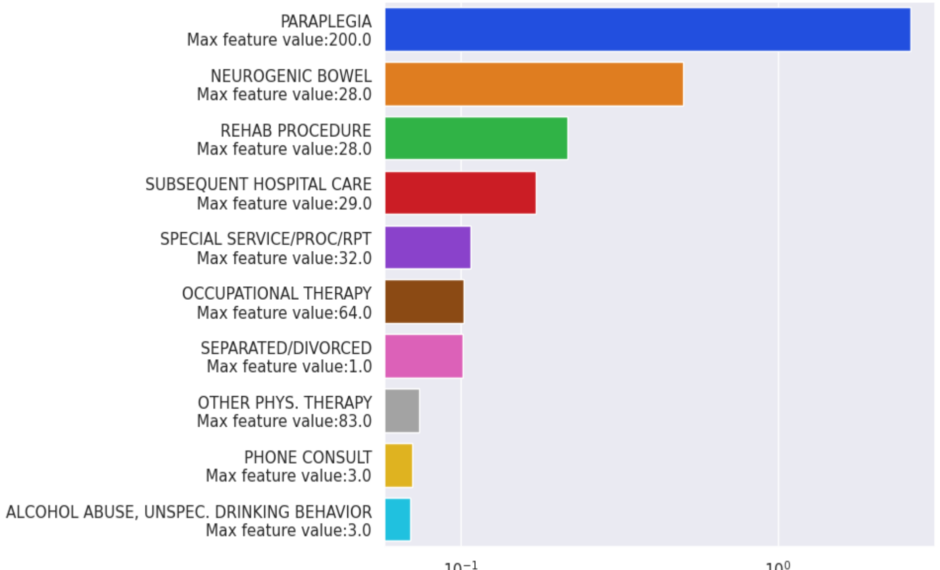
- **<u>SHAP values for each patient highlight the most impactful features contributing to an individuals' predicted risk score.</u>**
- **Clustering by SHAP values displays patient subgroups identified the CNN model** and produces higher quality clusters than those generated using raw patient data. **These subgroups may represent distinct trajectories towards death by suicide that could be targeted in future work.**

Top 1% of Patients by Risk Score

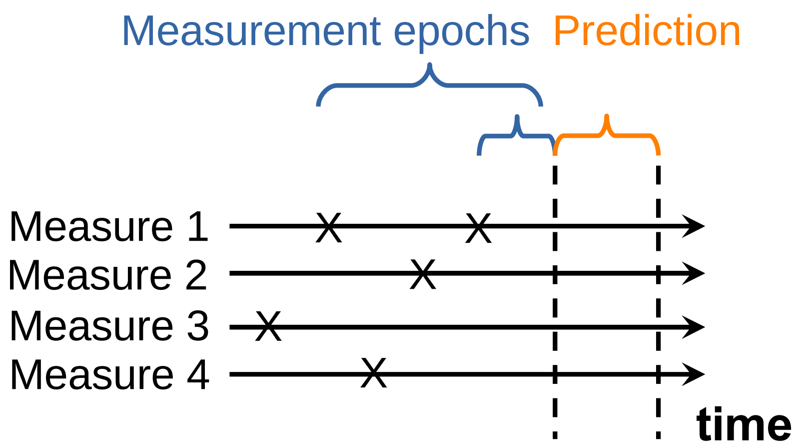


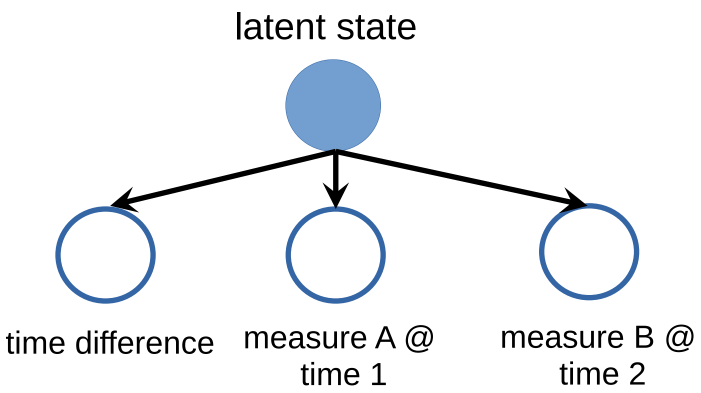
Clusters formed from SHAP values | Clusters formed from feature values





New Scalable Continuous-Time Method for Modeling Irregularly Sampled Data Points (Kaplan et al, 2022)

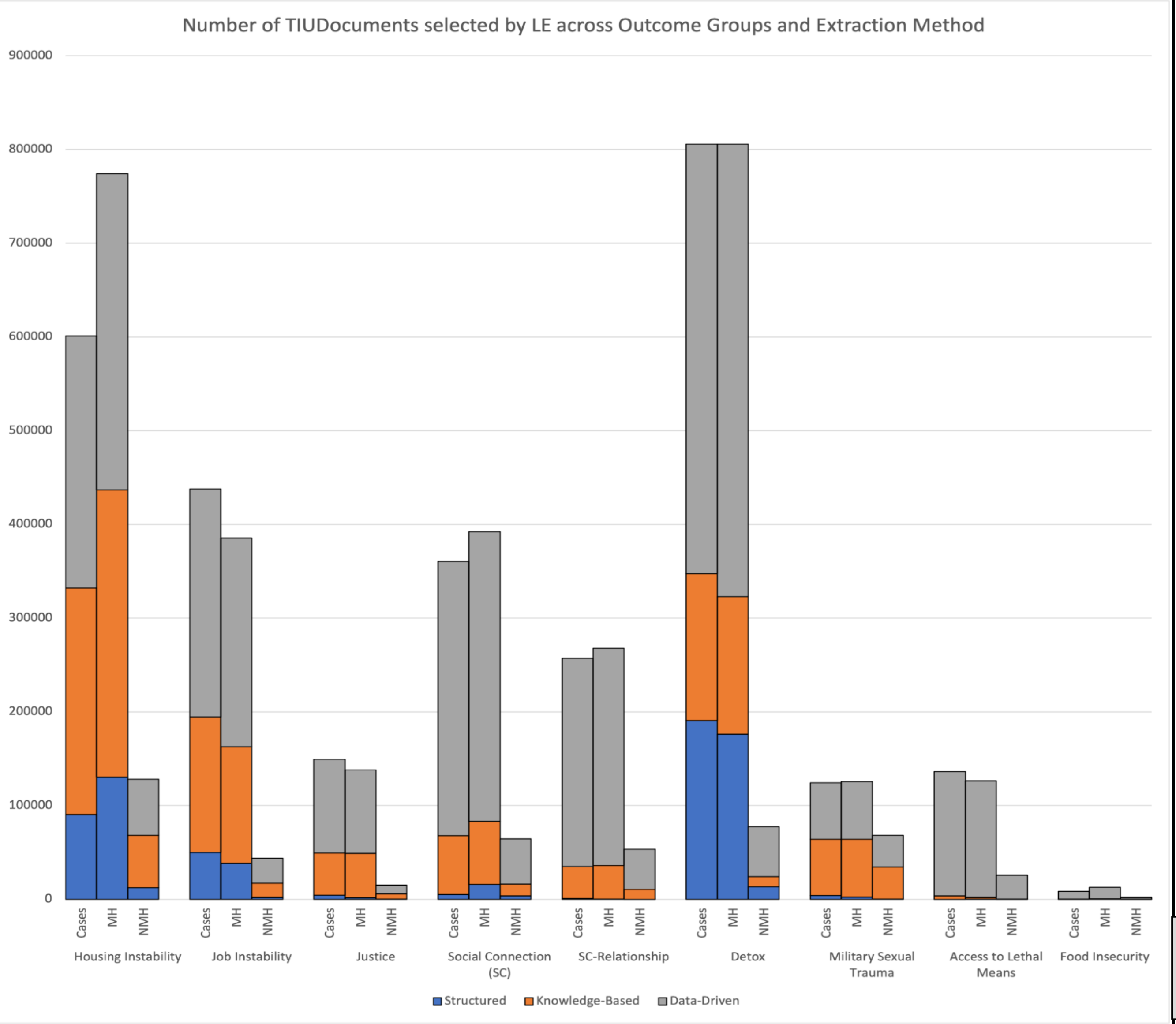




- Heterogeneous and irregular sampling of EHR data present challenges for ML approaches.
- To address this issue, Alan Kaplan et al. have developed an unsupervised probabilistic model that captures nonlinear relationships between variables over continuous-time.
- This method works with arbitrary sampling patterns and captures the joint probability distribution between variable measurements and the time intervals between them. As a result, this approach greatly reduces the loss of information and other problems associated with time binning)

Kaplan AD, Tipnis U, Beckham JC, Kimbrel NA, Oslin DW, McMahon BH; MVP Suicide Exemplar Workgroup. Continuous-time probabilistic models for longitudinal electronic health records. J Biomed Inform. 2022 Jun;130:104084.

Using Natural Language Processing (NLP) to Identify Stressful Life Events in the Electronic Health Record (Morrow et al, 2022; Silvia Crivelli's Lab)



Stressful life events are among the strongest predictors of death by suicide (Franklin et al., 2017), but such events are often underreported using structured codes.

NLP (orange and gray) enable us to identify far more events than are identified through structured data alone (blue).

Data-driven NLP approaches identify far more instances than knowledge-based approaches.

Morrow D, Zamora-Resendiz R, Beckham JC, Kimbrel NA, Oslin DW, Tamang S; MVP Suicide Exemplar Work Group, Crivelli S. A case for developing domain-specific vocabularies for extracting suicide factors from healthcare notes. J Psychiatr Res. 2022 Jul;151:328-338.

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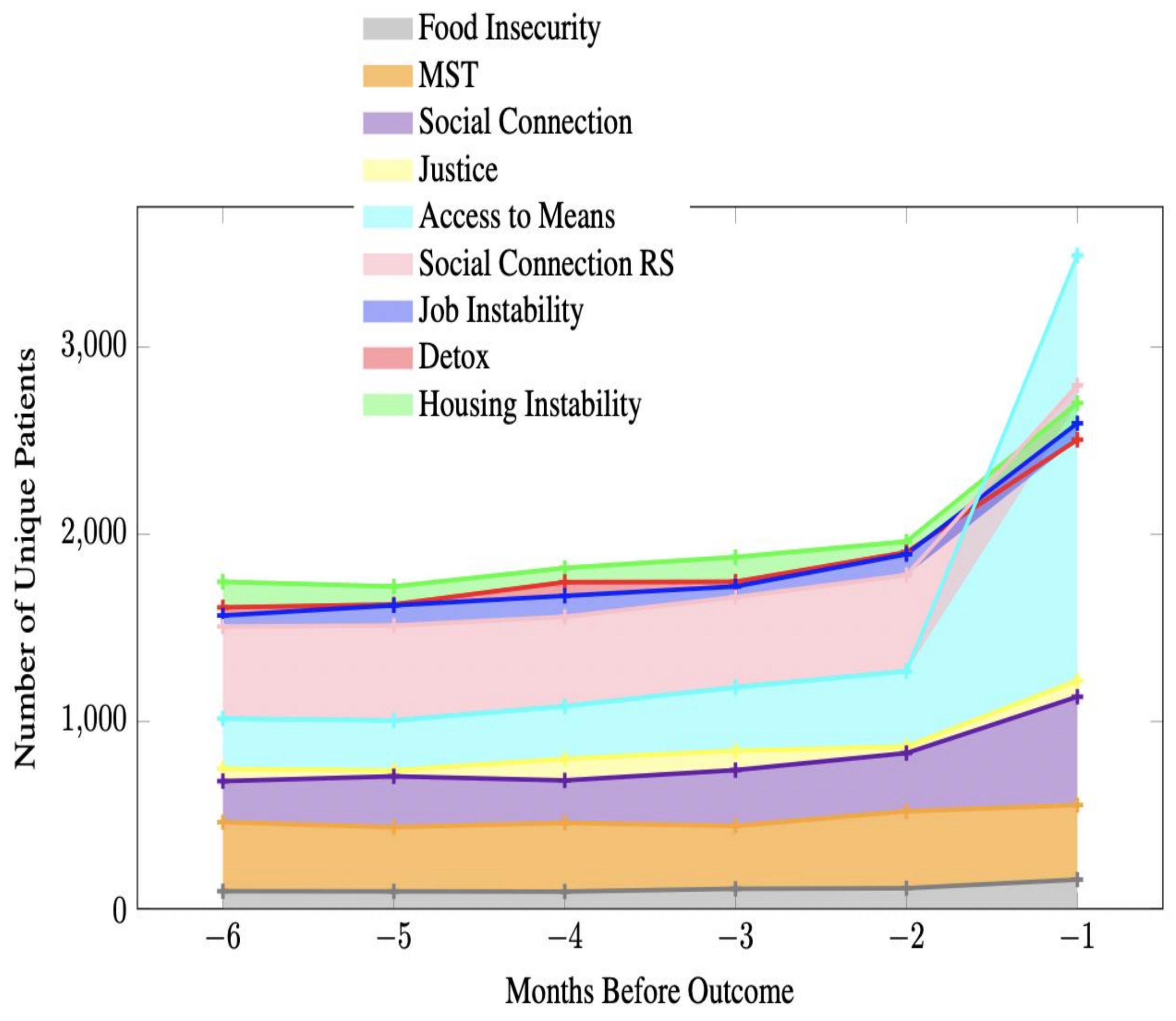

A variety of stressful life events identified through our data driven approach increase significantly in the month immediately preceding suicide deaths, such as:

- discussions of access to lethal means in clinical notes
- changes in social connections
- justice involvement
- job instability
- housing instability
- changes in romantic relationships

Morrow D, Zamora-Resendiz R, Beckham JC, Kimbrel NA, Oslin DW, Tamang S; MVP Suicide Exemplar Work Group, Crivelli S. A case for developing domain-specific vocabularies for extracting suicide factors from healthcare notes. J Psychiatr Res. 2022 Jul;151:328-338.

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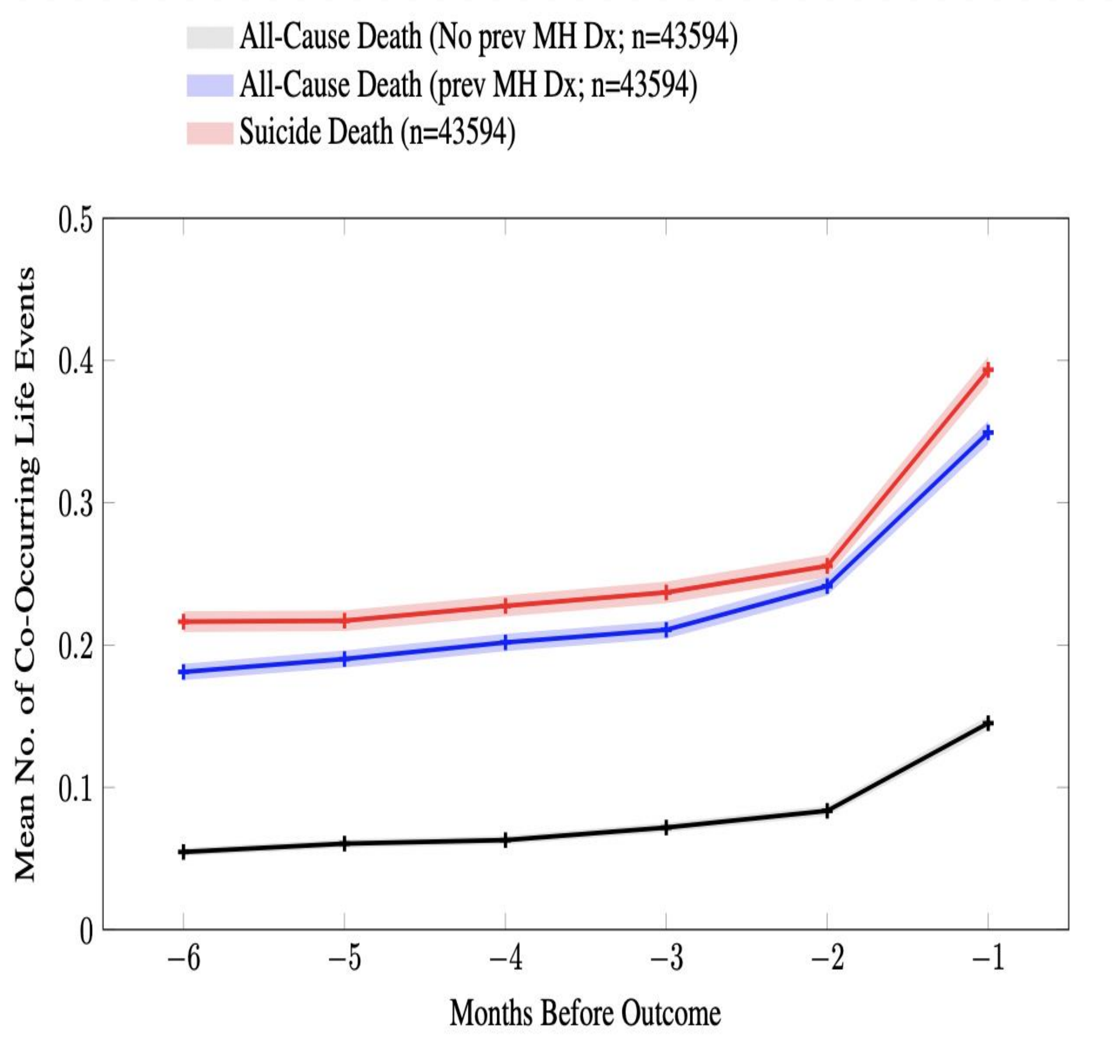


When we look at the average number of co-occurring life events extracted per month across patient groups over a 6-month period before date of death we observe:

- **Significant differences between suicide deaths (red) and non-mental health all-cause deaths (black)**

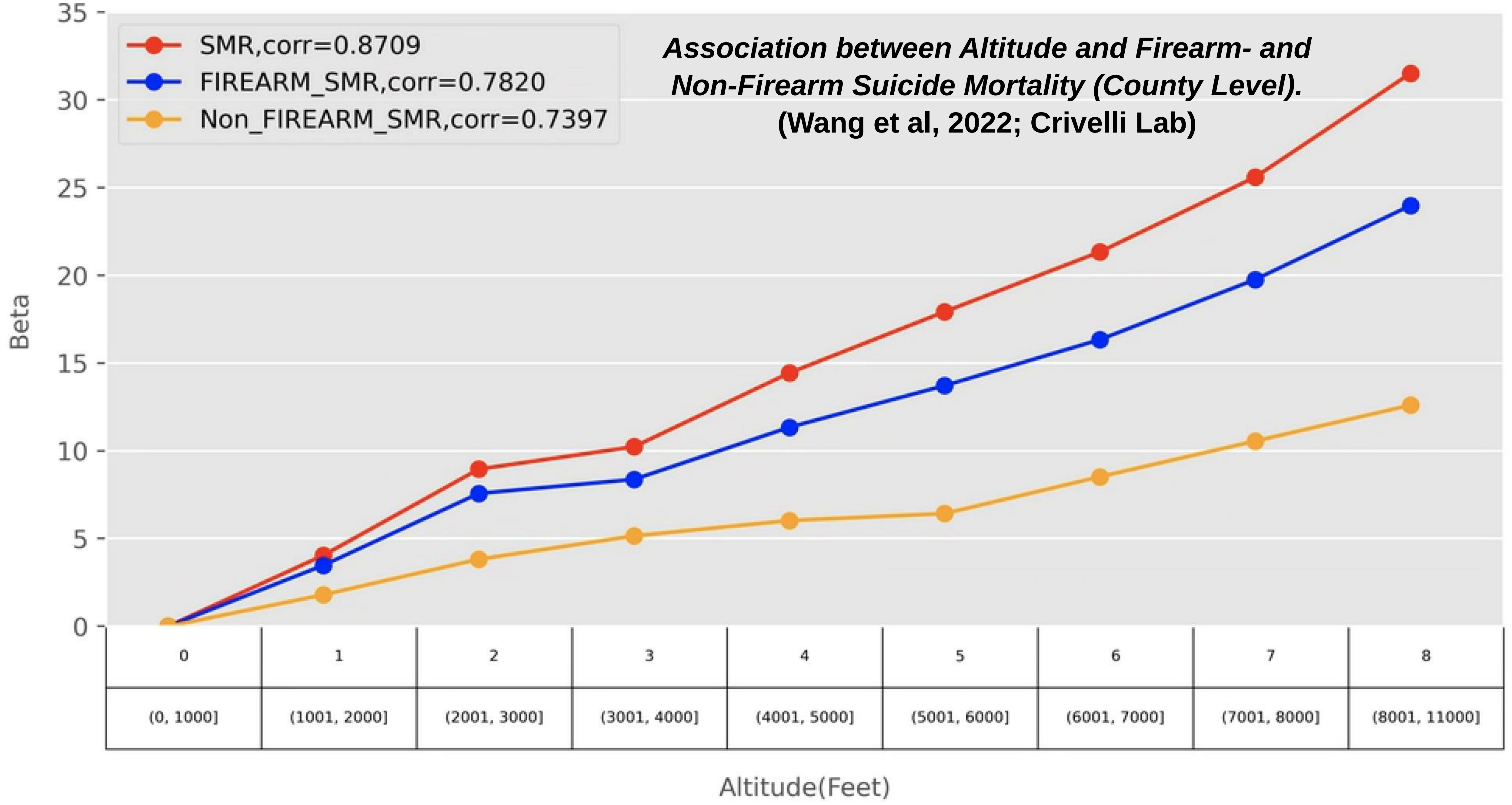
- **However, we are not yet able to effectively distinguish suicide deaths from mental health all-cause deaths (blue) using life events alone. This is a future direction.**

Morrow D, Zamora-Resendiz R, Beckham JC, Kimbrel NA, Oslin DW, Tamang S; MVP Suicide Exemplar Work Group, Crivelli S. A case for developing domain-specific vocabularies for extracting suicide factors from healthcare notes. J Psychiatr Res. 2022 Jul;151:328-338.

Consideration of Environmental Variables, including Altitude (Wang et al., 2022; Crivelli Lab)

- Shirley Wang and Silvia Crivelli have recently used geospatial (county and zip codes) and individual-level EHR data to comprehensively assess the association between altitude and suicide mortality, suicide attempts, and suicidal ideation among US Veterans between 2000 and 2018. Collectively these analyses revealed:
  - A strong association between altitude and death by suicide at all levels (i.e., county, zip, individual-level data), even after controlling for significant covariates, such as rurality, median household income, and age
  - A positive association between altitude and suicide attempts that was stronger when controlling for covariates
  - A fairly weak association between altitude and suicide ideation

Wang X, Zamora-Resendiz R… Oslin DW, McMahon B, Beckham JC, Kimbrel NA; MVP Suicide Exemplar Workgroup. An examination of the association between altitude and suicide deaths, suicide attempts, and suicidal ideation among veterans at both the patient and geospatial level. J Psychiatr Res. 2022 Sep;153:276-283.



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Incorporating Geospatial Data on Social Determinants of Health (Wang et al, in prep; Crivelli Lab)

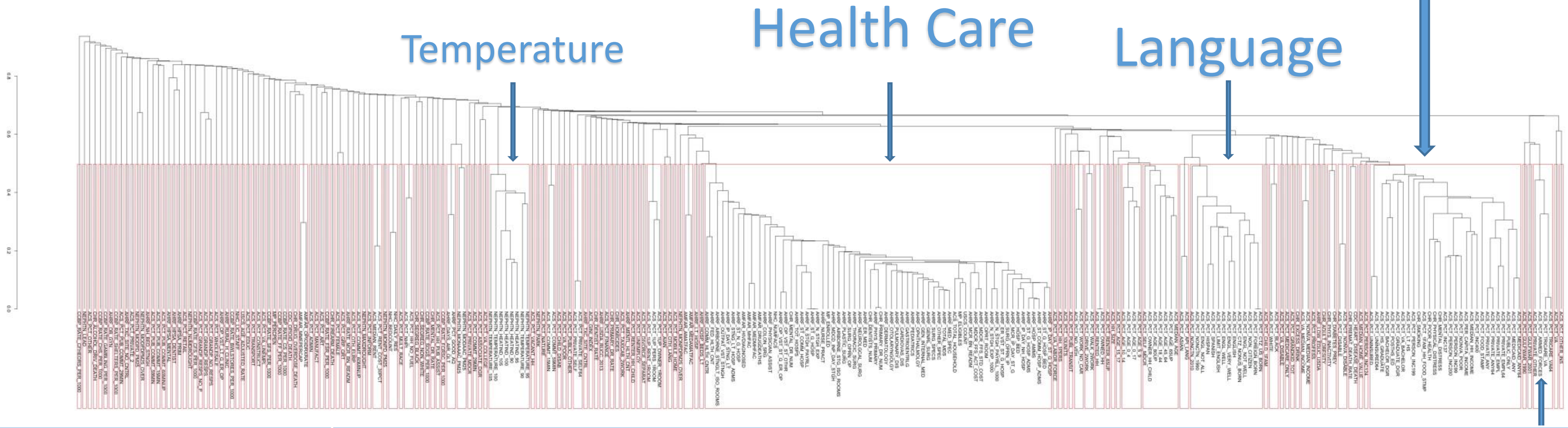
DATA SOURCES

- American Community Survey (ACS)
- Area Health Resources Files (AHRF)
- amfAR Opioid & Health Indicators Database (amfAR)
- U.S. Census Bureau County Adjacency File (CAF)
- U.S. Census County Business Patterns (CCBP)
- U.S. Census Bureau, TIGERweb and COVID-19 Demographic and Economic Resources (Census)
- Centers for Disease Control and Prevention (CDC) Interactive Atlas of Heart Disease and Stroke (CDC Atlas)
- CDC Wide-ranging ONline Data for Epidemiologic Research
- County Health Rankings (CHR)
- Civil Rights Data Collection (CRDC)
- Medicare Advantage Penetration Files (MAP)
- Economic Research Service (ERS)
- National Environmental Public Health Tracking Network
- National Center for Health Statistics, Urban-Rural Classification
- Nursing Home Compare (NHC)
- Social Vulnerability Index (SVI)
- U.S. Cancer Statistics (USCS)

SDOH Domains	SDOH topic areas
Social context	1. Demographics- population distribution
	2. Age
	3. Race/Ethnicity
	4. Social Vulnerability Index (SVI)
	5. Segregation
	6. Living conditions
Economic context	7. Workforce/Employment
	8. Poverty
	9. Income
Education	10. Education
Physical infrastructure	11. Environment
	12. Crime
	13. Housing
	14. Food access
	15. Transportation
Healthcare Context	16. Access
	17. Quality
	18. Health insurance status
	19. Health behavior
	20. Health status
	21. Utilization
	22. Healthcare system characteristics
	23. Health status-mortality
Other Socioeconomic	**Features**
Physical infrastructure	1. Food Insecurity
	2. Rurality
Health Context	1. Low birth Weight
Economic context	4. Credit/Debit Score
	5. Housing cost burdened
	6. Wage to afford fair market rent

Incorporating Geospatial Data on Social Determinants of Health (Wang et al, in prep; Crivelli Lab)

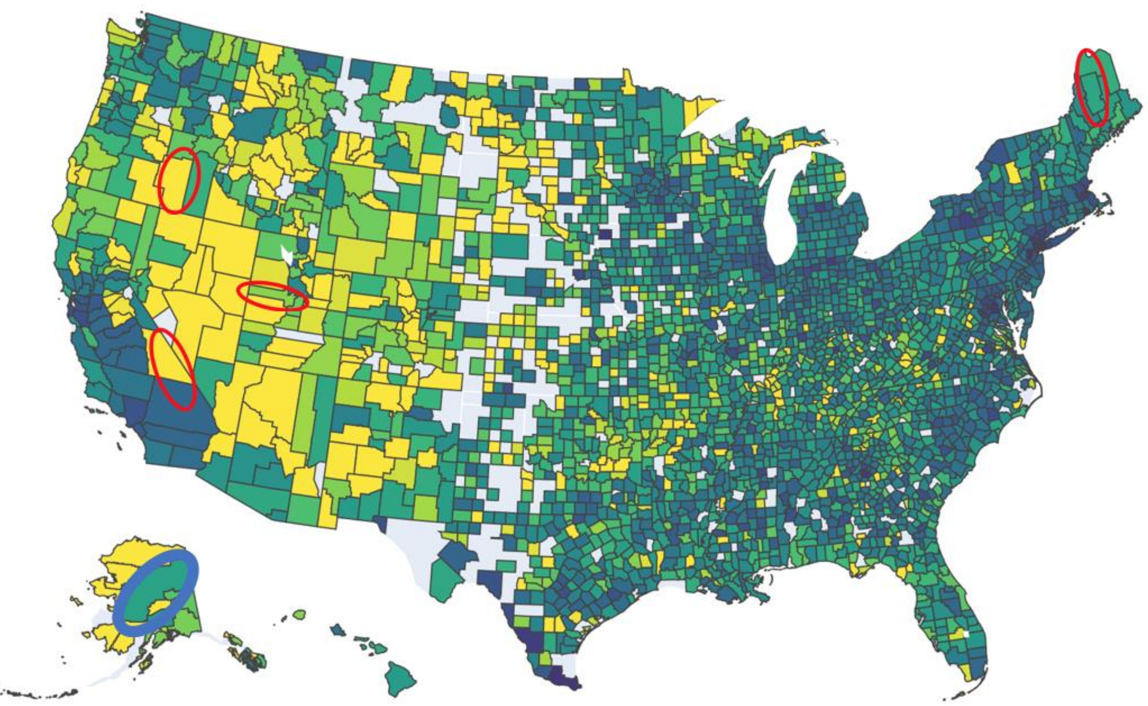
1. Define a correlation distance: $d_p(x, y) = \sqrt{1 - |cor(x, y)|}$
2. Hierarchically Cluster data(single linkage method)
3. Apply Multi-Criteria Optimization (MCO) to get optimal clusters



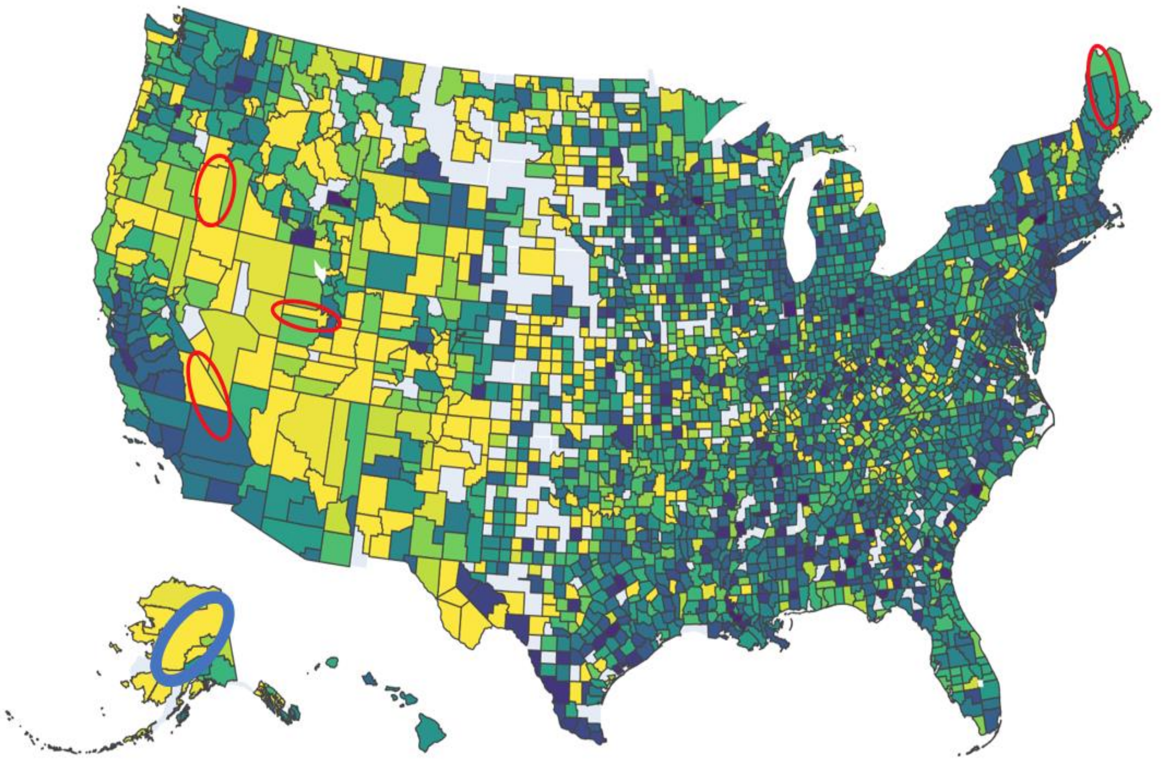
Major Cluster name	Representative feature
	NEPHTN_HEATIND_95 (Extreme heat - 95°F: Number of days with daily maximum heat index, absolute threshold: 95°F)
Health Care	AHRF_HOSP_AMMS (Total number of hospital admissions)
Language	ACS_PCT_HISPAN (Percentage of population reporting Hispanic ethnicity)
Income/Poverty/Education	ACS_PCT_PERSON_INC200 (Percentage of population with income to poverty ratio: 2.00 or higher)
VA	

Investigating the association between social determinants of health features and suicide mortality rates in the United States using spatial regression models (Wang et al., in preparation; Crivelli Lab)

Predicted Map of Suicide Mortality in 2016 based on 2015 Data



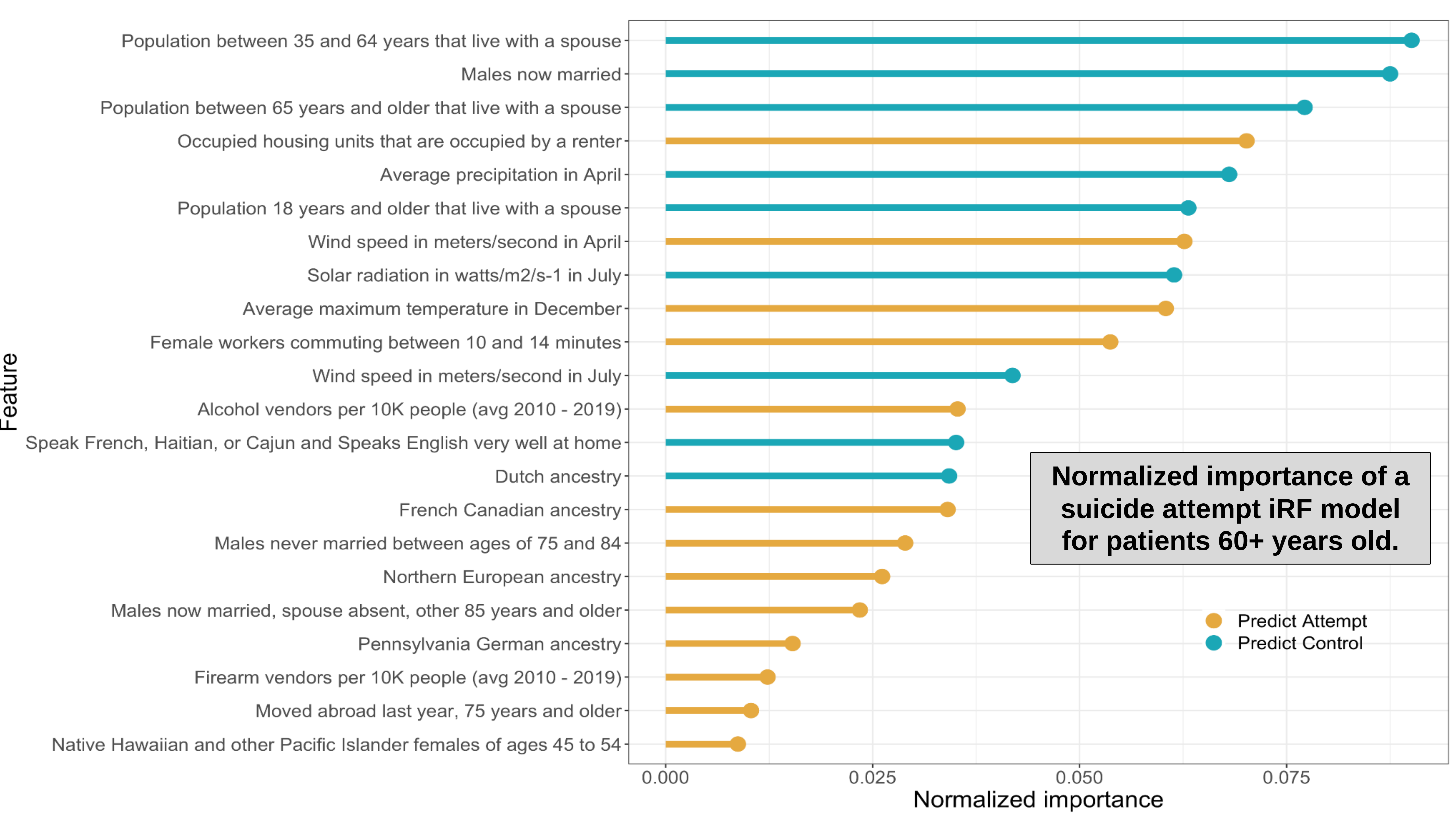
Actual Map of Suicide Mortality in 2016 based on 2016 Data

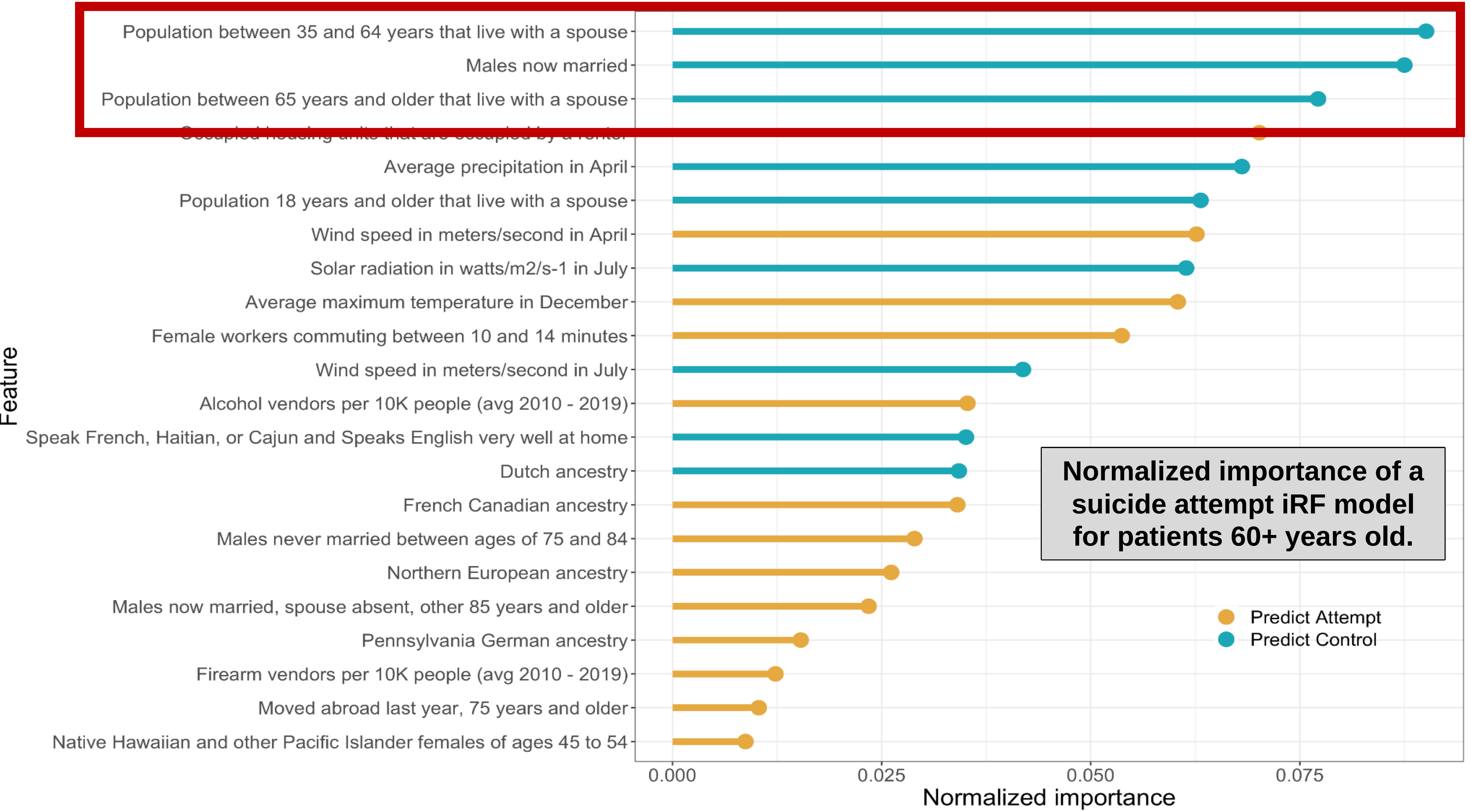


	2015 actual SMR Vs 2016 actual SMR	97 features Predicted Rate vs 2016 SMR
R^2	0.03	0.15
RMSE	177.07	154.64

Explainable AI (iterative Random Forest), Climate Data, and Social Determinants to predict Suicide Attempts (Pavicic et al, under review; Jacobson Lab)

- Mirko Pavicic and Dan Jacobson also recently led a study that utilized explainable AI to predict suicide attempts among Veterans from climate and social determinants data. This study found:
  - Geographic areas with higher concentrations of married males living with spouses were predictive of lower rates of suicide attempts
  - In contrast, geographic areas where males were more likely to live alone and to rent housing were predictive of higher rates of suicide attempts.
  - We also observed that firearm and alcohol vendors were associated with increased risk for suicide attempts irrespective of the age group examined, but that their effects were relatively small in comparison to the top features.


Normalized importance of a suicide attempt iRF model for patients 60+ years old.
Feature
Population between 35 and 64 years that live with a spouse
Males now married
Population between 65 years and older that live with a spouse
Occupied housing units that are occupied by a renter
Average precipitation in April
Population 18 years and older that live with a spouse
Wind speed in meters/second in April
Solar radiation in watts/m2/s-1 in July
Average maximum temperature in December
Female workers commuting between 10 and 14 minutes
Wind speed in meters/second in July
Alcohol vendors per 10K people (avg 2010 - 2019)
Speak French, Haitian, or Cajun and Speaks English very well at home
Dutch ancestry
French Canadian ancestry
Males never married between ages of 75 and 84
Northern European ancestry
Males now married, spouse absent, other 85 years and older
Pennsylvania German ancestry
Firearm vendors per 10K people (avg 2010 - 2019)
Moved abroad last year, 75 years and older
Native Hawaiian and other Pacific Islander females of ages 45 to 54
Predict Attempt
Predict Control
0.000
0.025
0.050
0.075
Normalized importance



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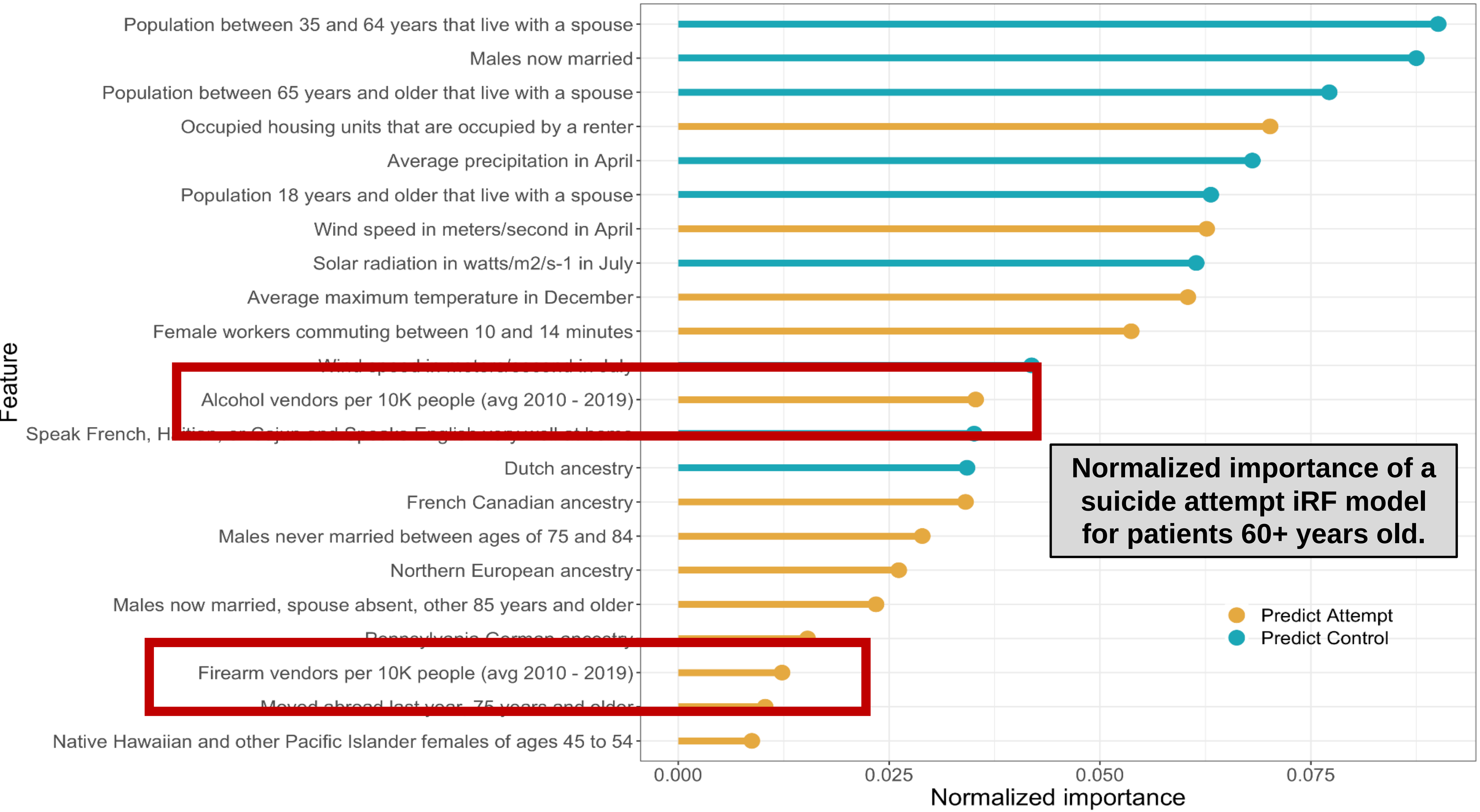
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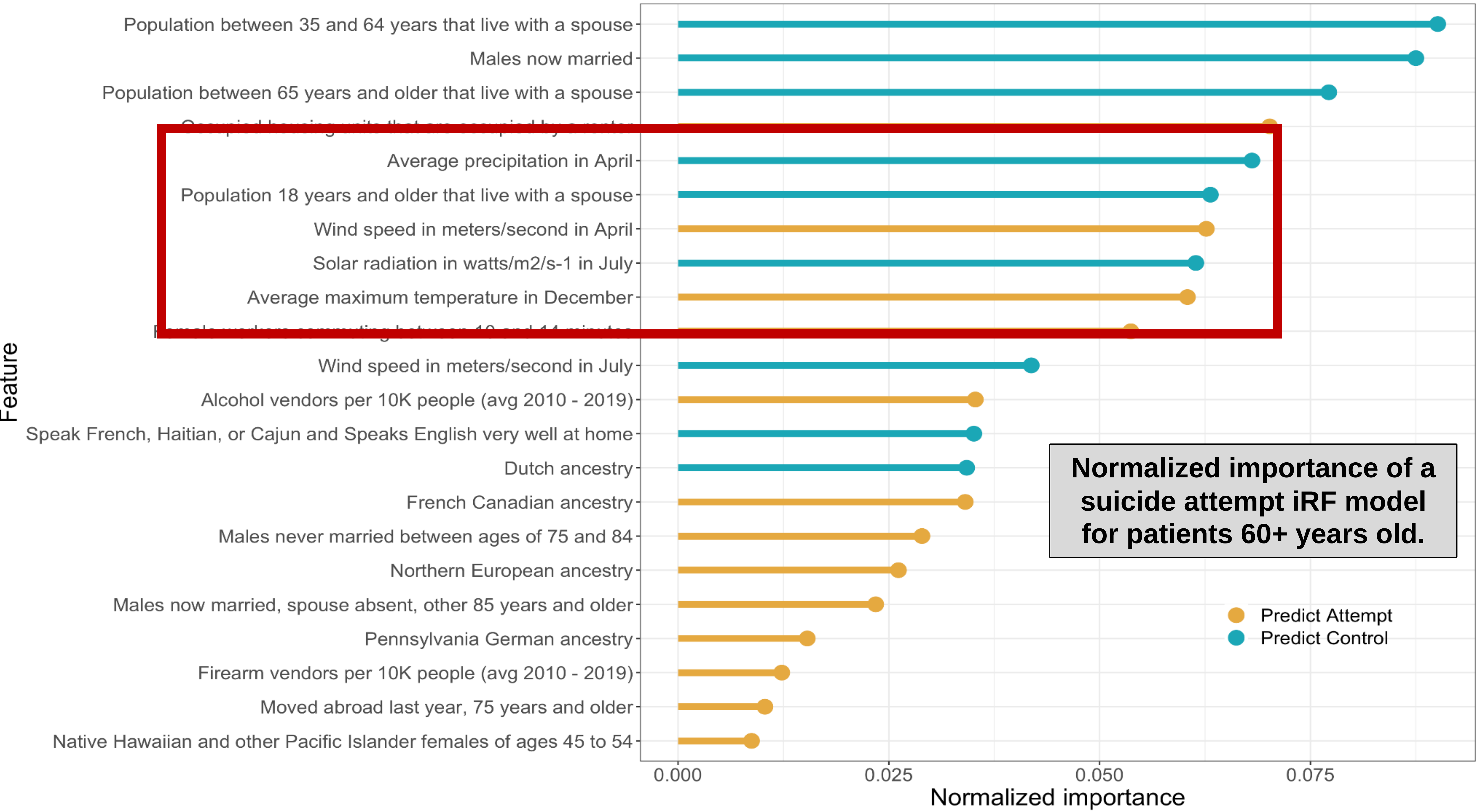

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Largest GWAS of Suicidal Thoughts and Behaviors Identifies 16 genome-wide significant risk loci (Kimbrel et al, in press)

We recently conducted the largest and most diverse genome-wide association study (GWAS) of suicidal thoughts and behaviors to date among 633,778 U.S. military veterans enrolled in the Million Veteran Program (MVP) study (N=121,211 cases).

This analysis revealed 16 genome-wide significant risk loci across analyses, nine of which were independently replicated in a large international cohort of civilians.

Among our top replicated cross-ancestry risk loci, ***ESR1, DRD2, TRAF3,*** and ***DCC*** appear to be particularly promising candidate risk genes for SITB.

Figure 1. *Manhattan Plots Summarizing Results from the Cross-Ancestry and Ancestry-Specific Genome-Wide Association Studies (GWAS).*

Figure 1a. *Meta-Analytic Cross-Ancestry GWAS Results.*

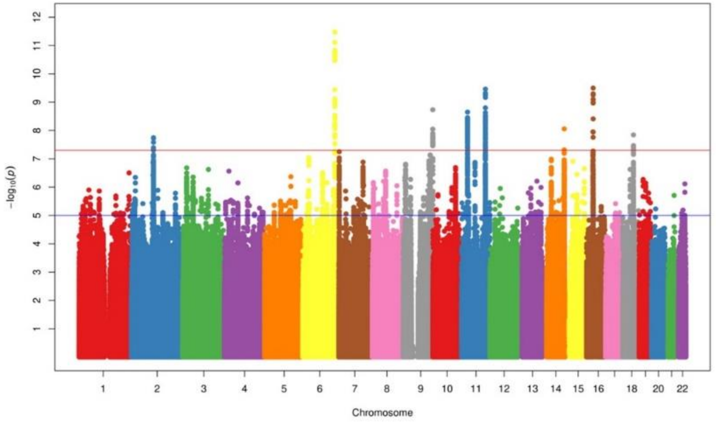


Figure 1c. *African Ancestry Subset GWAS Results.*

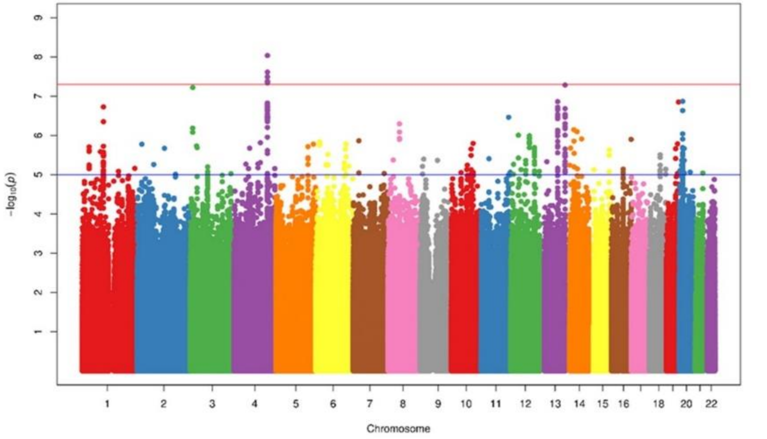


Figure 1b. *European Ancestry Subset GWAS Results.*

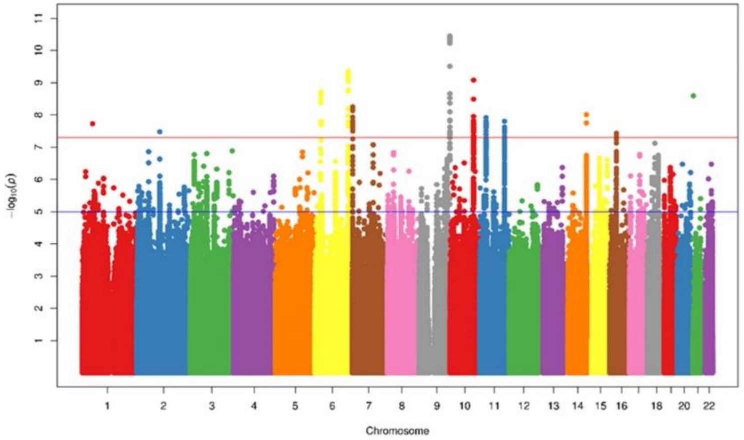
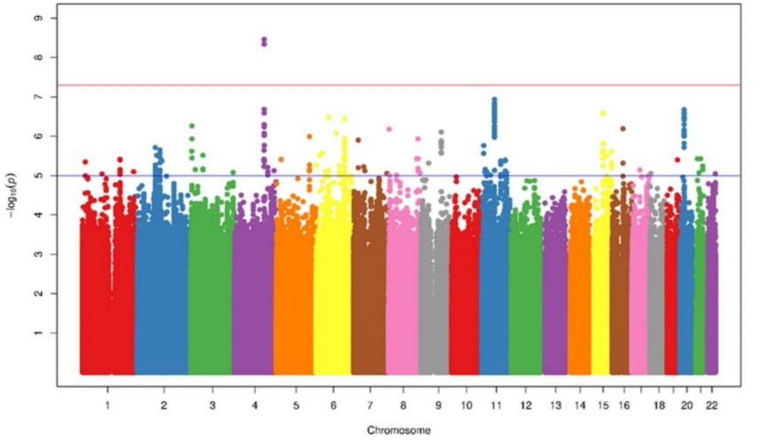


Figure 1d. *Hispanic Ancestry Subset GWAS Results.*



ESR1 (Estrogen Receptor 1)

- Our top replicated cross-ancestry risk locus was rs6557168, an intronic SNP in *ESR1,* which encodes estrogen receptor 1.
- An integrated multi-omics analysis[42] recently identified *ESR1* as a causal genetic driver gene for the development of PTSD and depression, both of which are risk factors for SITB among veterans.[24-25,43]
- Estrogen has also been hypothesized to potentially help to explain sex differences in depression rates,[44] and loss of ESR1 has been found to produce effects on brain tissue in men.[45]
- Notably, rs6557168 was also recently identified as a likely causal variant for the *ESR1* locus in relation to anxiety.[46]

DRD2 (Dopamine Receptor D2)

- Our second strongest, replicated cross-ancestry locus was rs12808482, an intronic variant in *DRD2*, which encodes the D2 dopamine receptor subtype.
- *DRD2* has been associated with many other disorders and phenotypes (e.g., schizophrenia, mood disorders, ADHD, risky behaviors, alcohol use disorder, impulsivity)[38] associated with increased risk for suicide
- DRD2 is highly expressed in brain tissue[47] including the PFC, nucleus accumbens, substantia nigra, and hippocampus.
- Notably, our prior study of suicide attempts-only in MVP also identified a strong cross-ancestry signal at *DRD2* (p=1.77×10^{-7}).[11]

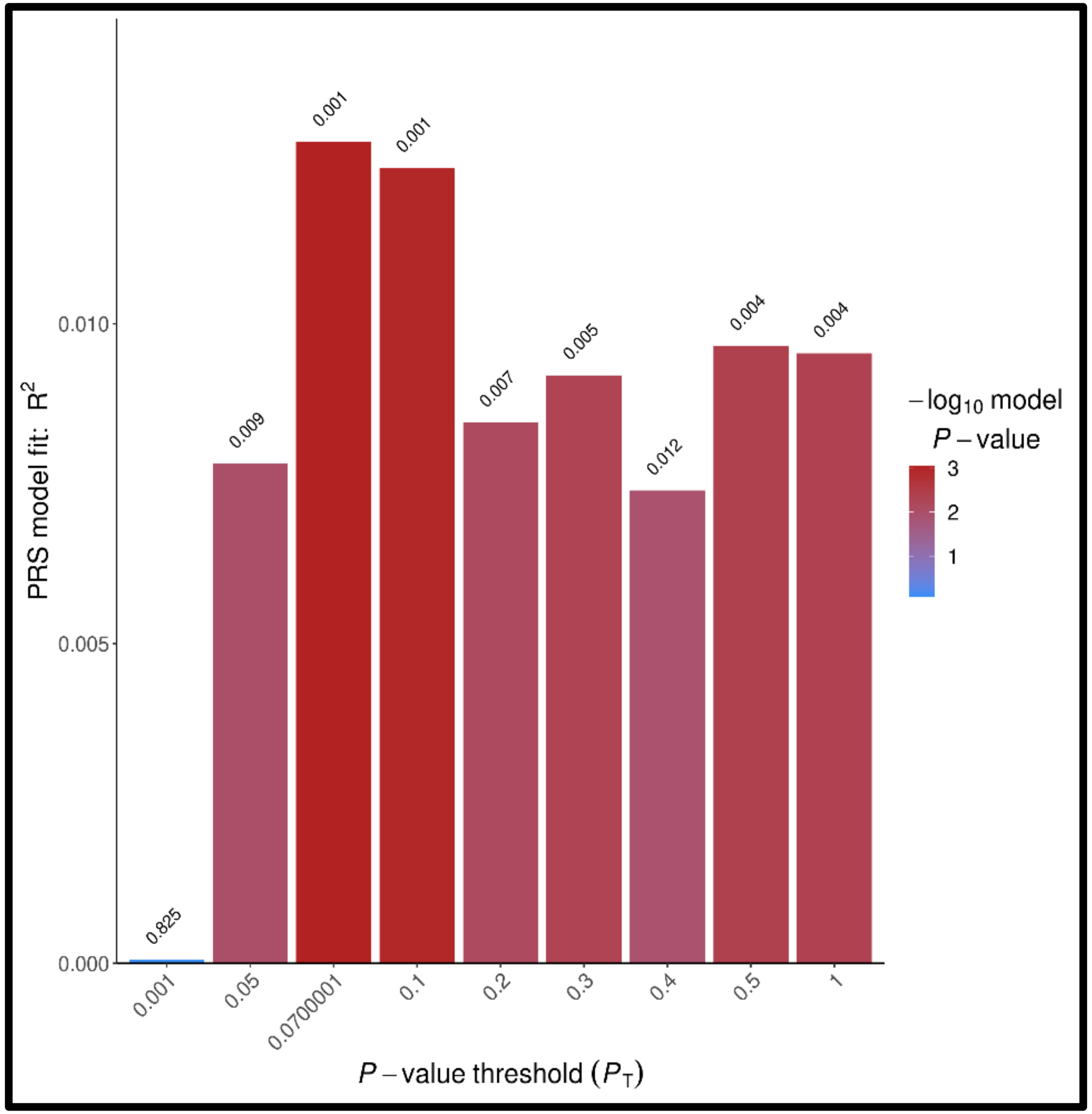
DCC (Netrin 1 Receptor)

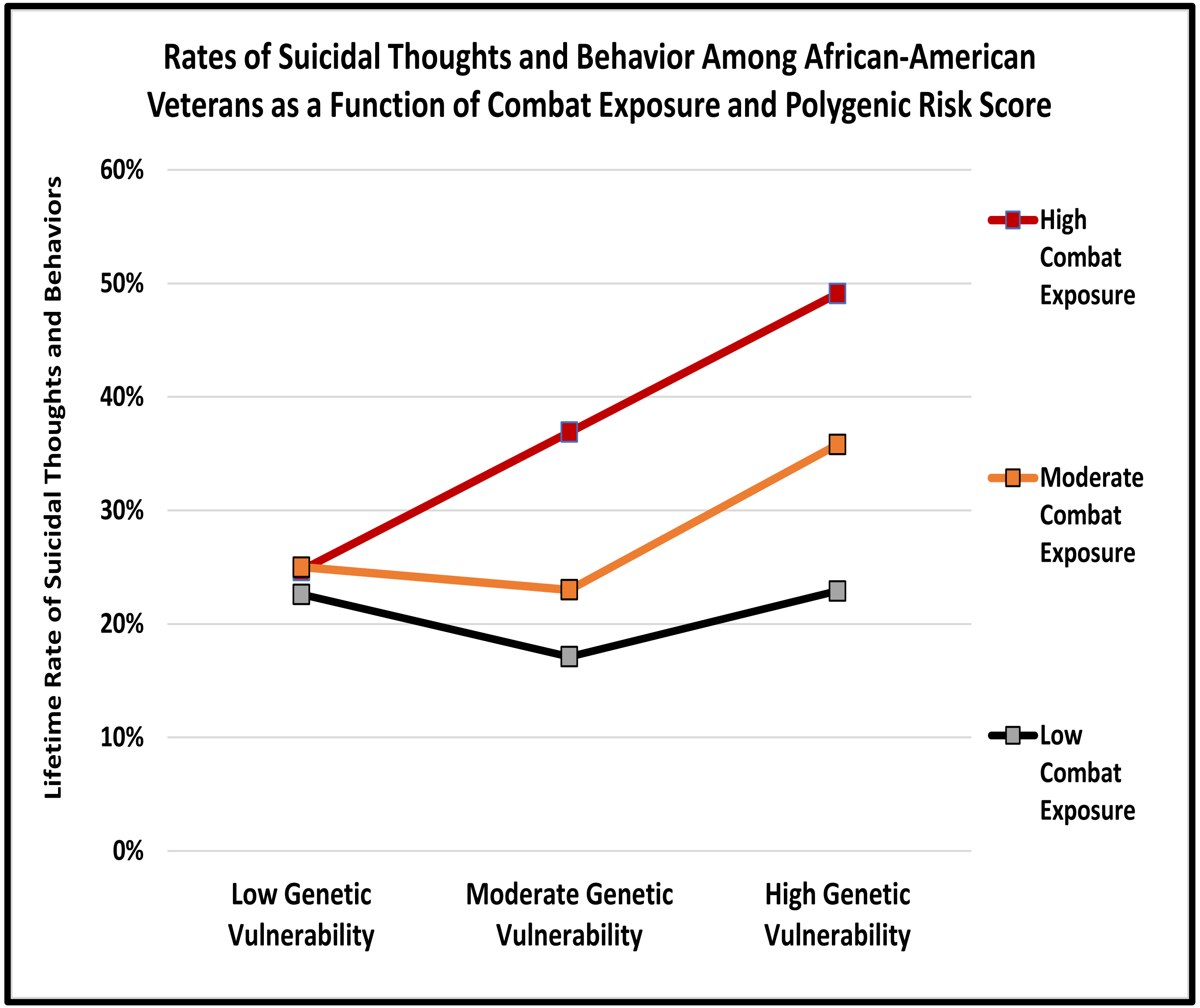
- A cross-ancestry GWS association was also replicated for rs10671545, an intronic insertion/deletion polymorphism in *DCC*, which encodes a netrin 1 receptor.
- DCC is highly expressed in brain tissue across the lifespan, though its peak expression occurs during prenatal development. It is highly involved in synaptic plasticity, axon guidance, circadian entrainment, and long-term potentiation.
- It is crucial for the development of medial PFC functioning and has been found to be elevated in the prefrontal cortex of individuals who die by suicide.[52]
- DCC is associated with multiple psychiatric phenotypes,[5,12,38] including suicidality.
- The PGC Cross Disorders Group identified DCC as the gene with the most pleiotropic associations (it associated with all 8 disorders considered; Lee et al, 2019)[100]

TRAF3 (TNF Receptor Associated Factor 3)

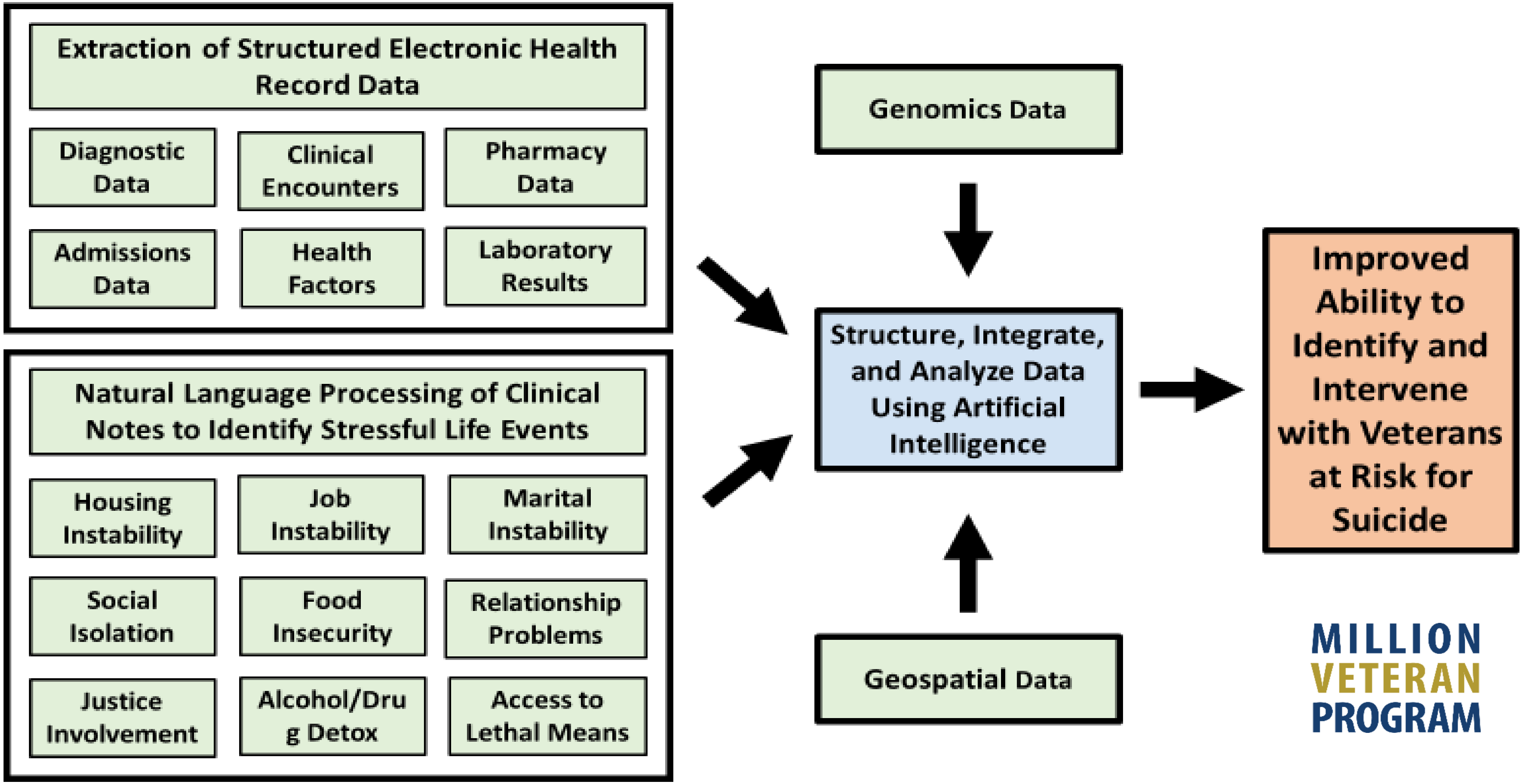
- *TRAF3* regulates type-1 interferon production, which is of interest given that large portions of patients receiving interferon therapy develop MDD and experience suicidal ideation.[53]
- *TRAF3* is also associated with MDD, antisocial behavior, substance use, and ADHD,[38] all of which are known risk factors for SITB.
- Additionally, lithium—a gold standard treatment for bipolar disorder shown to reduce suicide risk[54]—modulates the expression of *TRAF3* and several other inflammatory genes.[55]

We also observed significant main effects for the PRS and for PRS x Combat Effects in an Independent Sample (Kimbrel et al, in prep)





Our ultimate goal is to integrate all of these diverse sources of data in order to improve our ability to identify individuals at risk for suicide.



MILLION VETERAN PROGRAM

New/Recently Funded VA Projects that Build upon this Work with the Goal of Improving Suicide Risk Prediction among Veterans

- BLRD-funded study that to conduct the largest Gene x Environment Genome-Wide Interaction Study (GEWIS) of suicidal thoughts and behaviors to date in 800,000+ Veterans within MVP (Kimbrel & Beckham)
- MVP/CSRD-funded study aimed at scaling up our NLP, geospatial, and machine-learning approaches so that they can be put into use by our VHA operational partners (Beckham & Kimbrel)
- HSRD-funded study to better understand the mechanisms through which altitude affects risk for suicide among Veterans (Kimbrel & Beckham)
- New VA-funded suicide resource center that will be part of SPRINT that will be aimed at promoting a **precision medicine based approach to the prevention and treatment of suicide among Veterans** (SPRINT + Marx, Goodman, Kimbrel, & Interian)

Future Directions

- Predicting firearm suicide in military veterans outside the VA health system using linked civilian electronic health record data (VESPER)
  - NIMH-funded project currently under review that is aimed at using linked civilian healthcare records to identify Veterans in the community who are at elevated risk for death by suicide, and suicide by firearm, specifically (Swanson & Kimbrel)

- Combining Durham Risk Score data, ecological momentary assessment (EMA) data, and other sources of real-time data with EHR data to facilitate better short-term prediction among high-risk individuals

- Improving treatments for Veterans who engage in NSSI by integrating EMA into the treatment of self-injurious behaviors (T-SIB) protocol in order to facilitate patients' recognition of the function of NSSI behavior (Tate Halverson)

Questions?

Thank You!

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