Clinical and Genetic Evaluation of Suicide Death among Young Individuals Exposed to Trauma

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Background

- Suicide is the second leading cause of death in the United States for individuals aged 10-24[1] and remains difficult to predict despite being inherently preventable.
- Exposure to trauma is known to be a risk factor for suicidal behavior and to worsen mental health clinical trajectories.[2]
- Despite clear connections to suicidal behavior, trauma is frequently missed in clinical evaluations, and the interplay of trauma, comorbidities, and underlying genetic predisposition, particularly in the setting of suicide death, is poorly understood.
- This study leverages a unique collection of individuals who have died from suicide as part of the Utah Population Database (UPDB)[3] to evaluate clinical and genetic risk factors for death by suicide in young individuals (aged 12-25) who have a history of exposure to trauma.
- **Study Objectives:** (1) examine differences in clinical diagnostic categories between youth suicide deaths exposed versus not exposed to trauma and (2) use findings from the first objective to direct investigation of polygenic risk in youth suicide deaths exposed versus not exposed to trauma.

Sample Selection and Data Preparation

- A total of 1,658 UPDB de-identified individuals who died from suicide and had linked medical records were evaluated.
- Individuals aged 12-25 with a diagnosis of post-traumatic stress disorder (PTSD) or medically documented trauma were selected (N=214; **Young Trauma Suicide**, "**YTS**").
- YTS were compared with young (aged 12-25) individuals who died by suicide but had no medically documented history of trauma exposure (N=1,444; **Young Non-Trauma Suicide** "**YNTS**"; see table 1).
- YTS and YNTS were compared for differences in demographics and electronic health information, collapsed into 18 categories based on major pathological and physical processes.
- A subset of genotyped unrelated European suicides (YTS N=107; YNTS N = 628) were evaluated through polygenic risk score analyses (PRS).

Table 1: Population Demographics

Demographics	YTS	YNTS	*P*
Total – All N	214	1,444	
Total – Genotyped N	107	628	
Male – All N (Freq)	132 (62%)	1200 (83%)	$3.7x10^{-13}$
Female – All N (Freq)	82 (38%)	244 (17%)	
Male – Genotyped N (Freq)	60 (56%)	526 (84%)	$1.1x10^{-10}$
Female – Genotyped N (Freq)	47 (44%)	102 (16%)	
Age – All Mean	20.5	20.0	NS
Age – Genotyped Mean	20.3	19.8	NS
ICD Billing Codes Count – All Mean	47.0	17.0	$3.4x10^{-20}$
ICD Billing Codes Count – Genotyped Mean	50.4	18.5	$1.1x10^{-11}$

N: Number of individuals; Freq: Frequency; NS: Not significant ($P > 0.05$)

Analysis Methods

- All statistics, including for clinical category comparison and polygenic risk comparison utilized logistic regression and were adjusted for critical covariates and multiple tests.
- Significant clinical results were used to select studies with publicly available summary statistics from large studies (10k+ samples) for calculating polygenic risk scores.

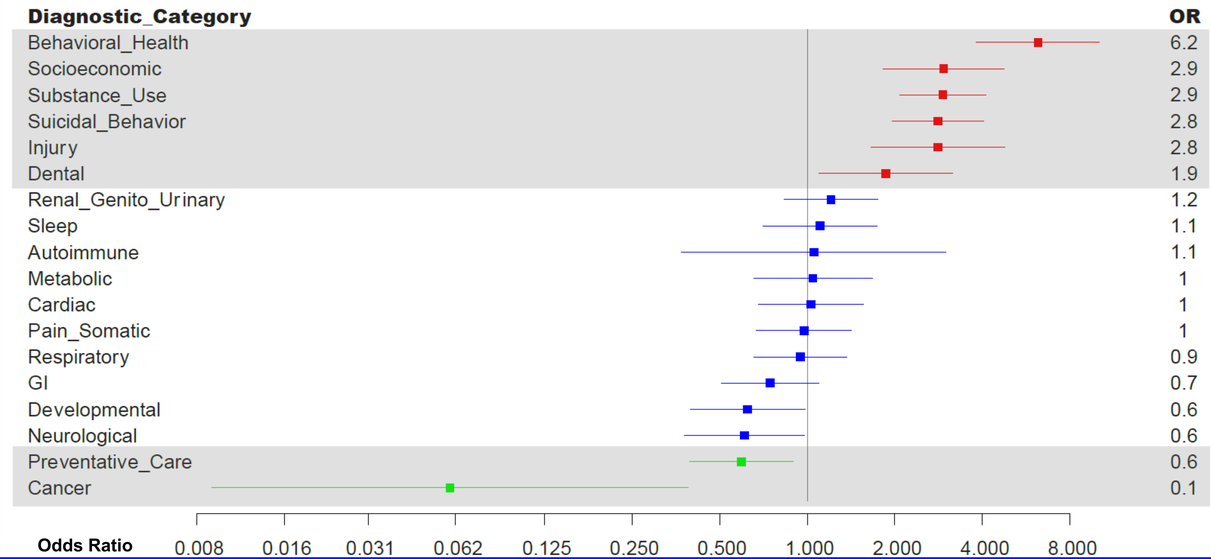

Figure 1: Forest plot representing the odds ratios of diagnostic categories in YTS versus YNTS. Whiskers represent 95% confidence intervals. Results colored in red represent significantly over-represented categories and green represent significantly under-represented categories in young trauma-exposed deaths, following correction for multiple testing. Calculated odds ratios (OR) are provided for each result in the right column.

Clinical Results

Clinical analyses yielded several diagnoses that were overrepresented within the YTS group as compared with YNTS, as demonstrated in Figure 1. A total of 8 diagnostic categories remained significant, even after correction for multiple testing and for critical covariates, including sex, age, and number of diagnostic encounters.

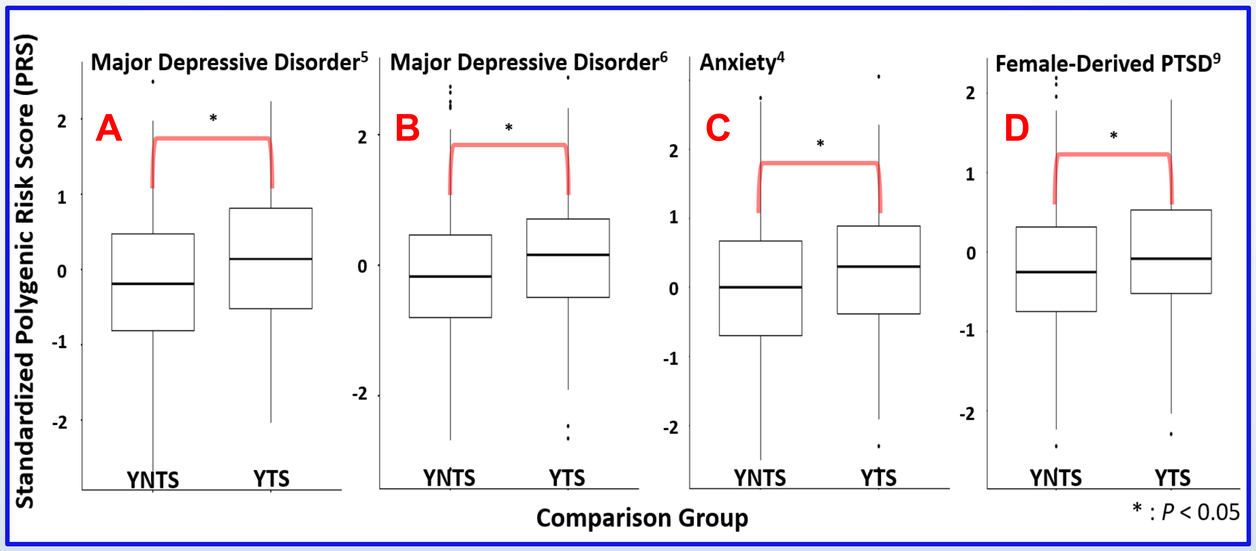

Figure 2: Bar chart representations of top findings from polygenic risk score association testing among YTS versus YNTS (noting that only genotyped, European, unrelated individuals were used in these comparisons). Each plot represents comparison group (x-axis) mean polygenic risk score for the given phenotype: Panel A: major depressive disorder PRS; Panel B: Depression PRS; Panel C: Anxiety PRS; Panel D: Female-derived post-traumatic stress disorder PRS. All results denoted by a * were significant with P < 0.05 after correction for multiple testing and critical covariates of sex, age, and the first 5 principal components for each subject.

Polygenic Risk Results

- Polygenic risk scores (PRS) essentially represent a summation of risk loci identified in large, existing genome wide association studies (GWAS) for a specific phenotype.
- PRS were selected and calculated based on significant diagnostic categories. Specifically, PRS for anxiety[4], depression[5,6], bipolar disorder[7], schizophrenia[8], PTSD[9], suicide attempt[10], smoking and alcohol use[11,12], and educational attainment[13] were calculated.
- Increased enrichment of polygenic risk within YTS for depression, anxiety, and PTSD was observed (See Figure 2).
  - It is particularly noted that the PTSD signal was identified within risk markers identified in a female-specific analysis in the original GWAS study.
  - This finding was driven by female YTS in the current study but was not significant after correction for multiple testing in a female-only analysis.

Conclusions

- A particular enrichment of behavioral health diagnoses, clinical evidence of previous suicide/self-harm behavior, prior clinically reported injury, substance use, indicators of socioeconomic disadvantage, and diagnosed dental issues were observed among trauma exposed youth who died by suicide.
- Conversely, a relative depletion of preventative health services and, interestingly, cancer diagnoses, were also found in YTS versus YNTS.
- It is particularly noteworthy that multiple behavioral health diagnosis PRS were enriched within YTS versus YNTS, providing converging evidence, when combined with clinical findings, toward the development of and predisposition for comorbid psychiatric diagnoses particularly within YTS.
  - Such results point to potential underlying biology that differentiates YTS from YNTS.
- It is also notable from evaluation of the demographics that the YTS sex distribution dramatically differs from that seen in the YNTS group.
  - The YNTS group more closely follows expectation with more males dying from suicide than females, but within trauma-exposed youths who died from suicide, the distribution is far more even..
  - This is interesting considering the female-driven PTSD finding, pointing at potential sex-specific effects.
- Ongoing work will refine significant diagnostic categories, look at interconnectivity within diagnostic categories, and add additional relevant PRS sets from recently published studies.

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