European Archives of Psychiatry and Clinical Neuroscience (2022) 272:355–358
https://doi.org/10.1007/s00406-022-01398-5

EDITORIAL

Completed suicide is associated with a higher polygenic burden for psychiatric disorders

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Published online: 14 March 2022

Keywords Completed suicide · Polygenic risk score · Schizophrenia · Bipolar disorder · Major depressive disorder · Suicide attempt

Suicide is one of the most relevant public health concerns nowadays, involving approximately 1 million annual deaths worldwide. According to World Health Organization (WHO) reports, deaths due to suicide have increased by 60% in the last 50 years, and they account for 1.4% of premature deaths worldwide.

Several studies have convincingly shown that major psychiatric disorders have substantially elevated suicide mortality risks compared with the general population. Psychological autopsies of suicide completers indicate that a large fraction (87.3%) of subjects dead by suicide had been previously diagnosed with a mental disorder [1]. Along these lines, long-term follow-up studies have shown that a diagnosis of psychosis or major depression or earlier suicide attempts at baseline represent the largest risk factors for suicide mortality [2].

Current evidence indicates that suicidal behavior (SB) results from a complex and not yet understood interplay

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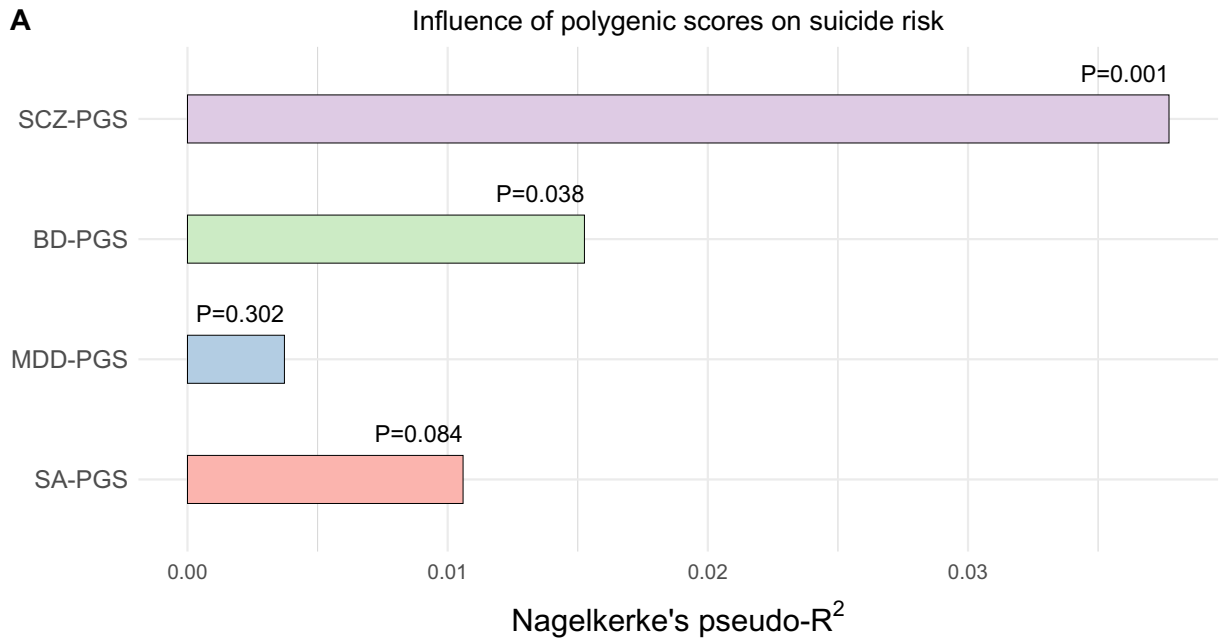
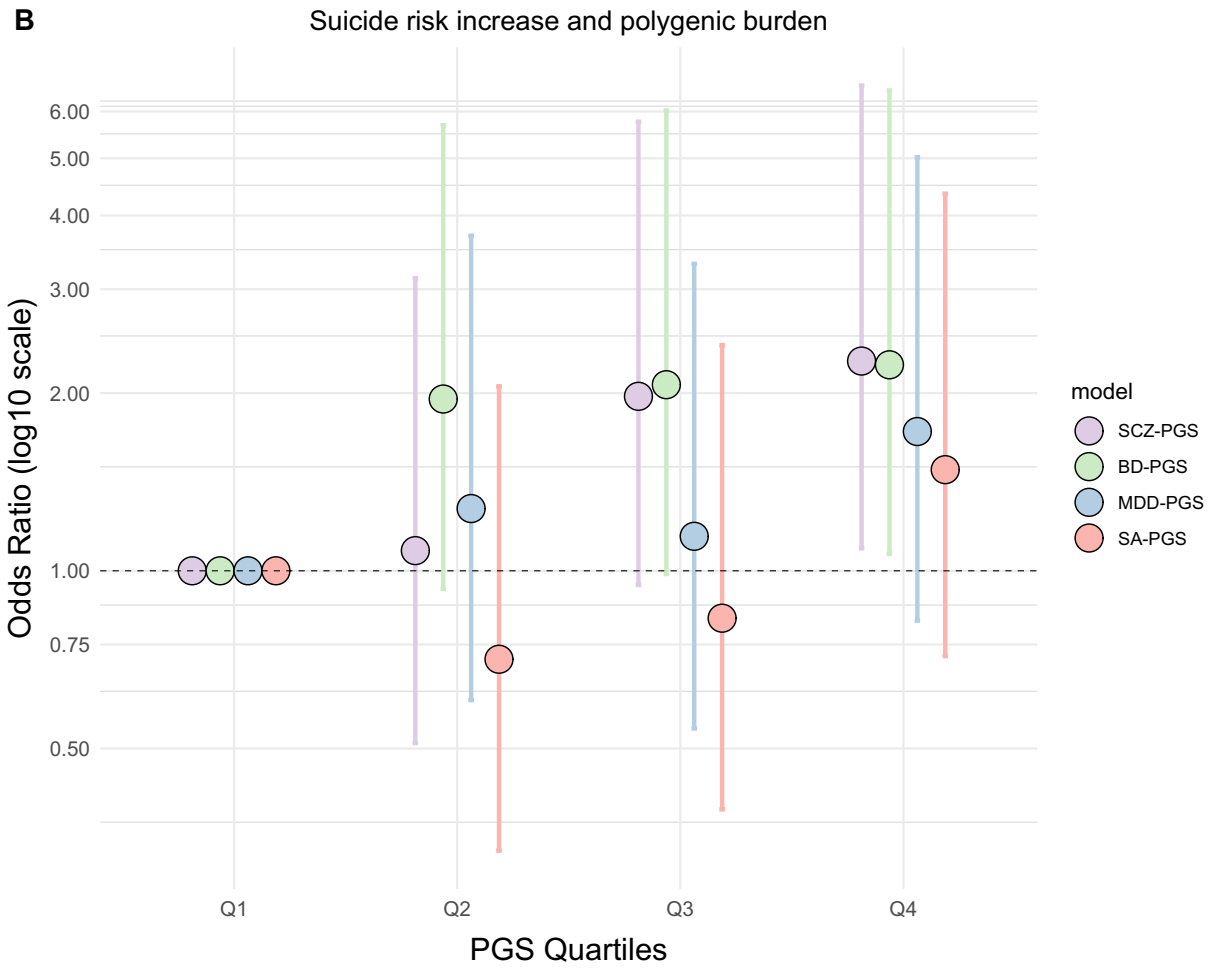

A
Influence of polygenic scores on suicide risk
P=0.001
SCZ-PGS
P=0.038
BD-PGS
P=0.302
MDD-PGS
P=0.084
SA-PGS
0.00
0.01
0.02
0.03
Nagelkerke's pseudo-R2


B
Suicide risk increase and polygenic burden
6.00
5.00
4.00
3.00
2.00
1.00
0.75
0.50
Odds Ratio (log10 scale)
Q1
Q2
Q3
Q4
PGS Quartiles
model
SCZ-PGS
BD-PGS
MDD-PGS
SA-PGS

◂**Fig. 1** **A** Percentage of the variance in completed suicide explained by SCZ-PGS, BD-PGS, MDD-PGS, and SA-PGS, respectively, after correction for age, sex, and the first two ancestry components. **B** Odds ratios (OR) from the comparison of the completed suicide-control ratio between high and low PGS groups after dividing the sample based on quartiles using the standard residuals of the PGS corrected by age, sex, and the first two ancestry components. *SCZ* Schizophrenia, *BD* Bipolar Disorder, *MDD* Major Depressive Disorder, *SA* Suicide Attempts, *PGS* Polygenic Scores

between premorbid clinical conditions, environmental factors, and biological factors. The study of Buoli et al. [3] in this issue provides a good example of such evidence, showing the relevance of several clinical variables in the lifetime suicide attempts in patients affected by bipolar disorder (BD). Likewise, increasing evidence indicates that personality traits like neuroticism or extraversion may influence SB [4]. However, as pointed out by Nishanth and Jha [5] in this issue, little is known about the biological/neural basis of SB. Hence, genetics could shed light and contribute to our understanding of the biological substrate of this behavior.

Family, twin, and adoption studies have provided convincing evidence of the involvement of genetic risk factors in SB, and the heritability (h^2) of completed suicide has been estimated at around 35–50%. Recent genome-wide association studies (GWAS) have just started to analyze the genetic architecture of suicidal behavior [6, 7]. These studies have provided compelling evidence of the polygenicity of suicide-related traits.

We have estimated the polygenic burden of schizophrenia (SCZ), BD, major depressive disorder (MDD), and suicide attempt (SA) in a sample of 172 suicide completers of unknown diagnostic status (26.2% females, 53.37 ± 19.57 years) from the Institut de Medicina Legal i Ciències Forenses de Catalunya (IMLCFC) and 130 healthy controls (47.7% females, 38.22 ± 11.92 years) from FIDMAG Germanes Hospitalàries Research Foundation. Written consent was obtained for all the samples, and the study was approved by the different ethical committees at the centers involved in the recruitment. All steps involving quality control and imputation of the samples were carried out as described elsewhere [4].

Polygenic Scores (PGS) were calculated using the imputation dosage for each risk allele based on the results of the following GWAS: SCZ [8], BD [9], MDD [10], and SA [6]. PRS-CS tool was used to infer posterior SNP effect sizes under continuous shrinkage priors and estimate the global shrinkage parameter (φ) using a fully Bayesian approach.

Logistic regression models show that SCZ-PGS and BD-PGS are associated with completed suicide in our sample, and they explain, respectively, 3.77% (p value $= 1 \times 10^{-3}$) and 1.53% (p value $= 3.8 \times 10^{-2}$) of the variance in the observed scale. No association was found when using MDD-PGS or SA-PGS (p value > 0.05) (Fig. 1A). Age, sex, and the first two ancestry components were used as covariates.

To estimate the risk increase, the sample was divided into quartiles of increasing polygenic load (using the standard residuals of the PGS corrected by age, sex, and the first two ancestry components), with Q1 (lowest genetic load) used as the baseline. The general tendency observed was that for all PGS, a higher genetic load increased the probabilities of suicide. The comparison of extreme quartiles (Q4 versus Q1) showed a statistically significant increase in risk of suicide for SCZ-PGS [OR = 2.27 95% CI (1.75–4.37); χ^2 p value = 0.022] and BD-PGS [OR = 2.23 95% CI (1.66–4.28); χ^2 p value = 0.023], but not for MDD-PGS or SA-PGS (Fig. 1B).

Our results align with the results derived from psychological autopsies of suicide completers, which indicate that a significant fraction of the subjects dead by suicide suffered mental disorders [1]. However, our positive results could derive not only from the proportion of individuals with a previous diagnosis of SCZ or BD in our sample of suicide completers but also from the shared genetic bases between SB and these psychiatric disorders.

Despite our relatively small sample size, our analyses detected genetic effects that converge with the results of a recent genetic study based on a larger population [7]. In this sense, larger samples, psychological autopsies, and information on the type of suicidal methodology will lay the foundation for fine-grained analyses of the relationship between polygenic burden and SB.

The lack of well-defined and well-powered GWAS for SB has made the estimation of its genetic correlation with psychiatric disorders difficult so far. In this regard, the ongoing efforts from many clinical investigators on establishing the International Suicide Genetics Consortium [6] will allow not only to elucidate the genetic bases of SB but also the estimation of the genetic correlations with psychiatric disorders. Moreover, identifying specific genetic variants shared/non-shared between psychiatric disorders and suicide will become possible.

Acknowledgements This research was funded by: (i) the Institute of Health Carlos III through projects (PI11/02006, PI16/01029, PI16/00998, PI17/01122, PI18/00467, PI18/01535) and contracts (FI19/0352 to MG-R, CP20/00072 to MF-V), co-funded by European Regional Development Fund (ERDF)/European Social Fund "Investing in your future", (ii) the Comissionat per a Universitats i Recerca del DIUE of the Generalitat de Catalunya (AGAUR: 2017SGR1577 and 2017SGR1271). MM was supported by Horizon 2020 Marie Sklodowska-Curie Individual Fellowship from the European Commission under grant agreement no. 841899 (GRASAD). TGS was supported by grants SCHU 1603/4-1, 5-1, 7-1 from the Deutsche Forschungsgemeinschaft (DFG).

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