

Genetic heterogeneity in depressive symptoms following the death of a spouse:

Polygenic score analysis of the US Health and Retirement Study

Supplemental Information

Supplemental Table 1. Coefficients estimated from nonlinear regression models. M1 estimates are for the model testing the main effect association between polygenic score and depressive symptoms. M2 estimates are for the model testing main effect associations between death of a spouse and depressive symptoms. M3 estimates are for the model testing genetic buffering of the association between death of a spouse and depressive symptoms. Coefficients are named corresponding to Equation 1. Briefly, α is the model intercept. β_1 is the main effect of the polygenic score. β_2 is the main effect of spousal death. β_3 is the genetic buffering effect. λ is the rate of attenuation in depressive symptoms with time since the death (the “decay” rate). γ is the estimate of genetic heterogeneity in the decay rate.

	M1*				M2**				M3			
	Est	SE	t	pv	Est	SE	t	pv	Est	SE	t	pv
α	0.2788	0.063817	4.37	1.25E-05	1.1754	0.7386	1.591	1.12E-01	1.1587	0.7383	1.569	1.17E-01
<u>Controls</u>												
Male Sex	-0.3612	0.027352	-13.2	8.27E-40	-0.1033	0.1165	-0.886	3.76E-01	-0.1053	0.1163	-0.905	3.66E-01
Birth Year	0.0165	0.001521	10.84	2.19E-27	0.0324	0.0107	3.023	2.54E-03	0.0325	0.0107	3.028	2.50E-03
Age	0.0162	0.000911	17.77	1.11E-70	0.0127	0.0106	1.201	2.30E-01	0.0129	0.0106	1.223	2.22E-01
<u>Effects</u>												
β_1	-0.1084	0.013487	-8.04	8.96E-16					-0.0192	0.0938	-0.205	8.38E-01
β_2					1.8981	0.2168	8.756	4.51E-18	1.8612	0.2139	8.703	7.09E-18
β_3									-0.4632	0.2026	-2.287	2.23E-02
λ					5.4693	1.4236	3.842	1.26E-04	5.6319	1.5505	3.632	2.89E-04
γ									0.4071	1.1288	0.361	7.18E-01
<u>N</u>												
observations	74,512				1,829				1,829			
N people	9,453				1,829				1,829			
Within Var	1.49				NA				NA			
Error Var	1.64				4.62				4.62			

* Model 1 restricts the values of β_2 and β_3 to be zero, resulting in a standard linear model.

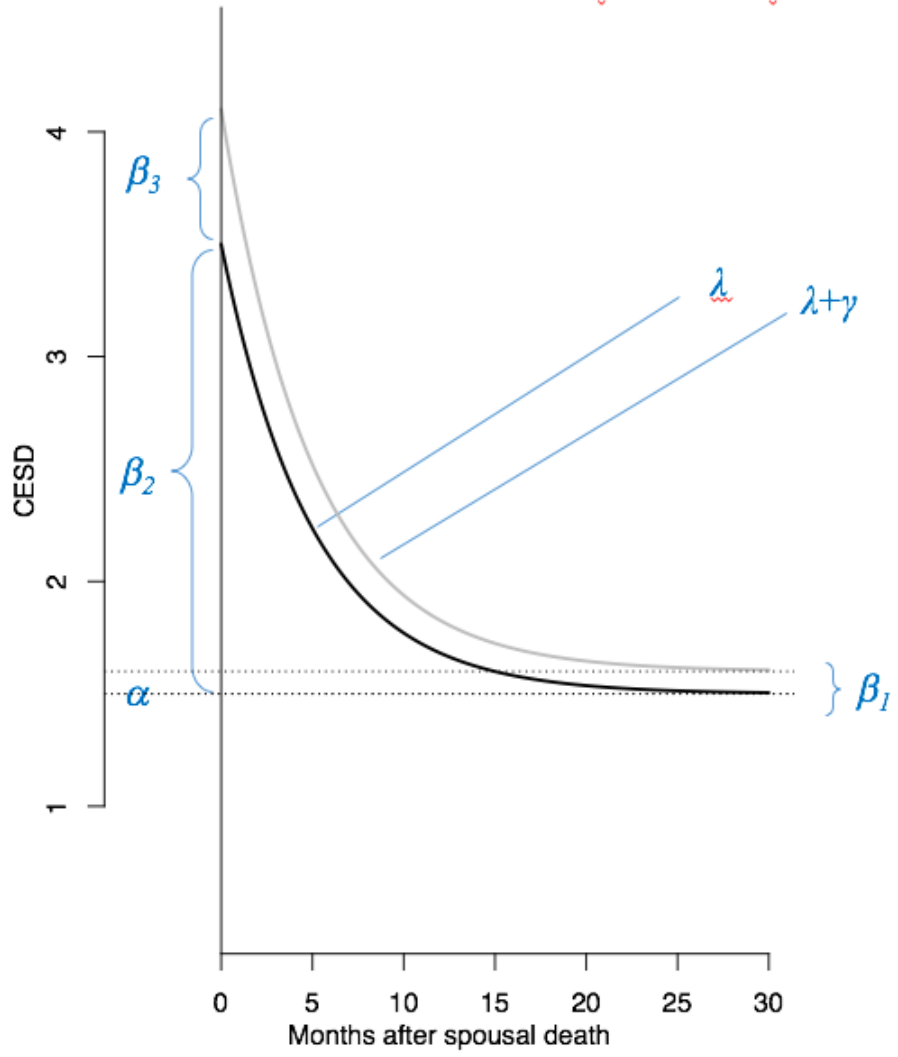
**Model 2 restricts values of β_1 , β_3 , and Delta to zero in order to estimate the main effect of the death of a spouse without regard to genotype.

Supplemental Figure 1. Prototype showing how coefficient estimates from the nonlinear regression contribute to estimation of depressive symptom trajectories following the death of a spouse. The regression equation is

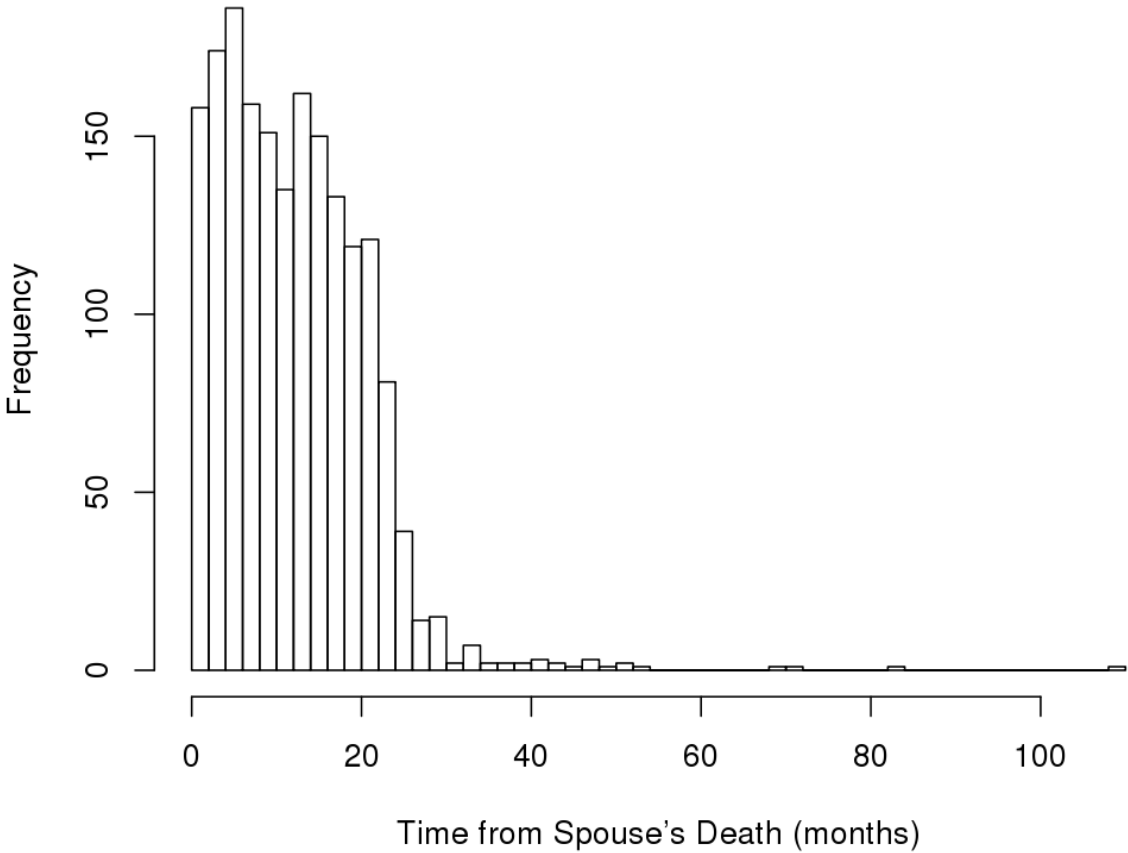
$$\text{CESD}_i = \alpha + \beta_1 \text{PGS}_i + (\beta_2 + \beta_3 \text{PGS}_i) \exp[t_i / (\lambda + \gamma \text{PGS}_i)] + \text{controls} + \varepsilon_i.$$

The figure shows trajectories of depressive symptoms with curved lines. The solid black curved line is the population average trajectory. The line begins on the left side of the graph immediately following increase in depressive symptoms following the spouse's death (estimated by the coefficient β_2). The slope of the line curves downward from left to right according to the rate of decline in depressive symptoms with time since the death (estimated by the coefficient λ). The dotted black line shows the estimate of baseline depressive symptoms which the symptom level approaches with increasing time since the death (estimated as the coefficient α). The other model parameters test how this population average trajectory varies according to an individual's polygenic score. A trajectory for a person with a polygenic score below the population mean is shown in light gray for illustration. Variation in the magnitude of increase in depressive symptoms immediately following the death is estimated by the coefficient β_3 . Variation in the rate of decline in depressive symptoms with time since the death is estimated by the coefficient γ . Variation in the baseline level toward which depressive symptoms decline with time since the death is estimated by β_1 .

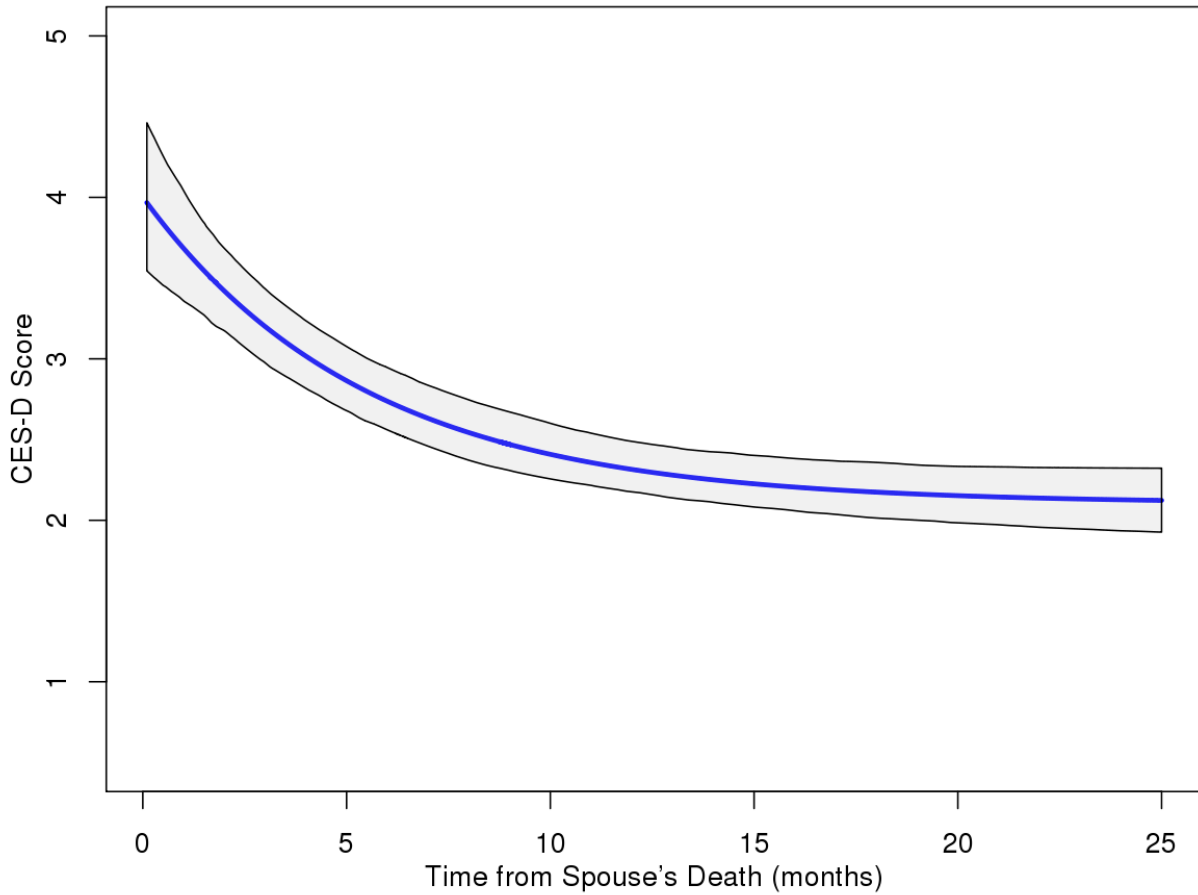
$$\alpha + \beta_1 \text{PGS}_i + (\beta_2 + \beta_3 \text{PGS}_i) \exp[-t_i / (\lambda + \gamma \text{PGS}_i)] + \text{controls} + \varepsilon_i.$$



Supplemental Figure 2. Distribution of time-since-death for depression measurements analyzed in nonlinear regression models (N=1,829). Nearly all observations occurred during the first two years following the death.



Supplemental Figure 3. Increase in depressive symptoms and subsequent recovery following death of a spouse. Trajectory based on nonlinear regression model described in equation 1 of the main text. The graph shows a fitted trajectory following spousal death for a 73-year old woman born at the mean birth year who had a polygenic score of zero.



Supplemental Figure 4. Depressive trajectories based on the first observations after death for those who lost spouses. The graph shows fitted trajectories following spousal death for 73-year old females born at the mean birth year who are one SD above and below the mean PGS using estimates from M3 of Supplemental Table 1.

