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

Polygenic score analysis of the US Health and Retirement Study

Supplemental Information

Supplemental Figure 1. Time from spousal death to the first follow-up assessment in N=1,829 non-Hispanic white Health and Retirement Study members. Average time between death and first follow-up assessment was 12 months. Nearly all observations occurred during the first two years following the death.
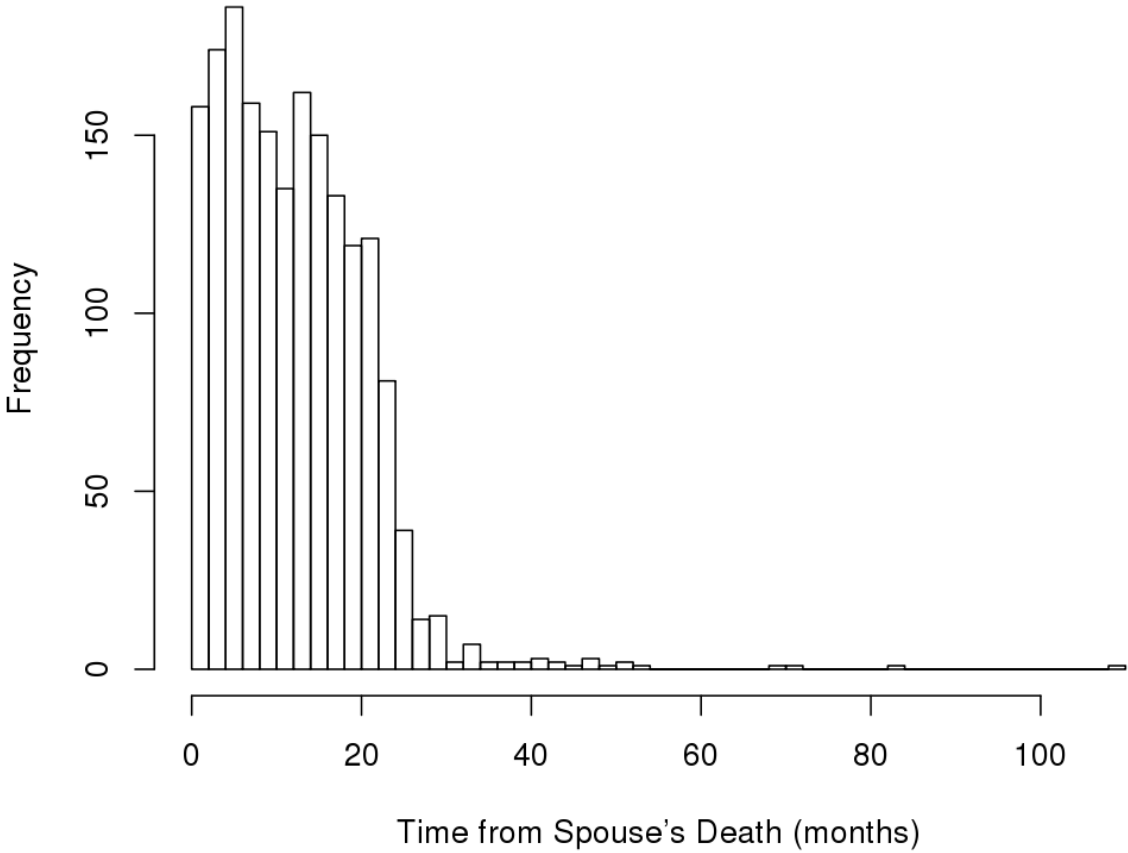
Supplemental Figure 2. Prototype showing how coefficient estimates from the nonlinear regression contribute to estimation of depressive symptom trajectories following the death of a spouse. The regression equation is

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

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.

$\alpha + \beta_1 \text{PGS}_i + (\beta_2 + \beta_3 \text{PGS}_i) \exp[t_i/(\lambda + \gamma\, \text{PGS}_i)] + \text{controls} + \varepsilon_i.$
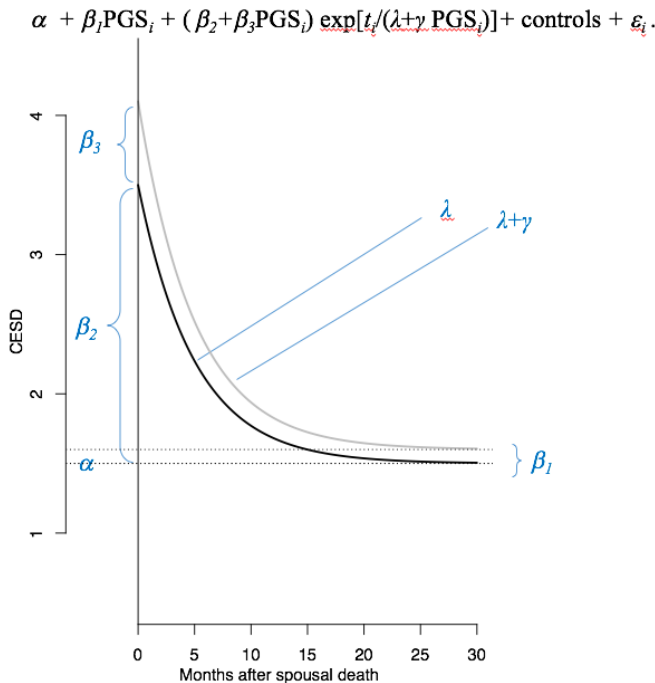
Supplemental Figure 3. Depressive trajectories based on the first observations after death for those who lost spouses. The graph shows fitted trajectories following spousal death for 73-year old females born at the mean birth year who are one SD above and below the mean PGS using estimates from M3 of Supplemental Table 1.
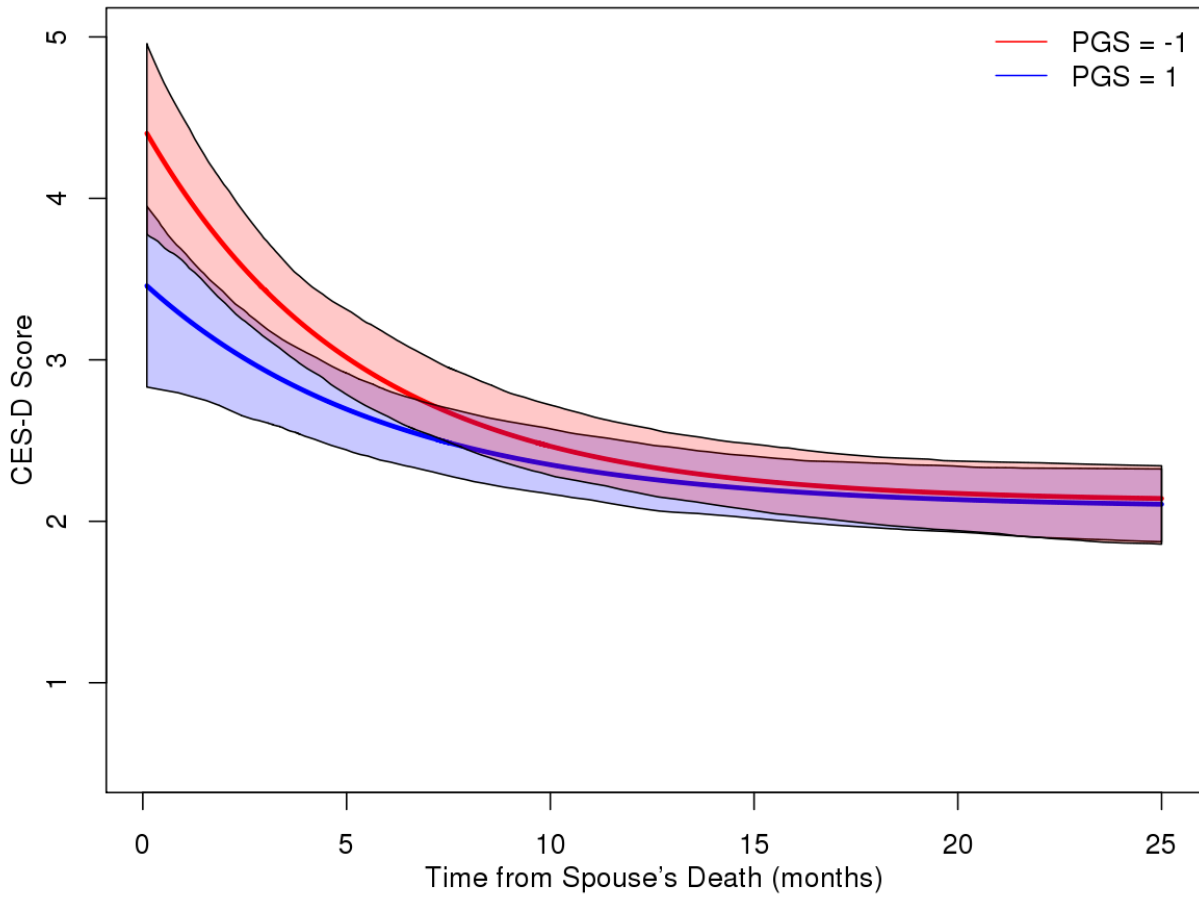
Supplemental Table 1. Regression Model Results for Subjective Wellbeing Polygenic Score. Coefficients are named corresponding to Equation 1. Briefly, α is the model intercept. β_1 is the main effect of the polygenic score. β_2 is the main effect of spousal death. β_3 is the genetic buffering effect. 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. Main Effect of Polygenic Score on Depressive Symptoms*				M2. Main Effect of Spousal Death on Depressive Symptoms**				M3. Buffering Effect of Polygenic Score on Depressive Symptoms following Spousal Death			
	Est	SE	t	p-value	Est	SE	t	p-value	Est	SE	t	p-value
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
Controls												
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
Effects												
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
N 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 Table 2. Regression Model Results for Subjective Wellbeing Polygenic Score in the Genetically-defined European-descent Subsample. The genetically-defined European-descent subsample was identified by the Health and Retirement Study (described at http://hrsonline.isr.umich.edu/sitedocs/genetics/HRS_QC_REPORT_MAR2012.pdf). 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. Main Effect of Polygenic Score on Depressive Symptoms*				M2. Main Effect of Spousal Death on Depressive Symptoms**				M3. Buffering Effect of Polygenic Score on Depressive Symptoms following Spousal Death			
	Est	SE	t	pv	Est	SE	t	pv	Est	SE	t	pv
α	0.2642	0.0660	4.0000	6.35E-05	1.0048	0.7680	1.3100	1.91E-01	0.9738	0.7672	1.2690	2.04E-01
Controls												
Male Sex	-0.3566	0.0282	-12.6700	9.04E-37	-0.1357	0.1233	-1.1000	2.71E-01	-0.1437	0.1230	-1.1680	2.43E-01
Birth Year	0.0171	0.0016	10.8600	1.87E-27	0.0352	0.0113	3.1100	1.87E-03	0.0354	0.0113	3.1390	1.72E-03
Age	0.0159	0.0009	16.8200	1.87E-63	0.0145	0.0110	1.3100	1.90E-01	0.0149	0.0110	1.3570	1.75E-01
Effects												
β_1	-0.1004	0.0139	-7.2300	4.90E-13					0.0133	0.0935	0.1430	8.87E-01
β_2					1.9656	0.2234	8.8000	3.41E-18	1.9411	0.2201	8.8190	2.90E-18
β_3									-0.6045	0.2098	-2.8810	4.02E-03
λ					5.4514	1.4241	3.8300	1.34E-04	5.5896	1.5243	3.6670	2.53E-04
γ									0.342	1.0257	0.3330	7.39E-01
N observations	67,805				1,647				1,647			
N people	8,588				1,647				1,647			
Within Var	1.42				NA				NA			
Error Var	1.61				4.54				4.54			

* 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 Table 3. Regression Model Results for Depression Polygenic Scores. Polygenic scores were calculated based on GWAS results posted by the Psychiatric Genomics Consortium (https://www.med.unc.edu/pgc/results-and-downloads) and the Social Science Genetic Association Consortium (http://www.thessgac.org/data). Coefficients are named corresponding to Equation 1.

	M1. Main Effect of Polygenic Score on Depressive Symptoms*				M2. Main Effect of Spousal Death on Depressive Symptoms**				M3. Buffering Effect of Polygenic Score on Depressive Symptoms following Spousal Death			
	Est	SE	t	pv	Est	SE	t	pv	Est	SE	t	pv
Panel A: Psychiatric Genomics Consortium Major Depressive Disorder Polygenic Score												
α	0.2785	0.0638	4.3600	1.28E-05	1.1754	0.7386	1.5910	1.12E-01	1.1562	0.7360	1.5710	1.16E-01
Controls												
Male Sex	-0.3633	0.0274	-13.2700	3.62E-40	-0.1033	0.1165	-0.8860	0.376	-0.0955	0.1162	-0.8220	0.411
Birth Year	0.0165	0.0015	10.8500	1.94E-27	0.0324	0.0107	3.0230	2.54E-03	0.0324	0.0107	3.0310	2.47E-03
Age	0.0162	0.0009	17.7900	7.87E-71	0.0127	0.0106	1.2010	2.30E-01	0.0131	0.0106	1.2380	2.16E-01
Effects												
β_1	0.0848	0.0135	6.2800	3.40E-10					-0.0650	0.0884	-0.7360	4.62E-01
β_2					1.8981	0.2168	8.7560	4.51E-18	1.9445	0.2274	8.5510	2.54E-17
β_3									0.5717	0.2162	2.6440	8.27E-03
λ					5.4693	1.4236	3.8420	1.26E-04	4.9949	1.2955	3.8560	1.19E-04
γ									0.8115	1.0964	0.7400	4.59E-01
N 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				4.58			

Panel B: Social Science Genetic Association Consortium Depressive Symptoms Polygenic Score

	Model 1				Model 2				Model 3			
α	0.2792	0.0638	4.3800	1.21E-05	1.1754	0.7386	1.5910	1.12E-01	1.2197	0.7360	1.6570	9.76E-02
Controls												
Male Sex	-0.3649	0.0273	-13.3600	9.82E-41	-0.1033	0.1165	-0.8860	0.376	-0.1010	0.1165	-0.8670	0.386
Birth Year	0.0162	0.0015	10.6800	1.3E-26	0.0324	0.0107	3.0230	0.00254	0.0312	0.0107	2.9060	0.00371
Age	0.0162	0.0009	17.8000	7.28E-71	0.0127	0.0106	1.2010	2.30E-01	0.0122	0.0106	1.1580	2.47E-01
Effects												
β_1	0.1328	0.0135	9.8800	5.34E-23					-0.0099	0.0841	-0.1180	9.06E-01
β_2					1.8981	0.2168	8.7560	4.51E-18	1.9202	0.2212	8.6800	8.63E-18
β_3									0.6001	0.2263	2.6520	8.08E-03
λ					5.4693	1.4236	3.8420	0.000126	5.2322	1.4039	3.7270	0.0002
γ									-0.2124	0.9379	-0.2260	8.21E-01
N observations	74,512				1,829				1,829			
N people	9,453				1,829				1,829			
Within Var	1.48				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