SUPPLEMENTAL MATERIALS TO Genetic heterogeneity in depressive symptoms following the death of a spouse: Polygenic score analysis of the US Health and Retirement Study

Genotyping

HRS SNP genotyping was conducted by the NIH Center for Inherited Disease Research using DNA extracted from saliva collected during face-to-face interviews in HRS respondents' homes in 2006 and 2008 and Illumina HumanOmni 2.5 Quad BeadChip arrays (http://hrsonline.isr.umich.edu/index.php?p=xxgen1).

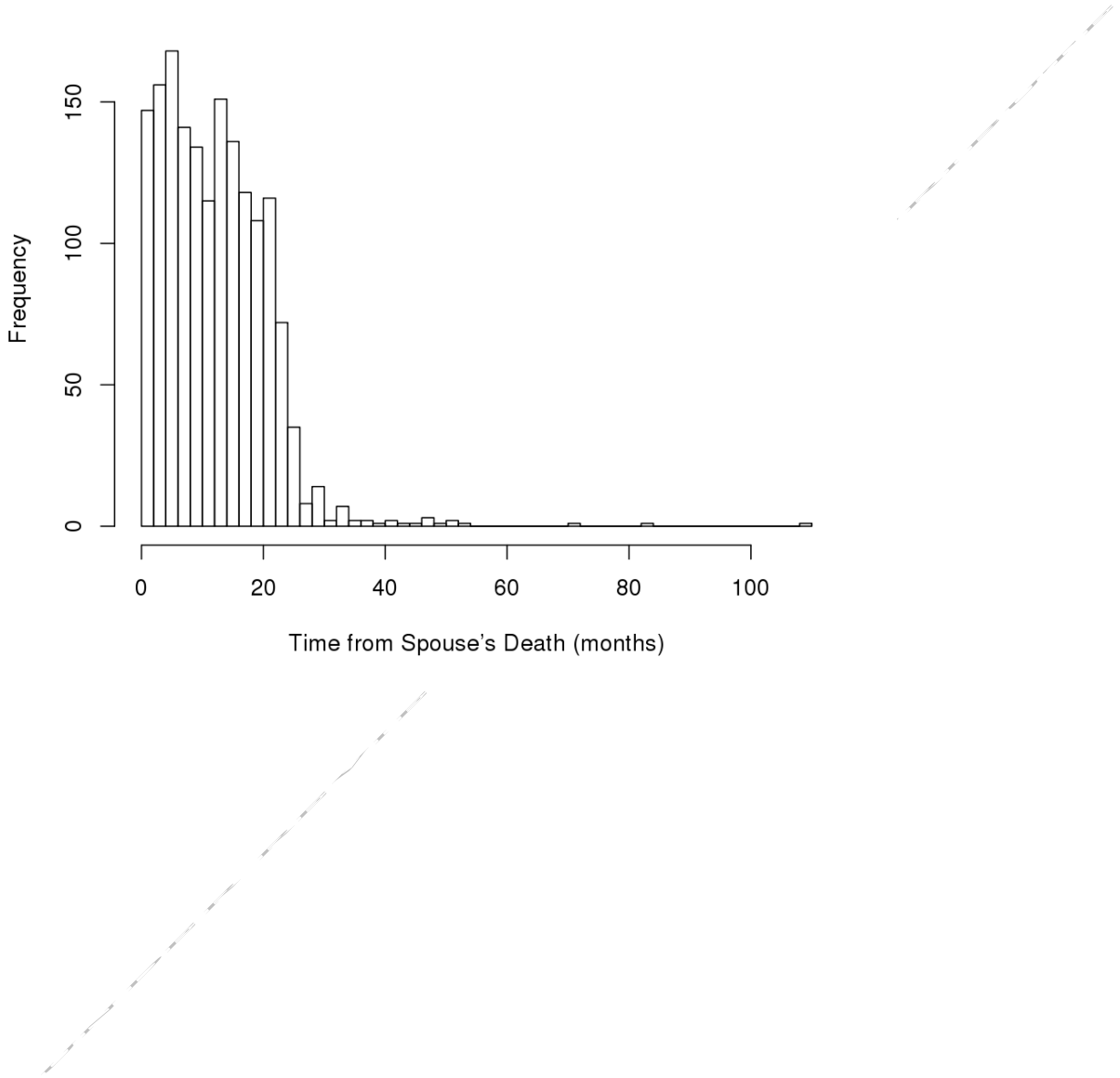
Nonlinear Regression Analysis Including All Observations Taken Following Spousal Death.

We conducted our primary nonlinear regression analysis using data only from only the first observation taken following spousal death, i.e. one observation per HRS respondent. We focused on this first observation because local regression analysis indicated that most spousal-death-related increase in depressive symptoms had dissipated by 24 months following spousal death. HRS assessments are conducted every two years. Thus, about half of all second observations following spousal death and all subsequent observations are expected to fall outside the normal recovery window. To focus nonlinear regression analysis on the initial increase in depressive symptoms following spousal death and recovery from that increase, we restricted our main analysis to only the first observation taken following spousal death.

SUPPLEMENT TO Genetic heterogeneity in depressive symptoms following death of a spouse

As a sensitivity analysis, we repeated nonlinear regression analysis including all observations following spousal death. This model yielded slightly different results. The main difference between the models was that the model including all post-death observations estimated a longer total recovery time as compared to the model based on only the first post death observation (λ=14.04 as compared to λ=5.59 in the original model). The model including all post-death observations also found more modest genetic buffering of depression immediately following spousal death (b=-0.37, CI -0.63, -0.12, p=0.004 as compared b=-0.60, CI -0.19, -1.02, p=0.004 in the original model), but larger genetic influence on the rate of recovery (γ=3.95, p<0.001 as compared to γ=0.34, p=0.739 in the original model). Substantively, the original model, based on the first post-death observation, suggested that genetics of subjective wellbeing influenced the magnitude of the initial depressogenic shock caused by spousal death and that recovery occurred over a relatively short time interval (about 12 months) at about the same rate regardless of genotype. In contrast, the model including all post-death observations suggested genetics of subjective wellbeing influenced both the magnitude of the initial depressogenic shock and the rate of recovery, with recovery occurring over a somewhat longer time interval (about 24 months).

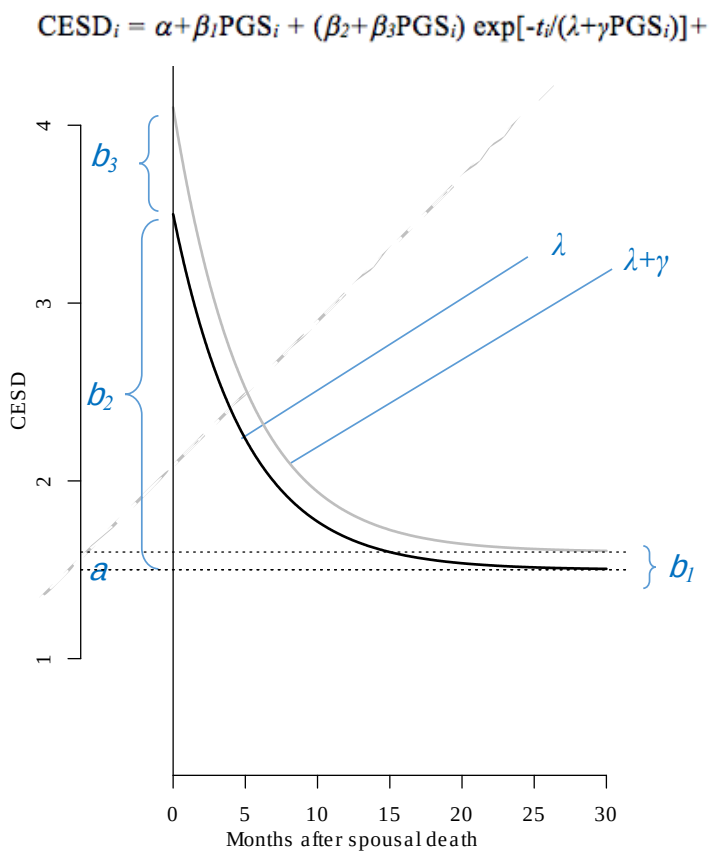
Supplemental Figure 1. Time from spousal death to the first follow-up assessment in N=1,647 non-Hispanic white Health and Retirement Study members. Average time between death and first follow-up assessment was 12 months. Nearly all observations occurred during the first two years following the death.



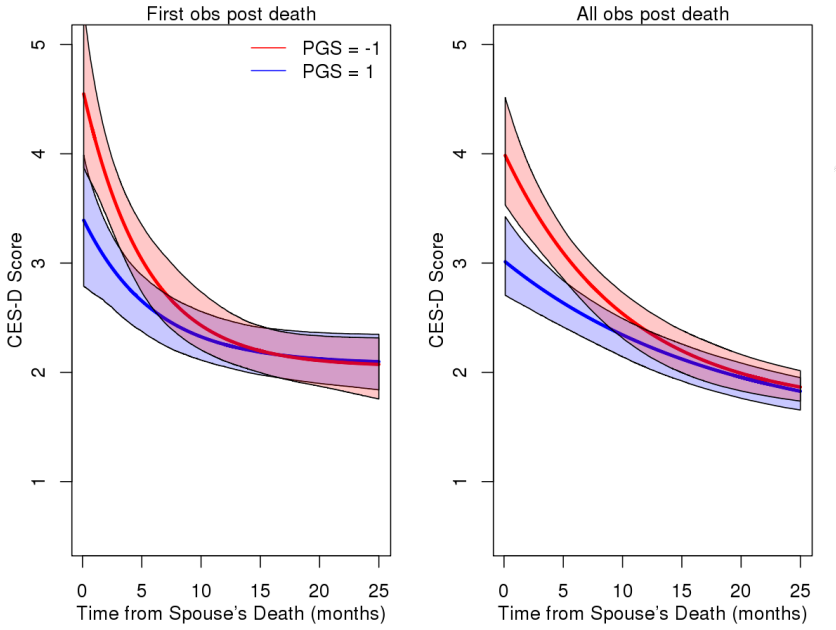
Supplemental Figure 2. Prototype showing how coefficient estimates from the nonlinear regression contribute to estimation of depressive symptom trajectories following the death of a spouse. The regression equation is

$$CESD_i = \alpha+\beta_1 PGS_i + (\beta_2+\beta_3 PGS_i) \exp[-t_i/(\lambda+\gamma PGS_i)]+ \chi+ \varepsilon_i$$

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.



Supplemental Figure 3. Trajectories of depressive symptoms following spousal death estimated from nonlinear regression models. The graph shows trajectories of depressive symptoms in the months following spousal death for individuals with low subjective wellbeing polygenic scores (1 SD below the mean, red lines) and high subjective wellbeing polygenic scores (1 SD above the mean, blue lines). Panel A (left side) shows trajectories estimated from models fitted to data from the first observation following spousal death. Panel B (right side) shows trajectories estimated from models fitted to data from all observations following spousal death. Model parameters are shown in the table below the figure. Trajectories are drawn assuming mean age and birth year and female sex.



Nonlinear Regression Model Parameters

	A. First post-death observation			B. All post-death observations		
	Est	SE	p-value	Est	SE	p-value
a	0.97	0.77	0.204	0.70	0.61	0.246
Covariates						
Male Sex	-0.14	0.12	0.243	-0.06	0.10	0.550
Birth Year	0.04	0.01	0.002	0.02	0.01	0.044
Age	0.01	0.01	0.175	0.01	0.01	0.156
Effects						
b_1	0.01	0.09	0.887	-0.12	0.05	0.018
b_2	1.94	0.22	2.90E-18	1.96	0.14	7.56E-43
b_3	-0.60	0.21	0.004	-0.37	0.13	0.004
λ	5.59	1.52	2.53E-04	14.04	1.96	8.73E-13
γ	0.34	1.03	0.739	3.95	1.01	9.22E-05
N observations	1,647			6,092		
N individuals	1,647			1,647		
Total Error Variance	4.54			3.88		

Supplemental Table 1. Regression Model Results for Subjective Wellbeing Polygenic Score. Coefficients are named corresponding to the equation in Supplemental Figure 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**		
	Est	SE	p-value	Est	SE	p-value	Est	SE	p-value
a	0.26	0.07	6.35E-05	1.00	0.77	0.191	0.97	0.77	0.204
Covariates									
Male Sex	-0.36	0.03	9.04E-37	-0.14	0.12	0.271	-0.14	0.12	0.243
Birth Year	0.02	0.00	1.87E-27	0.04	0.01	0.002	0.04	0.01	0.002
Age	0.02	0.00	1.87E-63	0.01	0.01	0.190	0.01	0.01	0.175
Effects									
b_1	**-0.10**	**0.01**	**4.90E-13**				0.01	0.09	0.887
b_2				**1.97**	**0.22**	**3.41E-18**	1.94	0.22	2.90E-18
b_3							**-0.60**	**0.21**	**0.004**
λ				5.45	1.42	1.34E-04	5.59	1.52	2.53E-04
γ							0.34	1.03	0.739
N observations	67,805			1,647			1,647		
N individuals	8,588			1,647			1,647		
Within-individual Variation	1.42			NA			NA		
Total Error Variance	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 2. Regression Model Results for Subjective Wellbeing Polygenic Score in All HRS Respondents Who Self-Reported Non-Hispanic White Race/Ethnicity. Coefficients are named corresponding to the equation in Supplemental Figure 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**		
	Est	SE	p-value	Est	SE	p-value	Est	SE	p-value
a	0.28	0.06	1.25E-05	1.18	0.74	0.112	1.16	0.74	0.117
Covariates									
Male Sex	-0.36	0.03	8.27E-40	-0.10	0.12	0.376	-0.11	0.12	0.366
Birth Year	0.02	0.00	2.19E-27	0.03	0.01	0.003	0.03	0.01	0.003
Age	0.02	0.00	1.11E-70	0.01	0.01	0.230	0.01	0.01	0.222
Effects									
b_1	**-0.11**	**0.01**	**8.96E-16**				-0.02	0.09	0.838
b_2				**1.90**	**0.22**	**4.51E-18**	1.86	0.21	7.09E-18
b_3							**-0.46**	**0.20**	**2.23E-02**
λ				5.47	1.42	1.26E-04	5.63	1.55	2.89E-04
γ							0.41	1.13	0.718
N observations	74,512			1,829			1,829		
N individuals	9,453			1,829			1,829		
Within-individual Variation	1.49			NA			NA		
Total Error Variance	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 3. Regression Model Results for Major Depressive Disorder and Depressive Symptoms 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 the equation in Supplemental Figure 1.

	M1. Main Effect of Polygenic Score on Depressive Symptoms*			**M2. Main Effect of Spousal Death on Depressive**			**M3. Buffering Effect of Polygenic Score on Depressive Symptoms**		
	Est	SE	pv	Est	SE	pv	Est	SE	pv
Panel A: Psychiatric Genomics Consortium Major Depressive Disorder Polygenic Score									
a	0.27	0.07	6.08E-05	1.01	0.77	0.191	0.99	0.77	0.196
Covariates									
Male Sex	-0.36	0.03	3.62E-37	-0.14	0.12	0.271	-0.13	0.12	0.305
Birth Year	0.02	0.00	1.70E-27	0.04	0.01	0.002	0.04	0.01	0.002
Age	0.02	0.00	1.37E-63	0.01	0.01	0.190	0.02	0.01	0.181
Effects									
b_1	**0.07**	**0.01**	**6.22E-07**				2.03	0.23	2.41E-18
b_2				**1.97**	**0.22**	**3.41E-18**	1.95	0.23	2.54E-17
b_3							**0.63**	**0.21**	**3.24E-03**
λ				5.45	1.42	1.34E-04	5.11	1.33	1.20E-04
γ							0.35	1.05	0.740
N observations	67,805			1,647			1,647		
N individuals	8,588			1,647			1,647		
Within-individual Variation	1.43			NA			NA		
Total Error Variance	1.61			4.54			4.54		
Panel B: Social Science Genetic Association Consortium Depressive Symptoms Polygenic Score									
a	0.26	0.07	6.34E-05	1.01	0.77	1.91E-01	1.05	0.77	0.170
Covariates									
Male Sex	-0.36	0.03	5.38E-38	-0.14	0.12	2.71E-01	-0.14	0.12	0.254
Birth Year	0.02	0.00	5.50E-27	0.04	0.01	1.87E-03	0.03	0.01	0.003
Age	0.02	0.00	1.27E-63	0.01	0.01	1.90E-01	0.01	0.01	0.204
Effects									
b_1	**0.13**	**0.01**	**5.62E-22**				-0.05	0.09	0.595
b_2				**1.97**	**0.22**	**3.41E-18**	1.99	0.23	4.71E-18
b_3							**0.69**	**0.23**	**0.003**
λ				5.45	1.42	1.34E-04	5.23	1.41	2.04E-04
γ							-0.18	0.89	0.839
N observations	67,805			1,647			1,647		
N individuals	8,588			1,647			1,647		
Within-individual Variation	1.42			NA			NA		
Total Error Variance	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