

Supplementary Table S1. Unadjusted associations of potential protective and risk factors with change in loneliness from pre-COVID-19 pandemic to during the pandemic, and with loneliness during the COVID-19 pandemic

Characteristic	Associations with change in loneliness from pre-pandemic to intra-pandemic		Associations with loneliness during pandemic	
	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value
Demographic				
Age (continuous, by 5-year increase)	0.10 (0.09, 0.12)	<0.0001	0.15 (0.13, 0.16)	<0.0001
Age ≥80	0.20 (0.16, 0.23)	<0.0001	0.28 (0.25, 0.32)	<0.0001
Race				
White (reference)				
American Indian/Alaska Native	-0.30 (-0.66, 0.06)	0.1039	0.03 (-0.36, 0.42)	0.8881
Asian/Pacific Islander	-0.17 (-0.28, -0.06)	0.0024	-0.28 (-0.40, -0.17)	<0.0001
Black/African American	-0.26 (-0.34, -0.18)	<0.0001	-0.20 (-0.29, -0.12)	<0.0001
More than one race	0.07 (-0.09, 0.23)	0.3695	0.25 (0.08, 0.42)	0.0042
Unknown/Not reported	-0.19 (-0.38, -0.01)	0.0422	0.08 (-0.12, 0.28)	0.4553
Hispanic/Latina ethnicity	-0.14 (-0.24, -0.04)	0.0056	-0.07 (-0.17, 0.04)	0.2225
Education				
College degree or higher (reference)				
School after high school	-0.01 (-0.05, 0.02)	0.5146	0.05 (0.01, 0.09)	0.0136
High school diploma or less	-0.02 (-0.07, 0.02)	0.3106	0.09 (0.03, 0.14)	0.0010
Lifestyle				
Walking continuously for at least 5 minutes				
≤3 times per week (reference)				
4 or more times per week	-0.11 (-0.14, -0.07)	<0.0001	-0.31 (-0.35, -0.27)	<0.0001
Alcoholic drinks per week				
None (reference)				
≤4	-0.06 (-0.09, -0.02)	0.0010	-0.18 (-0.22, -0.14)	<0.0001
5-7	-0.06 (-0.11, -0.01)	0.0034	-0.26 (-0.31, -0.20)	<0.0001
>7	-0.04 (-0.13, 0.05)	0.3601	-0.13 (-0.22, -0.03)	0.0104
Life events				
Number of stressful life events (0-11, continuous)	0.14 (0.13, 0.16)	<0.0001	0.29 (0.28, 0.31)	<0.0001
Death or serious illness of close friend or family member (other than spouse or partner)	0.13 (0.10, 0.16)	<0.0001	0.21 (0.17, 0.25)	<0.0001
Death of a pet	-0.01 (-0.08, 0.05)	0.6549	0.10 (0.03, 0.17)	0.0057
Death of a spouse or partner	0.73 (0.65, 0.81)	<0.0001	0.79 (0.70, 0.87)	<0.0001
Optimism (continuous)	-0.053 (-0.058, -0.049)	<0.0001	-0.143 (-0.147, -0.138)	<0.0001
Purpose in life (continuous)	-0.051 (-0.055, -0.048)	<0.0001	-0.110 (-0.114, -0.107)	<0.0001
Medical history				
CVD	0.16 (0.11, 0.21)	<0.0001	0.29 (0.24, 0.35)	<0.0001
Cancer	0.03 (-0.01, 0.07)	0.1414	0.06 (0.02, 0.10)	0.0027

Vascular risk factors score (0-4, continuous)	0.03 (0.01, 0.05)	0.0011	0.12 (0.10, 0.15)	<0.0001
History of depression (DIS)	0.72 (0.64, 0.80)	<0.0001	1.85 (1.77, 1.93)	<0.0001
Social connection variables				
Lives alone	0.20 (0.16, 0.23)	<0.0001	0.57 (0.53, 0.60)	<0.0001
Change in living arrangement due to pandemic	0.26 (0.19, 0.32)	<0.0001	0.41 (0.34, 0.48)	<0.0001
Living situation restrictions due to pandemic	0.25 (0.20, 0.29)	<0.0001	0.44 (0.39, 0.49)	<0.0001
Communication with others outside the home				
1-2 times per week or less	0.13 (0.09, 0.18)	<0.0001	0.43 (0.39, 0.48)	<0.0001
Less often now than before the pandemic	0.20 (0.16, 0.23)	<0.0001	0.29 (0.25, 0.33)	<0.0001
No in-person communication	0.08 (0.04, 0.11)	<0.0001	0.20 (0.17, 0.24)	<0.0001

Footnote. Estimates are the beta coefficients (slope) from unadjusted linear regressions where change in loneliness score and loneliness are modeled as a function of each characteristic. Loneliness scores range from 3 to 9, and changes in pre-pandemic to intra-pandemic loneliness scores range from -6 to 6.

P-value is for the Wald test of significance for each characteristic

Supplementary Table S2. Multivariable associations between changes in loneliness and social connection, clinically significant depressive symptoms, and moderate to severe anxiety during the COVID-19 pandemic

Characteristic	CES-D Depression 6-item scale score ≥ 5		PROMIS 4-item anxiety score ≥ 60	
	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Change in loneliness score, continuous (by increase of 3)	2.37 (2.18, 2.57)	<0.0001	1.55 (1.42, 1.70)	<0.0001
Lives alone	0.98 (0.91, 1.06)	0.6092	0.96 (0.88, 1.05)	0.3753
Changes in living arrangement due to the COVID-19 pandemic	1.20 (1.02, 1.40)	0.0245	1.38 (1.16, 1.63)	0.0002
Living situation restrictions due to the COVID-19 pandemic	1.14 (1.02, 1.28)	0.0222	1.16 (1.02, 1.32)	0.0288
Communication with others outside the home				
Every day or several times per week	Reference		Reference	
1-2 times per week or less	1.23 (1.11, 1.36)	<0.0001	1.10 (0.98, 1.24)	0.1114
Frequency of communication now, compared to before the pandemic				
About the same or more often	Reference		Reference	
Less often than before	1.14 (1.05, 1.24)	0.0024	1.25 (1.13, 1.38)	<0.0001
Ways of staying in touch with others				
Speaking in person	Reference		Reference	
Telephone, video, social media, email or postal mail, but not in person	1.24 (1.14, 1.34)	<0.0001	1.32 (1.20, 1.46)	<0.0001

Footnote. Odds ratio estimates are from logistic regression models where clinically significant depressive symptoms (CES-D ≥ 5) and moderate to severe anxiety (PROMIS T-score ≥ 60) are separately modeled as functions of change in loneliness score (intra-pandemic minus pre-pandemic) and social connection variables. Models include all variables shown in the table and are adjusted for sociodemographic factors (age, education, race, and ethnicity), lifestyle factors (physical activity, alcohol intake, number of stressful life events), and medical history (CVD history, cancer history, vascular factors risk score, past history of depression).

Center for Epidemiologic Studies Depression Scale (CES-D) ranges from 0 to 18 (≥ 5 considered to have clinically significant depressive symptoms).

PROMIS anxiety T-score ranges from 40.3 to 81.6. General population mean is 50 (SD=10), with scores ≥ 60 interpreted as moderate to severe anxiety.

Supplementary Table S3: Associations between change in loneliness and mental health measures, based on potential effect modifying factors

Subgroups	Perceived stress		Depressive symptoms (CES-D)		Anxiety (PROMIS 4 items)	
	Estimate (95% CI)	p-value, Interaction	Estimate (95% CI)	p-value, Interaction	Estimate (95% CI)	p-value, Interaction
Age						
<70	0.19 (-0.32, 0.70)	0.0239	0.44 (0.05, 0.84)	0.2959	0.78 (-0.61, 2.17)	0.1410
70-74	0.48 (0.30, 0.65)		1.04 (0.90, 1.17)		1.77 (1.30, 2.24)	
75-79	0.57 (0.41, 0.73)		1.08 (0.96, 1.20)		1.68 (1.26, 2.10)	
80-89	0.61 (0.46, 0.76)		1.02 (0.90, 1.13)		1.88 (1.47, 2.28)	
≥90	1.02 (0.51, 1.53)		1.11 (0.72, 1.49)		2.89 (1.57, 4.20)	
Race						
White	0.58 (0.49, 0.68)	0.2646	1.05 (0.98, 1.13)	0.0280	1.76 (1.51, 2.02)	0.4284
Asian/Pacific Islander	0.48 (-0.16, 1.14)		0.95 (0.44, 1.46)		1.38 (-0.38, 3.14)	
Black/African American	0.17 (-0.33, 0.67)		0.53 (0.14, 0.91)		2.61 (1.27, 3.94)	
Education						
College degree or higher	0.70 (0.58, 0.83)	0.0003	0.98 (0.88, 1.08)	0.0348	1.69 (1.35, 2.03)	0.2502
School after high school	0.51 (0.36, 0.66)		1.03 (0.91, 1.15)		1.69 (1.29, 2.09)	
High school diploma or less	0.22 (-0.01, 0.45)		1.21 (1.03, 1.39)		2.20 (1.58, 2.81)	
Lives alone						
No	0.72 (0.58, 0.86)	0.0024	1.15 (1.04, 1.25)	0.0029	1.95 (1.58, 2.31)	0.2186
Yes	0.44 (0.32, 0.56)		0.94 (0.84, 1.03)		1.64 (1.32, 1.96)	
Change in living arrangement due to the COVID-19 pandemic						
No	0.54 (0.45, 0.64)	0.0864	0.99 (0.92, 1.07)	0.0005	1.73 (1.48, 1.98)	0.2074
Yes	0.84 (0.51, 1.16)		1.45 (1.20, 1.70)		2.30 (1.45, 3.16)	
Living situation restrictions due to the COVID-19 pandemic						
No	0.50 (0.40, 0.60)	0.0044	1.02 (0.94, 1.09)	0.4357	1.81 (1.54, 2.08)	0.5704
Yes	0.83 (0.63, 1.04)		1.09 (0.92, 1.25)		1.63 (1.08, 2.18)	
Communication with others outside the home						
Every day or several times per week	0.59 (0.49, 0.69)	0.2235	1.07 (0.99, 1.14)	0.0278	1.84 (1.57, 2.11)	0.2699
1-2 times per week, or less	0.45 (0.26, 0.65)		0.87 (0.72, 1.03)		1.51 (0.98, 2.04)	
Frequency of communication now, compared to before the pandemic						
About the same, or more often	0.53 (0.42, 0.64)	0.2131	1.02 (0.93, 1.10)	0.6290	1.90 (1.61, 2.19)	0.1159
Less often than before	0.65 (0.49, 0.81)		1.05 (0.93, 1.18)		1.49 (1.05, 1.92)	
Ways of staying in touch with others						
Speaking in person	0.61 (0.46, 0.76)	0.4302	1.08 (0.97, 1.20)	0.2165	1.96 (1.57, 2.35)	0.2388
Telephone, video, social media, email or postal mail, but not in person	0.54 (0.42, 0.65)		0.99 (0.91, 1.08)		1.66 (1.36, 1.97)	
Walking for at least 5 minutes						
≤3 times per week	0.53 (0.41, 0.64)	0.2841	1.02 (0.93, 1.11)	0.7657	1.58 (1.27, 1.89)	0.0434
4 or more times per week	0.62 (0.48, 0.77)		1.04 (0.93, 1.15)		2.08 (1.70, 2.47)	
History of depression						
No	0.59 (0.50, 0.69)	0.0478	1.06 (0.99, 1.13)	0.0044	1.89 (1.63, 2.14)	0.0056
Yes	0.29 (0.01, 0.58)		0.71 (0.49, 0.94)		0.74 (-0.04, 1.51)	

Subgroups	Perceived stress		Depressive symptoms (CES-D)		Anxiety (PROMIS 4 items)	
	Estimate (95% CI)	p-value, Interaction	Estimate (95% CI)	p-value, Interaction	Estimate (95% CI)	p-value, Interaction
Stressful life events						
None	0.54 (0.40, 0.67)	0.5433	0.96 (0.86, 1.07)	0.0903	1.85 (1.49, 2.20)	0.5886
1 or more	0.56 (0.47, 0.65)		1.02 (0.95, 1.09)		1.78 (1.54, 2.02)	

Footnote. Estimates are from linear regression models and assess the linear change in each dependent variable with a change of 3 points change in the loneliness score from before the pandemic to during the pandemic.

Analyses for racial subgroups show only those groups with more than 300 participants in the sample who self-identified with that group.

Models include main effects for change in loneliness score and the variables shown in the table, and are further adjusted for education, Hispanic/Latina ethnicity, alcohol intake, and medical history (CVD history, cancer history, and vascular factors risk score).

Each interaction p-value was derived from a model that included an interaction term between change in loneliness score and the potential effect modifier. For evaluating age and education as effect modifiers, the interaction term was between change in loneliness score and linear age and education, respectively.