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Medical Comorbidity in Complicated Grief: Results from the HEAL Collaborative Trial

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Abstract

Objective—To describe medical comorbidity in persons with Complicated Grief (CG) and to test whether medical comorbidity in individuals with CG is associated with the severity and duration of CG, after adjusting for age, sex, race, and current depressive symptoms.

Methods—In exploratory analyses, we compared data from participants in an NIMH-sponsored multisite clinical trial of CG ("HEAL": "Healing Emotions After Loss") to archival data from participants matched on age, gender, and race/ethnicity, stratified by the presence or absence of current major depression. We used the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) as a measure of medical polymorbidity. We investigated the association between CG and medical comorbidity via multiple linear regression, adjusting for sociodemographic and clinical variables, including severity of depressive symptoms

Results—Chronological age and severity of co-occurring symptoms of major depression correlated with cumulative medical polymorbidity in persons with Complicated Grief. The severity of CG and the time since loss did not correlate with global medical polymorbidity (CIRS-G score). Nor was there an interaction between severity of depressive symptoms and severity of CG symptoms in predicting global CIRS-G score. Cumulative medical comorbidity, as measured by CIRS-G scores, was greater in subjects with current major depression ("DEPRESSED") than in CG subjects, and both DEPRESSED and CG subjects had greater medical morbidity than CONTROLS.

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Conclusion—Medical comorbidity is prevalent in Complicated Grief, associated with increasing age and co-occurring depressive symptoms but apparently not with chronicity and severity of Complicated Grief per se. This observation suggests that treating depression in the context of CG may be important to managing medical conditions in individuals with Complicated Grief to attenuate or prevent the long-term medical sequelae of CG.

Keywords

grief; bereavement; older adults; depression; medical illness

Introduction

Complicated Grief (CG) is a chronic and debilitating condition estimated to occur in 7% of bereaved people, thus affecting tens of millions of people worldwide (Kersting et al., 2011). Studies have shown that CG can reliably be distinguished from major depression both in response to treatment and primary symptomatology (Cozza et al., 2016; Shear et al., 2016, 2014; Supiano and Luptak, 2014). CG symptoms include prolonged yearning, longing, sorrow, persistent thoughts of the deceased, and difficulty imagining a future with purpose and meaning, together with impairment in social and occupational function (Kersting et al., 2011).

There is a strong association between bereavement, especially CG, and negative health outcomes. CG is known to shorten life expectancy, due to death from heart disease and/or cancer (Prigerson et al., 2002). CG has also been associated with physiologic symptoms, such as shortness of breath, palpitations, digestive difficulties, loss of appetite, weight loss, poor treatment adherence, sleep issues including restlessness, insomnia, and low sleep quality, and a 10-fold greater risk for hypertension and heart disease (Lannen et al., 2008; H. G. Prigerson et al., 1995; Prigerson et al., 1997; Shear, 2015; Stroebe et al., 2011).

CG also frequently co-exists with major depression, which is similarly associated with shortened life expectancy across a range of medical and neurological disorders (Gallo et al., 2013). Evidence-based treatment of depression in older primary care adults leads to substantial reduction in mortality risk (24% over eight years), secondary to reductions in cancer-related deaths (Gallo et al., 2013). We do not know whether evidence-based treatment of CG to remission also leads to reductions in mortality risk. However, to test whether evidence-based treatment of CG to remission also leads to reductions in mortality risk, we must first develop an understanding of the type, extent, and severity of medical comorbidity in persons with CG, with and without depression. Thus, this study addresses the following aims:

1. To describe medical comorbidity in persons with complicated grief, as compared with non-bereaved depressed subjects with current major depression and with non-bereaved, non-depressed control participants.

2. To test whether medical comorbidity in complicated grief is associated with the severity and duration of CG, after adjusting for the effects of age, sex, race, and severity of depressive symptoms.

Methods

Design

We analyzed data from a multisite clinical trial of CG ("HEAL": "Healing Emotions After Loss") (Shear et al., 2016), sponsored by the National Institute of Mental Health. HEAL is a double-blind, placebo-controlled, randomized clinical trial that evaluated the efficacy of antidepressant pharmacotherapy, with and without complicated grief psychotherapy, in the treatment of CG. Participants were recruited from four communities in the United States: Boston, MA; New York, NY; Pittsburgh, PA; and San Diego, CA. Further details of design, data collection, and outcomes are available in Shear et al., 2016. The present study used baseline (pre-intervention) data collected between 2010 and 2014. We also used data from comparison subjects without CG, but with current major depression from the Pittsburgh site of HEAL, collected under the auspices of an NIMH-sponsored center for the prevention and treatment of major depression in older adults (ACISR: P30 MH90333; PI: Reynolds CF; for further description of depressed subjects, see Reynolds et al., 2006). These archival data (1995–2016) were used as a benchmark to provide additional context for comparable measures in HEAL participants.

Participants

The original HEAL sample included 395 persons who ranged in age from 19 to 89 (Shear et al. 2016). Of these, we matched 149 with subjects from our Advanced Centers for Interventions and Services Research (ACISR), on age, gender, and race/ethnicity. Then, in order to address Aim 1, we compared HEAL participants to two groups of ACISR participants; those who were 1) non-bereaved and non-depressed (CONTROLS; n = 98); and 2) non-bereaved but depressed, with current major depression (DEPRESSED; n = 149). Diagnoses were made using the structured clinical interview for DSM-IV (SCID) (APA, 1994). To match HEAL participants with ACISR participants, we created seven age categories: 18–30, 31–40, 41–50, 51–60, 61–70, 71–80, and 81–90; two gender categories: women and men; and four race/ethnicity categories: White, Black, Asian Pacific, and Other/ Unknown. Each participant was then assigned a number that corresponds to a specific combination of categories of age, gender, and race. One hundred forty-nine HEAL participants were matched for the DEPRESSION comparison; of these, ninety-eight were matched for the CONTROL comparison. T tests, chi-square tests and Fisher exact tests were used to test whether comparison groups were comparable in terms of age, gender and race (Table 1). The same group of HEAL participants served in both comparisons. We did not account for family-wise comparison because each comparison was specified a priori as part of our hypothesis and not as part of a post-hoc analysis. We did not adjust for site in the analysis because we detected no site x treatment interactions in the parent clinical trial reported in JAMA Psychiatry (Shear et al., 2016). We chose to match instead of adjusting for covariates (age, sex, racial/ethnic group) because matching ensures that the proportion of covariates is roughly equal across groups, whereas with covariate adjustment, one may end up with a strong imbalance which can lead to balance and power issues. Moreover, our choice of covariates was done to achieve simple, clearly defined, and clearly bounded categories that result in minimizing contamination among matching variables. These variables tend to be strongly related to depression outcome (e.g., age, gender, ethnicity), thus

making it desirable to maintain a reasonable balance among them across the comparison groups. Finally, in order to address Aim 2, data from all 395 HEAL participants were included (please see table 2 and table 3).

Measures

The following measures were collected as part of a larger battery of assessments in both HEAL trial participants and ACISR comparison participants:

Medical comorbidity—The Cumulative Illness Rating Scale for Geriatrics (CIRS-G) (Miller et al. 1992) provides measures of both global medical comorbidity aggregated across all organ systems and organ- or system-specific measures of disease and severity. The scale includes 14 individual body systems and is rated on a severity scale of 0 (no problem affecting the system) to 4 (extremely severe problem and/or immediate treatment required and/or organ failure and/or severe functional impairment), for a maximum of 56 points. Higher scores reflect greater severity of medical comorbidity. The CIRS-G was completed by a trained clinician in all cases.

Correlates of medical comorbidity—We examined the relationship of the CIRS-G to several sociodemographic (age and gender) and clinical measures (time since loss, severity of CG, and severity of co-occurring depressive symptoms). Time since loss was calculated as the number of years from the date of death to the date of the baseline interview. The Inventory of Complicated Grief (ICG) (Prigerson et al., 1995) was used to assess current CG symptom severity. The scale consists of 19 grief symptoms, each scored 0–4, for a maximum of 76 points. Higher scores indicate a greater severity of grief symptoms and scores >29 present at six months after the identified loss are interpreted to indicate the presence of syndromal CG and resulting impairments in social, mental, and physical functioning. The ICG has good internal consistency and convergent and criterion validity (Prigerson et al., 1995). The Quick Inventory of Depression Symptomatology (QIDS) (Rush et al., 2003), a 16-item self-report inventory, was used to measure depression symptoms severity during the previous 7 days. Higher scores indicate a greater severity of depression symptoms and correlate with an increased risk of major depression. The psychometric properties of the QIDS are well established (Rush et al., 2003).

Statistical Analyses

For Aim 1 we compared total and organ-system specific CIRS-G scores between HEAL participants and ACISR participants who were non-bereaved and non-depressed (CONTROL), as well as with those who were non-bereaved but diagnosed with major depression (DEPRESSED), using t-tests or Wilcoxon rank sum tests for continuous variables. For our Aim 2 analysis, we fit both univariate linear regression models and a series of multiple linear regression models to investigate the association between CG and medical comorbidity in HEAL participants only. First, we included severity of complicated grief (ICG scores), time since loss, depression severity (QIDS), and age—all in the model. Although severity of CG and time since loss were not significant, we still kept them in the model because they were our primary interest, as stated a priori. Then, we also modeled gender and the interaction of gender with severity of CG and with severity of depression, but

none of these three terms was significant. Therefore, we chose not to retain any of these three terms in the final model but only the four variables originally hypothesized (ICG grief severity score, time since loss, QIDS depression severity score, and age.) In summary, we examined the relationship of the severity of CG (scores on the Inventory of Complicated Grief) and time since loss with the CIRS-G total score, adjusting for age and severity of co-occurring depression (QIDS total score). Additional models testing the effects of gender and interactions between covariates were used to explore potential relationships with medical comorbidity. The best fitting model (Table 3) was determined by examining individual coefficients for significance within the multivariable models. For the final model, p values smaller than 0.05 were declared to be statistically significant. All statistical analyses were performed using SAS version 9.4.

Results

Aim 1: Comparison of Medical Comorbidity in Persons with Complicated Grief, Major Depression, and Controls

Table 1 summarizes the comparison of those with CG (HEAL) to DEPRESSED and CONTROL subjects. The three groups had been matched for age, sex, and self-reported race/ethnicity. Cumulative medical comorbidity (total CIRS-G scores) was greater in DEPRESSED than in CG subjects, and both DEPRESSED and CG subjects had greater medical morbidity scores than CONTROLS.

Analyses by organ system using individual organ-system specific CIRS-G scores showed significant differences for CG versus CONTROLs in two organ systems: Head, Eyes, Ears, Nose and Throat (HEENT) (Wilcoxon rank sum test, $p<0.0001$) and Upper Gastrointestinal (Wilcoxon rank sum test, $p=0.0005$), but not in cardiovascular disease or any other organ system.

Aim 2: Relationship of Medical Comorbidity to Severity and Duration of Complicated Grief

Table 2 summarizes descriptive statistics from all 395 HEAL subjects used in the regression analyses. Total medical comorbidity scores (CIRS-G) and potential predictors (age, QIDS depression severity, and ICG complicated grief severity) were normally distributed, but time since loss was right-skewed with a median of 2.3 years. The distribution histograms of CIRS-G scores and of the four predictor variables are shown in figure 1. In univariate analysis, chronological age was observed to be linearly associated with total comorbidity scores (R-squared = 0.21, p<.0001). (See figure 2).

Table 3 presents the final multiple linear regression model investigating the association between CG and medical comorbidity. Chronological age and severity of depressive symptoms were significantly related to total comorbidity in people with CG. However, severity of CG, sex, and time since loss were not significantly associated with total CIRS-G scores. We also detected no significant interaction between severity of depression (QIDS) and severity of CG (ICG) in predicting total medical comorbidity scores. Regarding the magnitude of depression's effect, we calculated the R-squared coefficient to indicate its correlation with medical comorbidity (CIRS-G scores). For depression, the R-squared was

0.0027; and for age, 0.21—thus indicating greater variance explained by age than by depression.

Discussion

In this exploratory study, we observed that total medical comorbidity (CIRS-G scores) was greater in DEPRESSED than in CG subjects having similar age, sex, and race/ethnicity, and that medical comorbidity in either group exceeded that seen in non-depressed, non-bereaved CONTROLS. Medical comorbidity in CG was not found to be associated with severity and duration of CG after adjusting for chronological age and severity of co-occurring depressive symptoms. Medical comorbidity in complicated grief exceeded that observed in non-depressed, non-bereaved controls but was driven mainly by increasing age and, to a lesser extent, by co-occurring depression.

While previous studies have reported on the occurrence of medical comorbidity with prolonged grief (He et al., 2014; Stroebe et al., 2007), none have examined the effects of co-occurring psychiatric disorders, such as depression, on medical burden in prolonged grief. In this study, we did not detect a significant association between severity and duration of CG with medical comorbidity, after considering the effects of chronological age and depression. This is clinically relevant because depression itself is known to increase the risk for medical disorders, amplify the disability associated with medical comorbidity, and shorten life expectancy. Moreover, treating depression effectively may reduce risk for mortality over long periods (Gallo et al., 2013).

This work has several clinical implications. CG is a serious, prevalent, chronic, and debilitating condition. Our data underscore the importance of assessing for comorbid depression and for medical comorbidity in CG. While the HEAL study (Shear et al., 2016) demonstrated that a psychotherapeutic approach is efficacious to managing CG, co-prescription of an antidepressant was shown to have a beneficial impact on symptoms of depression (Shear et al., 2016). Combined treatment, addressing both prolonged grief and concurrent depression, may ultimately reduce medical comorbidity and its sequelae in complicated grief.

This study has several strengths and limitations. Data were derived from a large, multi-site clinical trial of CG sponsored by the NIMH. The trial provided detailed characterization of participants with respect to sociodemographic and clinical characteristics, together with an adequate sample size to model variance in total and organ-specific medical comorbidity. Because the data were derived from help-seeking persons rather than from a community probability sample, inferences may have limited generalizability. Our study also did not examine effects of other co-occurring psychiatric disorders, such as post-traumatic stress or panic disorders. The entry criteria for HEAL participants limited the acuity and severity of medical comorbidity and thus constrained the range of CIRS-G scores. The same limitation also applied to comparison subjects with major depression. Thus, given these limitations, our data should not be interpreted to mean that CG medical risk is carried by psychiatric comorbidity alone.

Future research should describe medical comorbidity in CG using a large, probability sample and address medical comorbidity in relation to other co-occurring psychiatric disorders (for example, PTSD, panic). Lastly, and perhaps of greatest clinical relevance, questions remain concerning whether combined treatment of CG and co-occurring psychiatric disorders has a beneficial effect on medical comorbidity and its long-term sequelae, such as risk for mortality.

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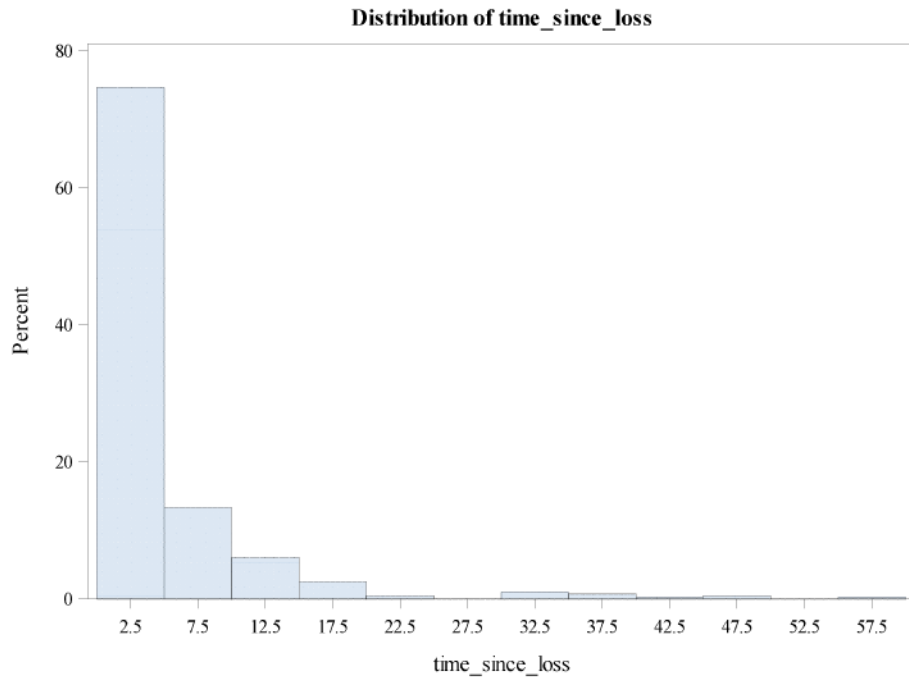Author Manuscript

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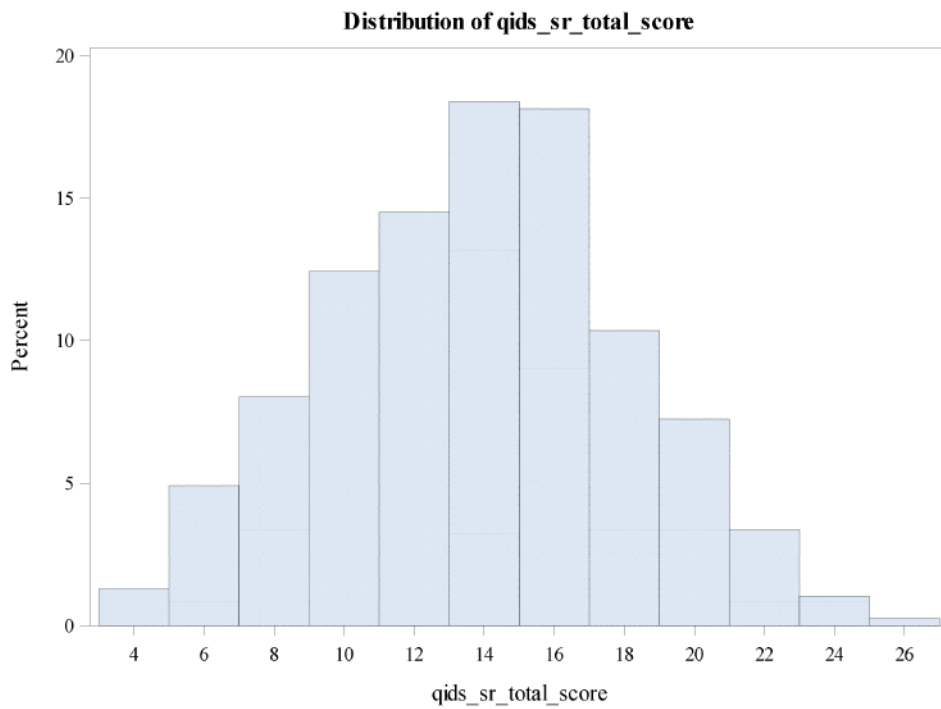
a. Total comorbidity.
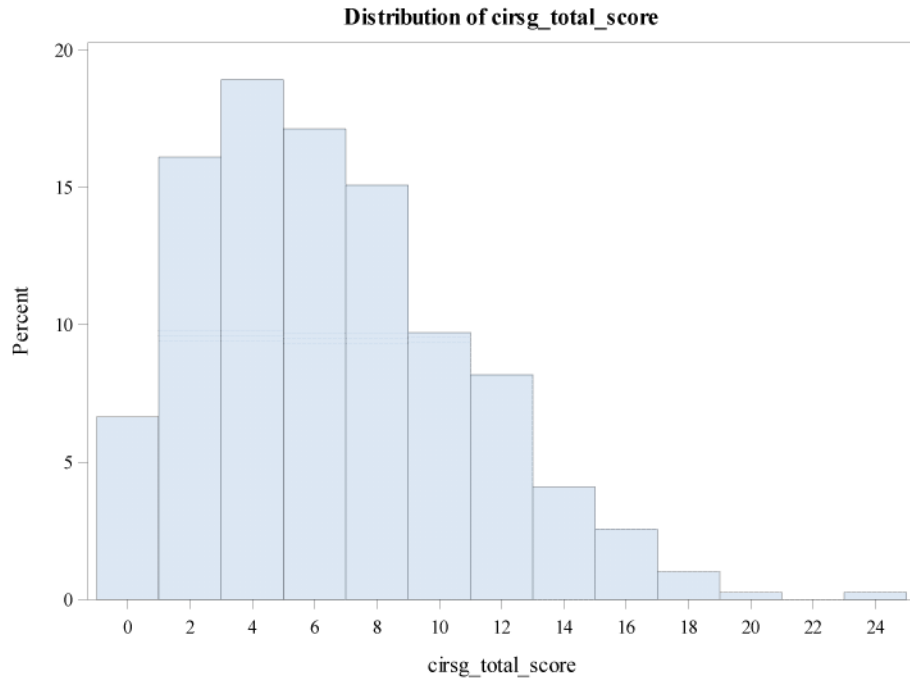
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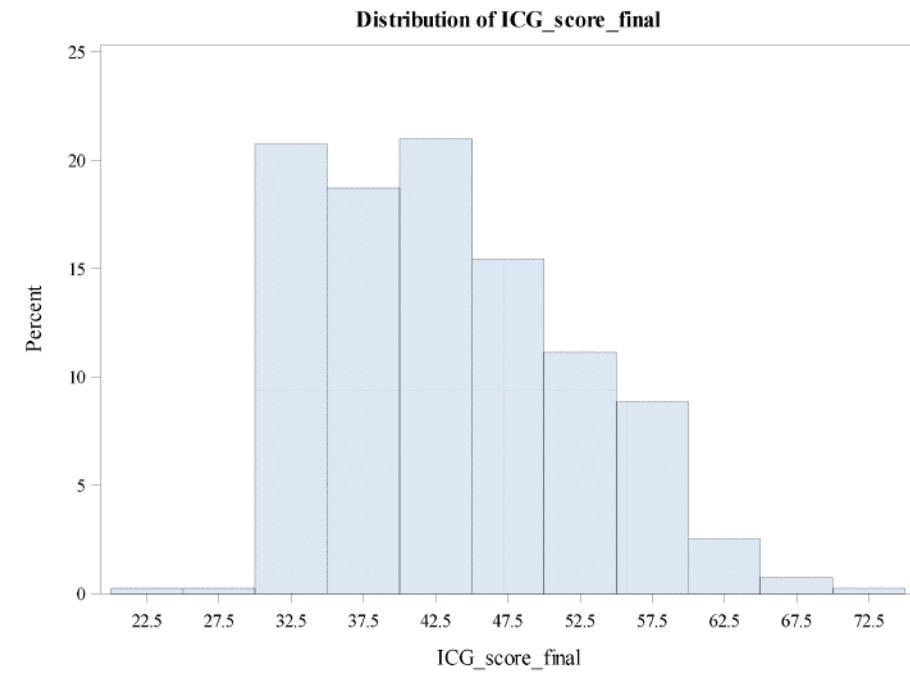
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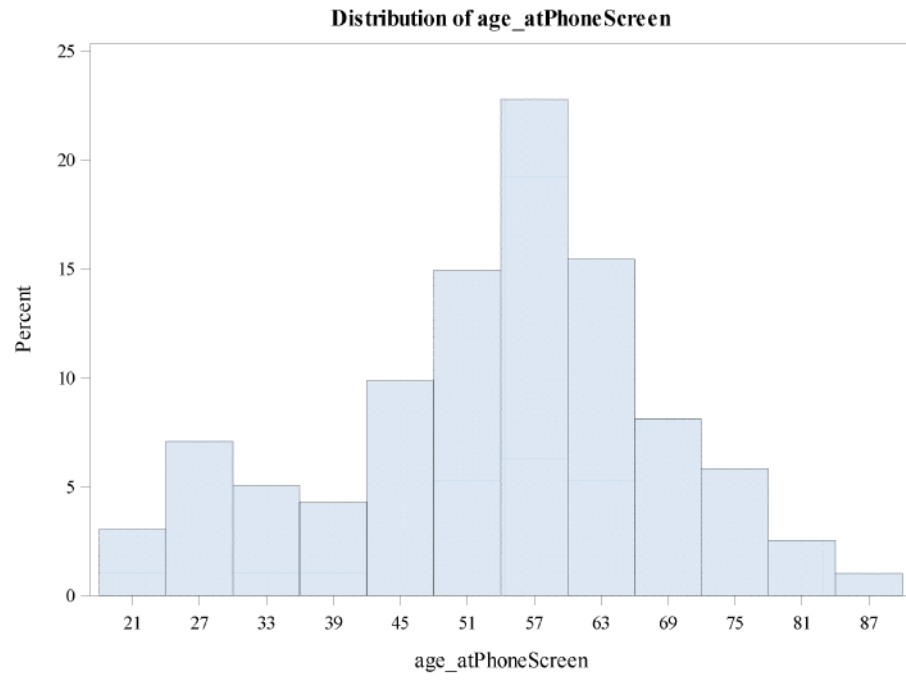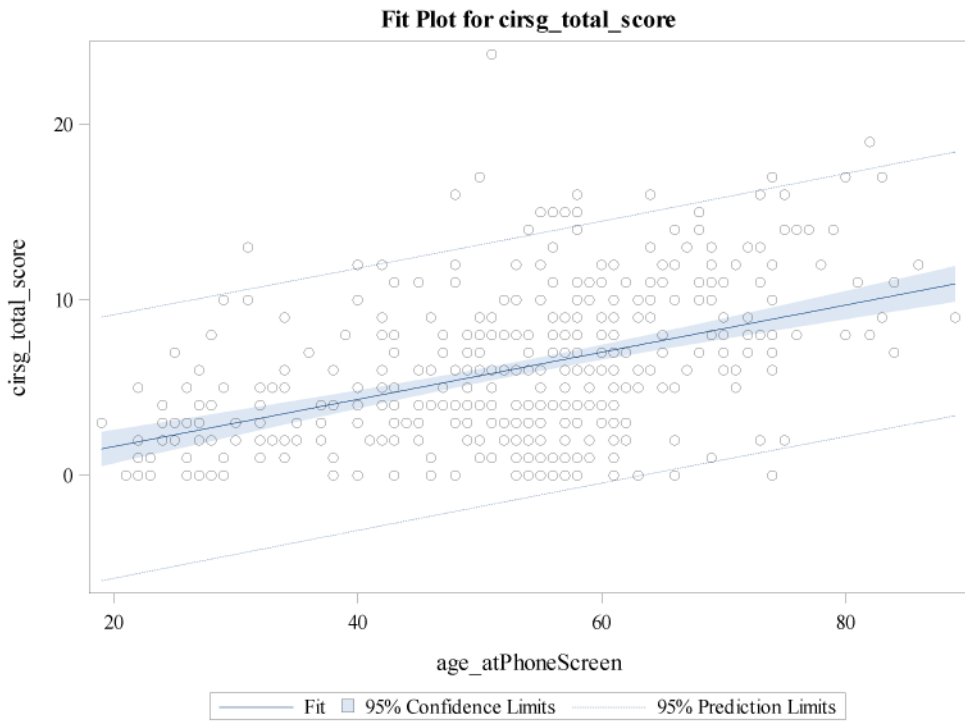d. Severity of depression

e. Age

Figure 1.
Histograms for total comorbidity, severity of complicated grief, time since loss, severity of depression and age among all 395 HEAL subjects.

Fit Plot for cirsg_total_score

R-Square	Coeff Var	Root MSE	cirsg_total_score Mean
0.208352	62.16506	3.788730	6.094629

Parameter	Estimate	Standard Error	t Value	Pr > |t|
Intercept	-1.041171973	0.73080246	-1.42	0.1550
Age at Phone Screen	0.134358964	0.01327882	10.12	<.0001

Figure 2.
Univariate relationship between age and total comorbidity.

Table 1

Participant characteristics in comparisons of medical comorbidity in Complicated Grief, Major Depression, and Controls

Covariate	Descriptive Statistics				Statistics for pairwise comparison		
	CG[1] (n=98)	CONTROL (n=99)	CG[2] (n=149)	DEPRESSED (n-150)	CG[1] vs CONTROL	CG[2] vs DEPRESSED	CONTROL vs DEPRESSED
Age (years), mean (SD)	68.5 (7.9)	68.8 (8.0)	63.8 (11.9)	64.1 (11.9)	$t(195)=0.330$, p=0.74	$t(297)=0.19$, p=0.85	$t(246.9)=-3.77$, p=0.0002
Gender, n (%)							
Men	24 (24.5)	25 (25.3)	37 (24.8)	38 (25.3)	$X^2(1)=0.0153$, p=0.90	$X^2(1)=0.01$, p=0.92	$X^2(1)=0.0002$, p=0.99
Women	74 (75.5)	74 (74.8)	112 (75.2)	112 (74.7)			
Race, n (%)							
Black	10 (10.2)	10 (10.1)	14 (9.4)	14 (9.3)	$X^2(1)=0.0006$, p=0.98	Fisher Exact, p=1	Fisher Exact, p=1
White/Hispanic	88 (89.8)	89 (89.9)	134 (89.9)	135 (90.0)			
Asian Pacific			1 (0.7)	1 (0.7)			
Global CISRS-G Medical comorbidity, mean (SD)	8.2 (4.5)	6.4 (3.8)	7.6 (4.4)	8.7 (4.4)	$t(195)=-3.08$, p=0.0024	$t(297)=2.19$, p=0.029	$t(247)=4.17$, p<0.0001

Note: CG[1] is the sample used in CG[1] vs CONTROL comparison, and CG[2] is the sample used in CG[2] vs DEPRESSED comparison. People with complicated grief are selected separately to match with CONTROL group and DEPRESSED group in age, gender and race.

Table 2

Characteristics of all 395 HEAL subjects *Table 2. Characteristics of all 395 HEAL participants.*

	Mean (SD)	Median	Range
CIRS- G Total Score	6.1 (4.3)	6.1	(0, 24)
Severity of Complicated Grief	42.8 (8.9)	42.0	(22, 72)
Time Since Loss (years)	4.7 (7.2)	2.3	(0.5, 58.7)
Severity of Depression	13.4 (4.3)	14	(3, 26)
Age	53.0 (14.5)	55.0	(19, 89)

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Table 3

Multiple regression model examining the relationship between complicated grief and medical comorbidity

	Estimate	Standard Error	t Value	Pr > |t|
Intercept	−1.717	1.239	−1.39	0.167
Severity of Complicated Grief	−0.018	0.023	−0.77	0.441
Time Since Loss	0.028	0.027	1.06	0.291
Severity of Depression	0.095	0.048	1.98	0.048
Age	0.136	0.013	10.09	<.0001