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A Marginal Structural Model Analysis for Loneliness: Implications for Intervention Trials and Clinical Practice

Tyler J. VanderWeele
Harvard University

Louise C. Hawkley, **Ronald A. Thisted**, and **John T. Cacioppo**
University of Chicago

Abstract

Objective—Clinical scientists, policy makers, and individuals must make decisions concerning effective interventions that address health-related issues. We use longitudinal data on loneliness and depressive symptoms and a new class of causal models to illustrate how empirical evidence can be used to inform intervention trial design and clinical practice.

Methods—Data were obtained from a population-based study of non-Hispanic Caucasians, African Americans and Latino Americans (N=229) born between 1935 and 1952. The UCLA-R and CES-D scales were used as measures of loneliness and depressive symptoms respectively. Marginal structural causal models were employed to evaluate the extent to which depressive symptoms depend not only on loneliness measured at a single point in time (as in prior studies of the effect of loneliness) but also on an individual's entire loneliness history.

Results—Our results indicate that if interventions to reduce loneliness by one standard deviation were made one and two years prior to assessing depressive symptoms, both would have an effect and would together result in an average reduction in depressive symptoms of 0.33 standard deviations (95% CI: 0.21, 0.44, P<0.0001).

Conclusions—The magnitude and persistence of these effects suggests that greater effort should be devoted to developing practical interventions on alleviating loneliness and that doing so could be useful in the treatment and prevention of depressive symptoms. In light of the persistence of the effects of loneliness, our results also suggests that, in the evaluation of interventions on loneliness, it may be important to allow for a considerable follow-up period in assessing outcomes.

Keywords

Causal models; marginal structural models; depression; loneliness

Introduction

Clinical scientists, health policy makers, and research funding organizations must make decisions about the merits of interventions for mental health problems and preventive mental health measures, as well as about the design features of clinical trials to assess the efficacy of these interventions. In the present paper, we use data on loneliness and depressive

symptomatology from a population-based longitudinal study of middle-aged and older adults to provide quantitative evidence relevant to such decisions. In the analyses we use a marginal structural model statistical technique that is new to the psychology literature.

Loneliness, a debilitating psychological condition characterized by a deep sense of social isolation, emptiness, worthlessness, lack of control, and personal threat (Booth, 2000; Cacioppo & Patrick, 2008; Weiss, 1973), is a major risk factor for depression (Cacioppo, Hughes et al., 2006; Green et al., 1992; Hagerty & Williams, 1999; Heikkinen & Kauppinen, 2004; Wei, Russell, & Zakalik, 2005) and suicidal ideation and behavior (e.g., Stravynski & Boyer, 2001; Goldsmith et al., 2002; Rudatsikira, Muula, Siziya, & Twa-twa, 2007; Wiktorsson et al., 2010). In addition, research over the past decade has shown loneliness also to be a risk factor for a variety of other deleterious psychological and physiological outcomes, including impaired cognitive performance and cognitive decline (Gow et al., 2007; Tilvis et al., 2004; Wilson et al., 2007), progression of Alzheimer's Disease (Wilson et al., 2007), diminished executive functioning (Cacioppo et al., 2000), impaired sleep (Cacioppo, Hawkley, Berntson et al., 2002; Pressman et al., 2005; Hawkley, Preacher, & Cacioppo, 2009), elevated blood pressure (Cacioppo, Hawkley, Crawford et al., 2002; Hawkley, Masi, Berry, & Cacioppo, 2006; Hawkley, Thisted, Masi, & Cacioppo, 2010), increased hypothalamic pituitary adrenocortical activity (Adam, Hawkley, Kudielka, & Cacioppo, 2006; Steptoe, Owen, Kunz-Ebrecht, & Brydon, 2004), and morbidity and mortality (Caspi, Harrington, Moffitt, Milne, & Poulton, 2006; Patterson & Veenstra, 2010). Importantly, these studies have found loneliness to be a *unique* risk factor for these deleterious outcomes, independent of social support, depressive symptomatology, perceived stress, hostility, or general negative affect– constructs that are often mistakenly equated with loneliness (Booth, 2000; Cacioppo et al., 2006; Wilson et al., 2007).

Loneliness, low social support, and depressive symptomatology are aversive, unpleasant states, and as a result these constructs are often correlated (Segrin, 1998). From a theoretical perspective, loneliness is distinct in its focus on feelings of social isolation, however (Weiss, 1973; see, also, Cacioppo, Hawkley, & Correll, in press). Finding oneself feeling socially isolated (lonely) – uncertain that one can confide in, depend on, or trust others – is not only an unhappy social environment, it is also a profoundly unsafe social environment (Cacioppo & Hawkley, 2009). Depressive symptomatology, in contrast, is not only the experience of an unhappy world *generally*, but it is also characterized by somatic symptoms such as lethargy. Social support differs conceptually from depressive symtpomatology and loneliness in that it refers to the perceived availability of help or support – including tangible, emotional, belonging, and appraisal support – that is received (see recent review by Taylor, 2007).

Psychometric studies designed to determine the relationship between loneliness, depressive symptoms, and social support have found them to be distinct constructs statistically (e.g. Bell, 1985; Cacioppo, Hawkley et al., 2006; Cacioppo, Hughes et al., 2006; Rook, 1987; Russell, 1996; Weeks et al., 1980) and functionally (e.g. Adam et al., 2006; Cacioppo et al., 2010; Cole et al., 2007; Hawkley et al., 2006), as well. As Booth (2000) notes, the conflation of loneliness with depressive symptomatology is especially common, so much so that epidemiologic measures of depressive symptomatology (CES-D; the Center for Epidemiologic Studies Depression Scale, Radloff, 1977) includes an item about feeling lonely. Empirical studies that have investigated this association in normal samples have found items from the loneliness and CES-D scales to load on separate factors. For instance, Cacioppo, Hawkley et al. (2006) performed a factor analysis of the responses a population-based sample of 229 middle age and older adults to the 20-item UCLA loneliness scale (Russell et al., 1980) and the 20-item CES-D (Radloff, 1977). Nine factors were extracted, and each factor was largely scale-specific: Five of the factors consisted of loneliness items, and four others consisted of CES-D items with the exception of the “I feel lonely item,”

which loaded more strongly on a loneliness factor. An additional factor analysis in which the number of factors was constrained to two also showed a clear separation of the two factors as indicated by scale-specific items on each factor. Item loadings showed an exact correspondence with the scale from which each item was derived – that is, the items from the loneliness scale loaded on the loneliness factor, and the items from the depressed affect scale loaded on the separate depressive symptomatology factor. [1]

The existing longitudinal research further supports the distinction among loneliness, depressive symptomatology and social support. For instance, loneliness has been found to predict increases in depressive symptomatology above and beyond what can be explained by initial levels of depressive symptomatology (e.g. Cacioppo, Hughes et al., 2006; Green et al., 1992; Hagerty & Williams, 1999; Heikkinen & Kauppinen, 2004; Wei, Russell, & Zakalik, 2005), and loneliness continues to predict increases in depressive symptomatology even when social support serves as a covariate (Cacioppo, Hughes et al., 2006). In a follow-up investigation, a five-year cross-lagged panel analyses in a population-based sample revealed loneliness in Year-n predicted increases in depressive symptomatology in Year n+1 beyond what could be predicted by depressive symptomatology in Year n, and this remained the case even when controlling statistically for covariates including social support, perceived stress, objective stressors, and hostility (Cacioppo, Hawkley & Thisted, 2010).

Marginal structural models, developed in the statistics and epidemiological literature (Robins et al., 2000; Hernán et al., 2002), are important in settings in which the exposures vary with time. When the variables that confound the relationship between the exposure and the outcome also change with time, analyses based on standard linear regression or growth curve modeling will often be inadequate in assessing effects of time-varying exposures (Robins et al., 2000; Hernán et al., 2002). Linear regression or growth curve modeling can assess the effects of exposures at a single point in time on an outcome that changes over time. However, such models will generally give biased estimates for time varying exposures because they cannot appropriately adjust for confounding variables that change over time and may also be affected by prior treatment. Marginal structural models can appropriately control for such time-varying confounding and will give valid estimates of the effects of time-varying exposures in these settings.

A causal interpretation of estimates from standard models (linear regression or growth curve) or marginal structural models is subject to the assumption of what is sometimes called “ignorability” or no unmeasured confounding. With observational data this is often an unrealistic assumption and it is important to use sensitivity analysis techniques to investigate the impact on one's conclusions of violations of this assumption.

Here we present a brief introduction to these models and techniques for researchers in psychology and we apply these models to assessing the time-varying effects of loneliness on depressive symptoms. We chose the effects of loneliness on depressive symptoms to illustrate this new class of models for two reasons. First, as summarized above, longitudinal evidence from multiple laboratories suggests that loneliness could influence depressive symptoms, even after control is made for initial levels of depressive symptoms. Because loneliness and depressive symptoms are both time-varying and there may be feedback between the two, the use of marginal structural models may be important in evaluating the effects of time-varying loneliness. The application of marginal structural models have the

[1]The results of factor analysis are, of course, dependent on the particular mix of items subjected to the analyses, so in a second study, the responses of 2,525 young adults to the UCLA loneliness scale and the Beck Depression Inventory were subjected to factor analyses. Items on the loneliness and depressive symptomatology scales again loaded on separate factors, and the loadings of loneliness items on the depressed affect factor were very low (i.e., < 0.10), as were the loadings of depressed affect items on the loneliness factors (Cacioppo, Ernst et al., 2006).

potential to elucidate not only the separability of loneliness and depressive symptoms but also aspects of their interrelationship that have heretofore not been quantified.

Second, a recent meta-analysis reveals that there are existing interventions that appear to reduce loneliness, but better designed intervention trials are needed (Masi et al., in press). Marginal structural models can help inform the design of clinical interventions for clinical trials and for clinical practice. By assessing the time-varying effects of loneliness on depressive symptoms we can attempt to evaluate what the effects of hypothetical interventions to change loneliness might be. When designing an intervention trial, it is important to have information about the magnitude of the effect of loneliness on depressive symptoms and also the persistence of this effect, that is, the extent to which depressive symptoms depend not only on a single level of past loneliness but on an entire history of an individual's level of loneliness. We use marginal structural models in this paper to illustrate how existing longitudinal data can be used to derive quantitative answers to these questions about the effects of time-varying loneliness and to inform intervention trial design and clinical practice.

Marginal structural models are now used routinely in epidemiologic research and have begun to be employed in sociology and education (Sampson et al., 2008; Hong & Raudenbush, 2008). They have been used to address important policy questions in HIV-AIDS research concerning the effects of antiretroviral therapy regimes (Sterne et al., 2005; Patel et al., 2008). We believe that such models will similarly be of use in assessing the effects of time-varying psychological exposures and in research on potential interventions on loneliness to address depressive symptomatology.

Methods

Sample and Design

Data were obtained from the Chicago Health, Aging, and Social Relations Study (CHASRS), a population-based study of non-Hispanic Caucasians, African Americans and Latino Americans born between 1935 and 1952 living in Cook County, Illinois. Sample participants were required to be able to come to the University of Chicago for day-long visits to the laboratory and were selected using a multistage probability design in which African Americans and Latino Americans were oversampled and gender equality maintained. First a sample of households was selected; then sampled households were screened by telephone for the presence of an age-eligible person who was sufficiently ambulatory to participate. If a household contained more than one age-eligible person, the person with the most recent birthday was selected. A quota sampling strategy was used to achieve an approximately equal distribution of respondents across the six gender by race/ethnic group combinations. The response rate was 45%, comparable to the response rate for well-conducted telephone surveys. The sample size at baseline was 229 individuals; due to attrition, the sample size at year 5 was 163. Data in CHASRS is available on age, gender, ethnicity, marital status, education, income and also on depressive symptoms, loneliness, social support, psychiatric conditions and psychiatric medications measured at baseline and measured at each of the four subsequent annual follow-up visits.

Measures

Loneliness was assessed using the UCLA-R, a 20-item questionnaire measuring general perception of social connection or isolation which has been shown to have good construct validity (Russell et al., 1980; Russell, 1996). Participants are asked to rate each item on a 1-4 scale indicating responses of never to always; after reverse coding appropriate items, the loneliness score is obtained by summing the 20 items, giving scores ranging from 20 to 80

with higher scores indicating higher levels of loneliness. Depressive symptoms were assessed using the Center for Epidemiologic Studies Depressive symptoms Scale (CES-D; Radloff, 1977), a 20-item measure in which participants rate each item on a scale from 0 to 3 indicating responses of rarely or none of the time to most or all of the time; after reverse coding appropriate items, the depressive symptomatology score is obtained by summing the 20 items, with higher scores indicating higher levels of depressive symptoms. Because one item of the CES-D asks if the participant felt lonely, this item was eliminated prior to calculating the total score on the CES-D to ensure that associations between depressive symptoms and loneliness were not due to item overlap. The resulting measure (referred to as CES-D-ML) ranges from 0 to 57. Social support was measured using the Interpersonal Support Evaluation List (ISEL) which consists of twelve statements to which participants responded on a 4-point Likert scale ranging from 1 (definitely false) to 4 (definitely true). Cohen & Hoberman (1983) and Cohen, Mermelstein, Kamarck, and Hoberman (1984) provide a discussion of scale design and psychometric properties. After reverse scoring appropriate items, subscale scores were calculated for appraisal support, belonging support, and tangible support. For the purposes of this study, an overall social support score (range = 4 – 16) was computed by averaging the subscale scores.

Psychiatric diagnosis was assessed by self-report according to whether participants indicated during a health interview having been told by a doctor that they had emotional, nervous, or psychiatric problems. Psychotherapeutic medications were coded using a standardized nomenclature derived from the Multum database, which permits coding of generic and brand name drugs by pharmacologic and therapeutic categories. For the present study, psychotherapeutic medications were coded as present if any antidepressant, CNS stimulant, antipsychotic or anxiolytic, sedative, or hypnotic was prescribed.

Models and Estimation

Marginal structural models (Robins et al., 2000) were fit for the effects of hypothetical interventions on loneliness at follow-up visit 1, 2 and 3 on depressive symptoms at follow-up 4. The models predict the expected outcomes, conditional on baseline loneliness, had there been interventions on loneliness at follow-up visits 1, 2 and 3. The models take the form:

$$E\left[Y_{a_1a_2a_3}|X=x\right]=\mu+\gamma x+\beta_1 a_1+\beta_2 a_2+\beta_3 a_3 \quad (1)$$

where $Y_{a_1a_2a_3}$ is the depressive symptoms outcome at follow-up 4 for an individual that would have resulted under hypothetical joint interventions to set loneliness at follow-up visits 1, 2, 3 to levels a_1, a_2 and a_3 respectively and where X denotes one or more covariates at baseline (here X is chosen to be baseline loneliness). The variable $Y_{a_1a_2a_3}$ is sometimes referred to as a “counterfactual outcome”, as it is the outcome that would have resulted had the exposure, loneliness at follow-up visits 1, 2 and 3, been set, possibly contrary to fact, to a_1, a_2 and a_3. In the model, the effects on depressive symptoms of joint interventions on loneliness at follow-up visits 1, 2 and 3 are β_1, β_2 and β_3 respectively for a one point change in loneliness on the UCLA-R scale. Marginal structural models can also be used to assess moderation by baseline covariates of the effects of the exposures on the outcome and they can also be fit to non-linear models (Robins et al., 2000). They can be used to assess possible interaction between the effects of exposure at different times. Here we also considered possible interaction between the effects of loneliness at different times. These interaction terms were not statistically significant and thus were not included in the final analysis which simply employed the model given above.

For a causal interpretation of estimates from traditional regression analyses or growth curve models or structural equation models or marginal structural models, assumptions sometimes called “ignorability” or “no unmeasured confounding” must be made. These assumptions essentially state that the groups receiving different exposure levels are, within strata of the measured covariates, comparable to one another in all ways related to the outcome. This would be the case if the exposure were randomized. In an observational study control is made for covariates thought to affect both the exposure and the outcome. If all such covariates are controlled for then a correctly specified model will warrant a causal interpretation.

The confounding issues that arise when one considers exposures that may vary over time are more complex. Traditional least-squares regression models cannot in general be used in the study to address questions of the effects of joint interventions (over multiple years) on loneliness because loneliness (the exposure of interest) varies over time and because some of the confounding factors, such as intermediate values of depressive symptoms, loneliness, social support, psychiatric conditions and psychiatric medications, vary over time as well. Regression models analogous to (1) will in general give biased estimates of the effects of time-varying exposures whenever there are variables which are simultaneously on the pathway from prior exposure and also affect both subsequent exposure and the final outcome (Robins et al., 2000). These issues arise when there are reciprocal cause-and-effect relationships over time between the exposure and other variables related to the final outcome. For example, loneliness at follow-up 1 may have an effect on levels of depressive symptoms at follow-up 2 which may in turn affect both loneliness at follow-up 3 and depressive symptoms at follow-up 4.

These relationships are depicted in Figure 1. We will use A_k to denote loneliness at follow-up k and we will use V_k to denote values of depressive symptoms, social support, psychiatric conditions and psychiatric medications at follow-up k. Depressive symptoms at follow-up 2 (denoted by V_2) is then potentially on the pathway from loneliness at follow-up 1 (denoted by A_1) to final depressive symptoms at follow-up 4 (denoted by Y) and furthermore depressive symptoms at follow-up 2 (V_2) may confound the relationship between loneliness at follow-up 3 (denoted by A_3) and final depressive symptoms, Y. If the joint effects of loneliness at follow-up visits 1, 2 and 3 are of interest then if, in a regression, adjustment is made for depressive symptoms at follow-up 2 this will block some of the effect of loneliness at follow-up 1. But if adjustment is not made for depressive symptoms at follow-up 2, then the effect of loneliness at follow-up 3 will be biased because depressive symptoms at follow-up 2 may confound the relationship between loneliness at follow-up 3 and final depressive symptoms at follow-up 4. The regression analysis would thus be biased, whether or not adjustment is made for V_2.

Note that the Figure here does not depict a linear structural equation model but instead simply illustrates the structural relationships amongst the variables. Although a structural equation model could potentially be used to address the same questions, doing so would require modeling each of the time varying variables (loneliness, depressive symptoms, social support, psychiatric conditions and psychiatric medication) at each point in time as a function of the past. In contrast the marginal structural model technique being described below will only require modeling loneliness at follow-ups 1, 2 and 3 and depressive symptoms at follow-up 4. Thus distributional and functional form assumptions (e.g. normality and linearity) are made for far fewer variables in the marginal structural model approach as contrasted with the structural equation model approach. Other more subtle biases to which simple regression adjustment and structural equation modeling techniques are subject can also be addressed with marginal structural models (Barber et al., 2004; Bray et al., 2006).

Although standard least squares regression analysis cannot address the questions of the effects of time-varying exposures in this context, one can still fit a marginal structural model, even in the presence of such time-dependent confounding, by using a weighting technique. Inverse-probability-of-treatment weighting controls for confounding not through regression adjustment but instead by predicting the probability, conditional on past covariate history, of each subject's having the level of loneliness that was in fact present and then weighting each subject by the inverse of this conditional probability. This weighting approach has been used in survey sampling for decades (Horvitz & Thompson, 1952) but was more recently extended to the context of longitudinal data and time-varying exposures (Robins et al., 2000). The weighting technique is somewhat analogous to the dynamic use of propensity scores (Rosenbaum and Rubin, 1983). The weights are used (like propensity scores) to adjust for confounding by the covariates. In the context of a time-varying exposure, a weight corresponding to the inverse of the probability of having the exposure level (loneliness) that was in fact present, conditional on past covariate history is estimated, often using logistic or probit regression in the case of binary exposures, at each point in time. When the exposures are continuous, conditional densities (rather than probabilities), obtained from linear regression, need to be employed (Robins et al., 2000). The overall weight for each subject is computed by taking the product of the weights at each period in time.

The marginal structural model for the expected counterfactual outcomes conditional on baseline exposure is then fit by regressing the observed outcome on the exposures at each time period but where each subject is weighted by the inverse-probability-of-treatment weights described above. The weighting controls for the confounding due to the time-varying variables. Robust variance estimation is used for standard errors to account for sampling error in the estimation of the weights (Robins et al., 2000).

Provided that at each period or visit k, the baseline covariates and the history of the time-varying covariates up through time k-1 suffice to control for confounding of the effect of the exposure, loneliness at time k, on the final outcome, this weighting technique will give consistent estimates of the parameters of the marginal structural model. This will allow inference about the effects on the outcome of the exposure as it varies over time (Robins et al., 2000). The assumption that the baseline and time-varying covariates suffice to control for confounding at each point in time is the critical assumption in allowing for a causal interpretation of the parameter estimates.

We fit marginal structural models for the effects of joint interventions on loneliness at follow-up visits 1, 2 and 3 on depressive symptoms respectively at follow-up 4, using a complete case analysis. Linear regression assuming normally distributed residuals were used in the model for the weights, regressing the loneliness measure at each time on the baseline covariates and the entire history of the time-varying covariates.

To attain greater precision in the estimates of the effects of loneliness and to offer potential further confirmation of the results, a “repeated measures” marginal structural model analysis was used which combines analyses in which the effect of loneliness at follow-up visits 2 and 3 on depressive symptoms at follow-up 4 is simultaneously assessed with the effect of loneliness at follow-up visits 1 and 2 on depressive symptoms at follow-up 3. The estimation of a repeated measures marginal structural model analysis proceeds as above but a weighted repeated measures regression is used (rather than a simple weighted linear regression) and the inverse-probability-of-treatment weight for each subject varies over time. Because depressive symptoms outcome data was used for both follow-ups 3 and 4, an indicator for year was included in the model. Weighting techniques can lead to imprecise estimates; one can improve the precision of estimates by reducing the variability of weights using what are

sometimes referred to as “stabilized weights” (Robins et al., 2000); this is especially important for continuous exposures; stabilized weights were used in the analysis (see Appendix for details). Further details on repeated measures marginal structural models are available elsewhere (Hernán et al., 2002); see also the Appendix. To examine the how measured confounding variables affected estimates we fit similar models without using weights to examine the direction of the confounding bias.

An additional analysis was conducted to take into account censoring and missingness using an inverse-probability-of-censoring technique. At each time-point, indicators for censoring and missingness were regressed on baseline covariates and on prior history of each of the time-varying covariates; none of the time-varying covariates was statistically significantly associated with censoring and missingness and these were excluded to avoid additional variability in the weights (Cole & Hernán, 2008; Westreich & Cole, 2010). Thus an overall adjustment for complete case versus missing/censored using the baseline covariates was done instead. Indicators for complete data were regressed on age, gender, race and baseline loneliness (which were available for nearly every subject) using logistic regression. Adjustment was made for missingness and censoring by weighting each complete case subject by the inverse-probability-of-censoring weight (Robins et al., 2000) defined as the probability of being uncensored conditional on age, gender, race and baseline loneliness. The weight given to each subject in the final marginal structural model analysis is then the product of the inverse-probability-of-treatment-weight and the inverse-probability-of-censoring weight. The adjustment for missingness/censoring assumes that conditional on age, gender, race and baseline loneliness, missingness is not predictive of what an individual's outcome would have been under loneliness interventions (i.e. missing/censored at random conditional on baseline covariates). Under this assumption and assuming that at each time period, the baseline covariates and the prior history of the time-varying covariates suffice to control for confounding of the effect of the exposure, loneliness, on the final outcome, this inverse-probability-of-treatment-and-censoring weighting technique will give consistent estimates of the parameters of the marginal structural model (Robins et al., 2000; Hernán et al., 2002). All analyses were implemented in SAS version 9.2.

Results

At baseline, the population-based Chicago Health, Aging, and Social Relations Study (CHASRS) sample (N=229), used in this analysis, was 52% female; mean age of 57.4; 61.3% married; 37.3% non-Hispanic Caucasian, 34.4% African American, 28.3% Latino American; mean years of education of 13.5; and mean household income of $67,728. Mean baseline level for loneliness on the UCLA-R scale for the CHASRS sample was 36.1; mean level for depressive symptoms on the CES-D-ML scale was 9.8; 12.7% reported psychiatric medications at baseline; 12.4% reported a history of psychiatric diagnosis at baseline. The standard deviations for loneliness and depressive symptoms at baseline were 10.0 and 8.4 points on the UCLA-R and CES-D-ML scales, respectively.

Table 1 presents results for the effects over time of loneliness on depressive symptoms. The coefficients reported give estimates of the effects of hypothetical joint interventions on loneliness at follow-up visits 1, 2 and 3 on depressive symptoms at follow-up 4. At each time-point, time-varying confounding variables include prior depressive symptoms, loneliness, social support, psychiatric conditions and psychiatric medications. At each time-point, each of these variables may be effects of prior loneliness and may in turn affect subsequent levels of loneliness and also the final depressive symptoms level at follow-up 4. Weights used in the marginal structural model are derived from the inverse of the probability of individuals having the exposure level they in fact had, conditional on the past

history of all variables. Adjustment for possible confounding from baseline age, gender, ethnicity, marital status, education, and income is also done by weighting.

The analysis indicates that if hypothetical interventions on loneliness were made in each of the three years prior to assessing final depressive symptoms then only the interventions in the prior two years (i.e. at follow-up visits 2 and 3) would have statistically significant effects on depressive symptoms. Specifically, intervening to decrease loneliness one year prior (at follow-up 3) would result in a 0.27 point CES-D-ML reduction in final depressive symptoms level at follow-up 4 (95% CI: 0.04, 0.51; P=0.02) for each point that an intervention reduces loneliness on the UCLA-R scale relative to what it otherwise would have been. Intervening to decrease loneliness two years prior (at follow-up 2) would result in a 0.395 point CES-D-ML reduction in final depressive symptoms at follow-up 4 (95% CI: 0.13, 0.66; P=0.003) for each point of reduction in loneliness the UCLA-R scale relative to what it otherwise would have been, even after also intervening on loneliness one year prior to assessing final depressive symptoms at follow-up 4. That is, intervening at follow-up 2 still has an effect when also intervening at follow-up 3; this is essentially the direct effect of an intervention on loneliness at follow-up 2 controlling also for loneliness at follow-up 3 (VanderWeele, 2009). The effect of intervening to decrease loneliness three years prior (at follow-up 1) on final depressive symptoms assessment was not statistically significant (P=0.14) after intervening also on loneliness one and two years prior (at follow-up 2 and 3). The results indicate that not simply recent loneliness (in the year prior) but the history of loneliness (over the preceding two-year period) has relatively strong effects on depressive symptoms.

Sensitivity analysis (VanderWeele, 2010) was used to assess the extent to which an unmeasured confounding variable would have had to affect both loneliness and depressive symptoms in order to invalidate our conclusions about the persistence of the effect of loneliness. Such unmeasured confounders might include a variable such as self-esteem. We consider how strong the effect of an unmeasured binary confounding variable (e.g. high versus low self-esteem) would have to be to invalidate the conclusion that intervening at follow-up 2 still has an effect on depressive symptoms at follow-up 4 even when also intervening on loneliness at follow-up 3. The estimates above suggest that a 5 point shift in loneliness at follow-up 2 would result in a 5x0.395=1.98 point difference in depressive symptoms at follow-up 4 if loneliness at follow-up 3 were fixed to the same level. The results of a sensitivity analysis indicate that this effect could be explained away by confounding if (i) for a fixed level of loneliness at follow-up 3, the prevalence of high self esteem differed by 30 percentage points for a five point difference in loneliness at follow-up 2 and (ii) the difference in depressive symptoms (CES-D-ML scores) comparing high self-esteem versus low-self esteem, with loneliness history constant, were 6.58. The values for the prevalence difference and effect of high self-esteem needed to explain away the effect are substantial but perhaps not entirely implausible. Nevertheless, we see that fairly substantial confounding would be needed (beyond the covariates for which we have already adjusted) to explain away the effect.

Table 2 presents results from a similar analysis in which the effect of loneliness at follow-up visits 2 and 3 on depressive symptoms at follow-up 4 is simultaneously assessed with the effect of loneliness at follow-up visits 1 and 2 on depressive symptoms at follow-up 3. By effectively combining analyses of the depressive symptoms outcome data at follow-up visits 3 and 4, it is possible to attain greater precision in the estimates of the effects of loneliness and to assess the sensitivity of the results presented in Table 1 to relying on depressive symptoms at follow-up 4 only as the final outcome. The analysis again uses weighting to adjust for prior depressive symptoms, loneliness, social support, psychiatric conditions and

psychiatric medications, treated as time-varying variables, and also for baseline age, gender, ethnicity, marital status, education, and income.

The analysis again indicates that interventions on loneliness in both of the prior two years would have statistically significant effects on depressive symptoms. The effect sizes are somewhat smaller but the estimates are indeed more precise (i.e. smaller standard errors). The analysis suggests that intervening to decrease loneliness one year prior to assessing depressive symptoms would result in approximately 0.14 point decrease in depressive symptoms (95% CI: 0.01, 0.28; P=0.04) for each point of reduction in loneliness on the UCLA-R scale. The effect of intervening to decrease loneliness two years prior to assessing depressive symptoms would result in a 0.13 point reduction in depressive symptoms (95% CI: 0.00, 0.26; P=0.04) for each point of reduction in loneliness on the UCLA-R scale, even after also intervening on loneliness one year prior. Expressed in terms of standard deviations, an intervention to decrease loneliness by one standard deviation one year prior would result in a 0.17 standard deviation reduction in depressive symptoms (95% CI: 0.01, 0.33) and an intervention to decrease loneliness by one standard deviation two years prior would result in a 0.16 standard deviation reduction in depressive symptoms (95% CI: 0.00, 0.31), even after also intervening on loneliness one year prior. Thus a joint intervention to decrease loneliness by one standard deviation relative to what it otherwise would have been, both one year and two years prior to assessing depressive symptoms would result in a 0.17+0.16=0.33 standard deviation reduction in depressive symptoms (95% CI: 0.21, 0.44, P<0.0001).

In this analysis had confounding been ignored and the models been fit without the weights, we would obtain estimates that intervening to decrease loneliness one year prior to assessing depressive symptoms would result in approximately 0.19 point decrease (rather than 0.14) in depressive symptoms (95% CI: 0.07, 0.30; P=0.002) for each point of reduction in loneliness on the UCLA-R scale. The effect of intervening to decrease loneliness two years prior to assessing depressive symptoms would result in a 0.30 point reduction (rather than 0.13) in depressive symptoms (95% CI: 0.19, 0.41; P<0.001) for each point of reduction in loneliness on the UCLA-R scale, even after also intervening on loneliness one year prior. The measured confounding variables clearly bias effect estimates in an upward direction.

The results presented in Tables 1 and 2 constitute complete-case analyses in which only subjects with complete information on all baseline covariates and complete history of all time-varying variables are included in the analysis (n=127). An analysis was also conducted to assess the sensitivity of these results to biases arising from missing data and censoring. Baseline loneliness was 0.21 standard deviations lower (P=0.10) for complete cases than for non-complete cases; baseline CES-D-ML was 0.29 standard deviations lower (P=0.03) for complete cases than for non-complete cases. Although the differences are not particularly large they indicate that it may be important to attempt to adjust for missing data. After adjustment for missingness and censoring (Robins et al., 2000), the same qualitative conclusions as those presented above held and estimates changed only slightly. Interventions to decrease loneliness one and two years prior to assessing depressive symptoms would decrease these symptoms by 0.16 (95% CI: 0.02, 0.29; P=0.02) and 0.13 (95% CI: 0.00, 0.26; P=0.04) points respectively on the CES-DML scale for each point of reduction in loneliness on the UCLA-R scale.

Discussion

Studies of depressed patients point to feelings of loneliness as a frequent complaint, but these studies do not address the extent to which loneliness may contribute to changes in depressive symptomatology (Booth, 2000; Weiss, 1973). Loneliness has been described as a

strong sense of social pain, emptiness, isolation, sadness for lack of confidants, unimportance and worthlessness (Weiss, 1973). Prior studies in which loneliness has been experimentally manipulated have found loneliness to produce more negative moods (Cacioppo, Hawkley, Ernst et al., 2006), and longitudinal analyses, which have relied on linear regression or growth curve modeling, have pointed to loneliness as a potential contributor to changes in depressive symptomatology above and beyond what would be expected based on extant levels of depressive symptomatology even when controlling for various covariates such as perceived stress or social support (e.g., Cacioppo et al., 2010; Heikkenen & Kauppinen, 2004).

In the present research, we used a new class of causal modeling to quantify the effects of loneliness on depressive symptomatology over a five year period in a population-based sample of middle-aged and older adults. We used marginal structural analysis because it is better suited to assessing the time-varying effects of loneliness on depressive symptomatology when potential confounding variables also vary with time (Hernán et al., 2002). The results indicate that effects of intervening to improve loneliness can be expected to have an impact on depressive symptoms. Because these models are designed in part to disentangle the correlation/causation muddle, they provide a stronger basis for clinical intervention, precisely because they go beyond simply showing that loneliness and depression are correlated and that each affects the other in lagged analyses. Thus the results here reinforce and extend the results seen using other forms of longitudinal analysis.

Moreover, the results suggest that the effect of loneliness on depressive symptoms is not only of considerable magnitude as noted in prior literature (Green et al., 1992; Hagerty & Williams, 1999; Heikkinen & Kauppinen, 2004; Wei et al., 2005; Cacioppo et al., 2006, 2010) but the effect is more persistent than has been appreciated. Specifically, we found that an individual's loneliness over the past two years has an effect on depressive symptoms. The marginal structural analysis also suggested that intervening to reduce loneliness two years prior to assessing depressive symptoms would have a greater effect on depressive symptoms than would a one-year intervention to reduce loneliness.

Together, these results thus contribute to our understanding of the dynamics governing the relationship between loneliness and depressive symptoms, and they provide preliminary support for the hypothesis that interventions that decrease loneliness may have significant effects on depressive symptoms. Our most conservative estimates suggest that interventions to reduce loneliness by one standard deviation (on the UCLA-R scale) relative to what it otherwise would have been one year and two years prior to assessing depressive symptoms would result in a reduction of depressive symptoms of 0.33 standard deviation (on the CES-D-ML scale i.e. 2.7 points, 95% CI: 1.7, 3.7). The magnitude of this effect would be comparable to the effect on CES-D depressive symptoms of the use of an SSRI amongst cancer patients reported in a recent study (Morrow et al., 2003). A one standard deviation change in loneliness may be difficult to achieve in practice. By similar reasoning to that above, a 0.5 standard deviation change in loneliness would result in a 0.16 standard deviation change in CES-D-ML depressive symptoms according to our more conservative estimates.

The results also suggest that effects of intervening to reduce loneliness will need to be maintained over an extended period (circa 2 years) in order to have their maximum effect on alleviating depressive symptoms. This, in turn, suggests that treatment plans for psychotherapy or cognitive-behavioral therapy may need to incorporate components that address loneliness and social integration over the extended time of therapy. These results also suggest that when evaluating interventions on loneliness, it will likely be important to allow for a considerable follow-up period, again up to two years, to fully assess outcomes.

As noted above, loneliness has been found to be associated with suicidal ideation in convenience and population-based samples (Stravynski & Boyer, 2001; Goldsmith et al., 2002; Rudatsikira, Muula, Siziya, & Twa-twa, 2007; Wiktorsson et al., 2010). The causal directionality of the relationship is not clear, however, and it is possible that a third variable is the proximate cause. The present study provides indirect support for the directionality because of the established temporal relations between loneliness and depressive symptoms in the current study and the correlation of other symptoms of depression measured with suicidality. The study here also provides a roadmap for further research, which could study the impact of pre-existent loneliness on *incident cases* of suicidal acts or incident suicidal ideation. Previous studies linking loneliness to suicidal ideation are based on relatively poor instruments for assessing loneliness. The UCLA (long and short forms) is a reliable, validated measure that clinicians should have in their tool belt to monitor loneliness over time. A limitation of the study is the use of depressive symptoms rather than suicide or clinical depression as an outcome (necessitated by limited sample size) but the results are nonetheless suggestive.

Finally, the results of our analyses illustrate how marginal structural models can be useful in investigating important questions in treatment design or of policy interest in the context of time-varying exposures. We noted above that interventions to reduce loneliness by one standard deviation relative to what it otherwise would have been one year and two years prior to assessing depressive symptom would result in a 0.33 standard deviation reduction in depressive symptoms on the CES-D-ML scale. An actual intervention program to alter loneliness may require time to take effect. Using the results presented above, we could assess the effect of more complex intervention programs. Suppose, for example, the program initially reduced loneliness by 0.5 standard deviation relative to what it otherwise would have been. Suppose then, after the first year, the program reduced loneliness thereafter by one standard deviation, again relative to what it otherwise would have been. The results from the marginal structural analysis above would suggest if the program began in year 0 then that after one year of such an intervention program, depressive symptoms would be reduced by $0.5 \times 0.17=0.08$ standard deviations (measured at year 1). After two years depressive symptoms would be reduced by $1 \times 0.17 + 0.5 \times 0.16 = 0.25$ standard deviations (measured at year 2). In every subsequent year depressive symptoms would be reduced $1 \times 0.17 + 1 \times 0.16 = 0.33$ standard deviations (measured at years 3 and onwards), again all relative to what the depressive symptoms otherwise would have been. An intervention that only had half of these effects in changing loneliness would also have half of the aforementioned effects in changing depressive symptoms. In practice, one would not want to wait multiple years for alleviation of depressive symptoms by changing loneliness. Other interventions for depressive symptoms which would have more immediate effects would be desirable. Nevertheless interventions on loneliness, if successful, may be of use in further reducing more chronic depressive symptoms. Moreoever, as noted in the introduction, loneliness also appears related to a number of other health outcomes as well.

It is important to emphasize here that for questions of the effects of time-varying exposures in the context of time-varying confounding variables, marginal structural models are not simply an alternative to regression and growth curve modeling. With time-varying confounding, regression and growth curve modeling will give biased estimates of the effects of time-varying exposures irrespective of whether or not control is made for the time-varying confounders. Analyses concerning hypothetical interventions and time-varying exposures such as those described in this paper are not accessible to regression and growth curve model techniques.

Similar estimates to those above could also be obtained using the marginal structural model for the effects of other potential intervention programs manifesting different patterns of

subsequent loneliness. For example, our estimates suggest that an intervention that initially reduced loneliness by one standard deviation but was such that loneliness after the first year then returned to the level it otherwise would have been without the intervention would have the following effects on depressive symptoms: after the first year depressive symptoms would be 0.17 standard deviations lower than it would otherwise would have been; after the second year depressive symptoms would be 0.16 standard deviations lower than it would otherwise would have been (because the effect of the initial loneliness persists on into the second year); but then depressive symptoms from the third year onward would return to what they otherwise would have been without the intervention. We see here again the importance of developing interventions that reduce loneliness permanently rather just in the short term.

Although the putative effects of loneliness on depressive symptomatology may provide sufficient justification to pursue interventions to reduce loneliness, there is growing evidence that such interventions may benefit the health as well as the well-being of lonely individuals. Longitudinal analyses show that loneliness in middle aged and older adults is a risk factor for cognitive decline and dementia (Wilson et al., 2007), elevated blood pressure (Hawkley, Masi, et al., 2010), higher morning rises in cortisol (Adam et al., 2006), physical exercise (Hawkley, Thisted, & Cacioppo, 2009), and less salubrious sleep (Hawkley, Preacher, & Cacioppo, 2009) –effects that remain even after controlling for depressive symptomatology. It is not clear whether these effects also unfold over a two year period, but the marginal structural analyses illustrated in the present research provide a means for addressing this question.

The current research is subject to some important limitations. First, the validity of the analyses assumes that the models used in the weights and the model used for the effects of the loneliness exposure are correctly specified. In the present study, as in prior research, these relationships were assumed to be linear, as suggested by visual inspection of the association between loneliness and depressive symptomatology. Second, the sample size of this study was limited with only 229 subjects in the study and only 127 subjects available for a complete case analysis. The limited sample size was partially mitigated by the relatively large effect sizes and by the fact that for the complete cases we had data on the constructs of interest at baseline and at four follow-up visits. We were thus able to conduct repeated measures analyses. Because of the repeated measures longitudinal data and because the effects of loneliness were fairly large we were able to detect them, but the relatively small sample size does limit the certainty with which we can draw conclusions from the study. Third, the analyses assumed that at each time period, the baseline covariates and the prior history of the time-varying covariates suffice to control for confounding of the effect of the exposure, loneliness, on the final outcome. Although we have adjusted for a number of baseline characteristics including age, gender, ethnicity, marital status, education, and income and although we attempted to address time-dependent confounding by prior depressive symptoms, loneliness, social support, psychiatric conditions and psychiatric medications through appropriate statistical and causal models, there may be other factors that confound the relationships under study, a limitation of all observational studies. We used sensitivity analysis techniques to partially address this limitation. To fully overcome the limitations of observational data, a trial of effective loneliness interventions randomized over time would be desirable. Again, the design of such a trial could be informed by the marginal structural model longitudinal data analysis used in this study. Our results suggest that the trial should consider interventions on loneliness over multiple points in time and that considerable follow-up should be allowed in assessing depressive symptom outcomes.

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Appendix

The repeated measures marginal structural model (Hernán et al., 2002) combines analyses in which the effect of loneliness at follow-up visits 2 and 3 on depressive symptoms at follow-up 4 is simultaneously assessed with the effect of loneliness at follow-up visits 1 and 2 on depressive symptoms at follow-up 3. In this model it is assumed that depressive symptoms depend only on the values of loneliness of the prior two years. The model takes the form:

$$E\left[Y_{a_{t-1}a_{t-2}}(t)\,|X=x\right]=\mu+\lambda t+\gamma x+\beta_1 a_{t-1}+\beta_2 a_{t-2}$$

for t=3 and t=4, where $Y_{a_{t-1}a_{t-2}}(t)$ is the depressive symptoms outcome at follow-up t for an individual that would have resulted under hypothetical joint interventions to set loneliness at follow-up visits t-1 and t-2 to levels a_{t-1} and a_{t-2} respectively and where X here denotes baseline loneliness. In the model, the effects on depressive symptoms at time t of joint interventions on loneliness at follow-up visits t-1 and t-2 are β_1 and β_2 respectively for a one point change in loneliness on the UCLA-R scale.

The parameters of the model can be estimating by fitting a weighted conditional repeated measures model with time-varying weights. The conditional repeated measures model is:

$$E\left[Y(t)\,|X=x, A_{t-1}=a_{t-1}, A_{t-2}=a_{t-2}\right]=\mu+\lambda t+\gamma x+\beta_1 a_{t-1}+\beta_2 a_{t-2}$$

where Y(t) is the observed depressive symptoms at follow-up visit t. The weights for visit t are given by the stabilized weights (Hernán et al., 2002):

$$W(t)=\prod_{k=1}^{t}\frac{p\left(A_k|A_0,\ldots,A_{k-1},X\right)}{p\left(A_k|A_0,\ldots,A_{k-1},X,C_0,V_1,\ldots,V_{k-1}\right)}$$

where C_0 denotes the baseline values of the covariates and $V_1,\ldots,V_{k-1}$ denotes the history of the time-varying covariates up through follow-up visit k-1. Linear regression models with normally distributed residuals are used to estimate the probability density functions, $p(A_k \mid A_0,\ldots,A_{k-1}, X)$ and $p(A_k \mid A_0,\ldots,A_{k-1}, X,C_0,V_1,\ldots,V_{k-1})$. The estimates obtained from this weighting procedure will have a causal interpretation as the parameters of the marginal structural model under the assumption that the effect of loneliness at each follow-up visit k on depressive symptoms at subsequent times is unconfounded conditional on the baseline covariates, the history of the time-varying covariates up through follow-up visit k-1 and the history of loneliness up through follow-up visit k-1. See Hernán et al. (2002) for further details on the repeated measures marginal structural model.

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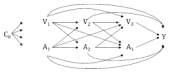

Figure 1. Structural relationships over time between loneliness and depressive symptoms

C_0 denotes baseline demographic characteristics along with baseline loneliness, depressive symptoms, social support, psychiatric conditions and psychiatric medications; it is assumed C_0 may affect all other variables; A_1, A_2, A_3 denote loneliness at follow-up visits 1, 2 and 3 respectively; V_1, V_2, V_3 denote depressive symptoms, social support, psychiatric conditions and psychiatric medications at follow-up visits 1, 2 and 3 respectively; Y denotes final depressive symptoms at follow-up 4. Time-dependent confounding is present because e.g. V_2 is an effect of prior loneliness, A_1, but V_2 also confounds the effect of subsequent loneliness, A_3, and final depressive symptoms Y.

Table 1

The Effects on Depressive Symptoms at Follow-up 4 of Hypothetical Interventions on Loneliness at Follow-ups 1, 2 and 3.*

Parameter	Estimate	Standard Error	95% Confidence Limits		Z	Pr > |Z|
uclaVl	–0.137	0.092	–0.318	0.044	–1.49	0.137
uclaV2	0.395	0.135	0.131	0.660	2.93	0.003
uclaV3	0.274	0.120	0.039	0.508	2.28	0.022

*Assumes interventions are made in all three years; analysis is conditional on baseline loneliness; adjustment for baseline and time-varying covariate is done by weighting; measures are changes in CES-D-ML per one point change in UCLA-R

Table 2

The Effects on Depressive Symptoms at Follow-ups 3 and 4 of Hypothetical Interventions on Loneliness One and Two Years Prior to Assessment of Depressive Symptoms.*

Parameter	Estimate	Standard Error	95% Confidence Limits		Z	Pr > |Z|
Two Years Prior	0.130	0.064	0.004	0.256	2.04	0.043
One Year Prior	0.144	0.069	0.009	0.280	2.10	0.037

*Analysis is conditional on baseline loneliness; adjustment for baseline and time-varying covariate is done by weighting; measures are changes in CES-D-ML per one point change in UCLA-R; expressed in terms of standard deviations these are 0.16 (Two Years Prior) and 0.17 (One Year Prior) standard deviation changes in CES-D-ML per standard deviation change in UCLA-R