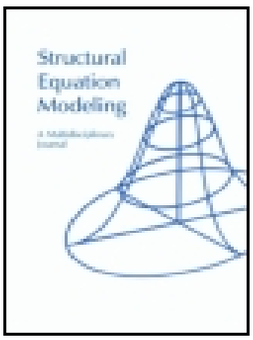

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On the Potential of Discrete Time Survival Analysis Using Latent Variable Modeling: An Application to the Study of the Vascular Depression Hypothesis

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Analysis and modeling of time to event data have been traditionally associated with nonparametric, semiparametric, or parametric statistical frameworks. Recent advances in latent variable modeling have additionally provided unique analytic opportunities to methodologists and substantive researchers interested in survival time modeling. As a consequence, discrete time survival analyses can now be readily carried out using latent variable modeling, an approach that offers substantively important extensions to conventional survival models. Using data from the Health and Retirement Study, the discussed approach is applied to the study of the increasingly prominent vascular depression hypothesis in gerontology, geriatrics, and aging research, allowing examination of the unique predictive power of depression with respect to time to stroke in middle-aged and older adults.

Keywords: depression, discrete time survival analysis, latent variable modeling, multiple testing, unique predictive power, vascular depression hypothesis

Latent variable modeling (LVM; e.g., Muthén, 2002) has steadily become very popular over the past several decades in the behavioral, social, clinical, biomedical, educational, marketing, and business sciences. A main reason for this growing interest in LVM is that it offers the opportunity to account for measurement error in predictor variables, in addition to modeling relationships among latent variables as well as between them and their presumed indicators (e.g., Bollen, 1989). Furthermore, LVM has played an instrumental role in the development, estimation, and testing of multivariable models of complex phenomena studied in these and cognate disciplines, as well as in the construction and revision of high-quality measuring instruments (e.g., Raykov & Marcoulides, 2011).

In what might be seen as a potentially unrelated parallel process, since the 1960s the study of time to event has also attracted a great deal of attention in the clinical, behavioral, and social sciences within the framework of what has been traditionally referred to as survival analysis (SA; e.g., Kleinbaum & Klein, 2011). SA permits investigators to evaluate the relationships of explanatory variables with main response variables in various research settings in these and related disciplines when time to an event is of special interest—such as death; disease relapse; high school dropout; first drug, alcohol, cannabis, or alcohol use; employment and unemployment spells; length of marriage; or birth of first child in cohabitating couples, to name but a few examples (e.g., Blossfeld, Grolsch, & Rohwer, 2007; Collett, 2014). When time to event can only be measured in terms of discrete units or the underlying process is inherently discrete, the counterpart of the "classical" continuous time SA is typically referred to as discrete time survival analysis (DTSA; e.g., Cleves, Gould, & Marchenko, 2016). In recent years, it has been shown that DTSA can also be conducted within an appropriately developed LVM framework (e.g., Muthén & Masyn, 2005). This framework is especially promising for clinical, behavioral, social, and

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educational scientists, as it offers multiple opportunities and benefits of extending earlier used survival models.

Largely independent of these methodological developments, in the past 20 years or so interest in the so-called vascular depression hypothesis (VDH) has been on the rise among clinical and biomedical scientists as well as aging researchers, gerontologists, and psychologists (e.g., Alexopoulos et al., 1997). According to this hypothesis, elevated depression could raise important warning signs for an impending stroke. To date, limited research has been carried out that bears directly on the validity of the VDH. Utilizing correspondingly designed and conducted empirical studies, DTSA can help shed light and possibly determine the conditions under which the VDH might be seen as indicating a potentially important relationship between depression in middle age and late life on the one hand and time to stroke on the other. The nationally representative Health and Retirement Study (HRS) is one such empirical investigation, which offers multiple opportunities to examine various aspects of the VDH. (For detailed information on the study as well as access to its data, we refer readers to its Web site at http://hrsonline.isr.umich.edu.) In this article, we illustrate the potential of the LVM approach to DTSA by addressing an important aspect of the VDH employing data from the HRS. Specifically, of focal interest in the remainder will be the unique predictive power of depression with respect to time to first stroke after accounting for a set of important medical and demographic covariates.

The plan of this article is as follows. In the next section, we provide a brief introduction to SA and in particular DTSA. We then discuss the LVM approach to DTSA and indicate some of the opportunities it offers for modeling time to event. In the subsequent section, we apply this approach to the study of unique predictive power of depression with respect to time to first stroke, using data from the HRS. We conclude with a discussion of the limitations of the utilized modeling procedure, findings, and substantive interpretations with respect to the VDH.

MODELING TIME TO EVENT USING SURVIVAL ANALYSIS

In many empirical studies in the behavioral, social, clinical, and cognate sciences, researchers are interested in examining individual differences in time to a particular event of concern and their explanation in terms of relevant covariates (e.g., Singer & Willett, 2003). In these investigations, it is not only important to account for the fact that the event has occurred (e.g., relapse to a disease, heart attack, stroke, high school dropout, teacher leaving the profession, death, losing one's employment, birth of first child, etc.), but also how long it took for the event to occur since the start of the study or observation of the individuals participating in it. The traditional statistical theory underlying SA, which has been usually employed to respond to these and related questions, received its major boost in the 1950s in the engineering field (e.g., Kaplan & Meier, 1958; see also Greenwood, 1926). The relevance of SA also for the social, behavioral, and clinical sciences and well beyond was quickly recognized in subsequent years, as documented by numerous applications of SA in various empirical studies (e.g., Blossfeld et al., 2007, and references therein).

In a number of settings and empirical investigations, time to event is a main response variable and can be measured on what can be treated as a continuous scale. This is usually the case where the length of the study is considerable relative to the density with which observations can be carried out. Under those circumstances, "conventional" SA modeling approaches can be used, such as Kaplan–Meier curves, Cox regression, or parametric models (e.g., Collett, 2014). In other settings, (a) time to event can only be observed in a discrete metric (i.e., observations can only be made within certain time windows—occasionally referred to as observation periods that might be limited in number relative to the length of the study), or (b) the examined process is inherently discrete. For instance, in a panel (longitudinal) study with several waves, where data on certain variables are collected using surveys, some events—such as heart attack, stroke, or death—might only be recorded to have happened between consecutive waves. (This was in fact the mode of data collection, for example, with regard to first stroke in the HRS, whereby a pertinent question was asked of the respondents if that event had occurred since the last wave.) Under these circumstances, therefore, appropriate modifications of the classical SA methods need to be used, leading to DTSA (e.g., Rabe-Hesketh & Skrondal, 2012). A prominent generic approach to studying time to event within a DTSA framework is logistic regression (e.g., Singer & Willett, 2003). More recently, a generally applicable LVM approach has been also developed (Muthén & Masyn, 2005), which has marked potential for traditional survival model extensions and underlies the remainder of this article.

DISCRETE TIME SURVIVAL ANALYSIS USING LATENT VARIABLE MODELING

One of the most popular modeling approaches used in continuous time survival analysis (CTSA), especially in the clinical, biomedical, and life sciences, is the proportional hazards model, also referred to at times as Cox regression (Cox, 1972). In this semiparametric approach, the hazard function (HF)—or risk for experiencing the event of concern—is modeled in terms of a set of explanatory variables under consideration (e.g., Kleinbaum & Klein, 2011). The HF is defined in the continuous time setting at a given point in time as the instantaneous risk for the event assuming it did not occur earlier, or more formally as the pertinent conditional probability density function for time to event (e.g., Collett, 2014). In the discrete-time setting, the HF

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remains similarly of focal relevance throughout the modeling effort, but is defined as the probability of experiencing the event in a given observation period assuming it has not occurred prior to it (e.g., Rabe-Hesketh & Skrondal, 2012). The HF is of special interest also in the remainder of this article, specifically the HF for experiencing first stroke, so we attend to it in more detail next.

To define the HF in the DTSA setting of relevance for this article, assume that a study consists of J observation periods ($J > 1$). If an event occurs for the ith subject during the jth period, no differentiation is made (or possible to be made) as to when exactly it has occurred, and thus the recorded datum for him or her is $T_i = j$, where T denotes the time to event occurrence since the start of the study for that person ($i = 1, \ldots, n$, with n denoting sample size throughout the article; $1 \leq j \leq J$). A typical setting in which this would be the case is the multiwave (panel) longitudinal study. In this type of study, usually a sample of cases is evaluated at J consecutive waves, and suppose an event of concern—such as first stroke—is assessed for occurrence using a question administered at each wave (after the first) whether the respondent has experienced it since the last wave. (This question is to be obviously asked of respondents with no stroke until the start of the study; see the conclusion section.) Denote the response to this question by E_{ij}, with a value of 1 or 0 for the event having occurred to the ith subject in the jth observation period or not, respectively ($i = 1, \ldots, n, j = 1, \ldots, J$). (Obviously, if a sample of persons is studied or considered, as is the case later in this article, who have not had a stroke before the beginning of the investigation, then for the first wave all individual realizations of this random variable are $E_{i1} = 0$, $i = 1, \ldots, n$). Because some subjects might not experience the event by the end of the study, or are lost to follow up during it, they are censored (e.g., Collett, 2014).

In this DTSA context, the HF at the jth observation period, denoted h_j, is generally defined as

$$h_j = P(T = j | T \geq j) \tag{1}$$

where $P(.|.)$ designates conditional probability ($j = 1, \ldots, J$); that is, the value of the HF in any observation period is the probability of experiencing the event during it, given that it has not occurred before that period (e.g., Rabe-Hesketh & Skrondal, 2012). We emphasize that in this article, of main concern is the HF for a first stroke; that is, the HF for the event being first stroke (see earlier).

The interest in HF is motivated by the fact that in SA a main analytic approach is given by modeling the HF in terms of explanatory variables of concern. In the continuous SA setting, this is the essence of the popular Cox regression method, and relatedly it is also of relevance (indirectly) in various parametric models (e.g., Cleves et al., 2016). In the DTSA setting, modeling the HF (i.e., the probability in Equation 1) is also of natural interest. In fact, a widely used traditional approach for analyzing DTSA data is provided by an appropriate application of logistic regression (e.g., Singer & Willett, 2003), as indicated earlier, but this method is arguably not readily extended to include, for instance, fallible covariates or accommodate unobserved heterogeneity.

As an alternative, recently an LVM approach to DTSA has been advanced by Muthén and Masyn (2005). Accordingly, to begin applying this approach one commences by modeling the probability in Equation 1; that is, of the HF at jth period, using the logistic function

$$\wedge(z) = \exp(z)/[1 + \exp(z)] = 1/(1 + \exp(-z)) \tag{2}$$

where exp(.) denotes exponentiation (i.e., raising the mathematical constant $e = 2.718 \ldots$ to the power stated within parentheses), which function is obviously defined for all real numbers z (e.g., Raykov & Marcoulides, 2017; $j = 1, \ldots, J$). Using Equation 2, the HF for the ith person at jth observation period is thus postulated as

$$h_{ij} = 1/\left[1 + \exp\left(-l_{ij}\right)\right] \tag{3}$$

where l_{ij} denotes the log odds, or logit, associated with the HF (as a probability) of this individual and interval, h_{ij}; that is,

$$l_{ij} = ln\left[h_{ij}/\left(1 - h_{ij}\right)\right] = logit\left(h_{ij}\right) \tag{4}$$

with $ln(.)$ denoting natural logarithm (i.e., logarithm with base e) and $logit(.)$ is the log odds of the probability within parentheses (with $h_{ij} < 1$ assumed throughout this article, to avoid triviality considerations; $i = 1, \ldots, n, j = 1, \ldots, J$).

As a next step of an LVM application for the purpose of DTSA, one can model the logit in Equation 4 (i.e., in effect the HF of concern) in the following way that will be of relevance in the rest of this article (cf. Muthén & Masyn, 2005; see also later):

$$l_{ij} = logit\left(h_{ij}\right) = a_j + b_j' x_i \tag{5}$$

where a_j is an intercept, b_j' is the $k \times 1$ vector of logistic regression coefficients ($k \geq 1$) associated with the used k explanatory variable (values) $x_{i1}, \ldots, x_{ik}$ collected in the $k \times 1$ vector xi (for the ith individual; $i = 1, \ldots, n, j = 1, \ldots, J$; priming denotes transposition throughout this article). These coefficients, for convenience referred to as effects in the rest of this article (that is not concerned with or aims at any causality related statements or implications), represent the unique predictive power of the pertinent explanatory variable once the (linear) relationship of the remaining covariates with the logit of HF is accounted for. As such, the b coefficients on the right side of Equation 5 will be of special interest to us in the remainder of the article, and especially the coefficient associated with depression, as it directly

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relates to the VDH aspect of concern in this discussion as mentioned earlier. Furthermore, for the sake of completeness we mention that the intercept in Equation 5 can be interpreted as the log-odds (logit) of the HF for individuals having all covariate values of 0; this HF value is also known as baseline hazard, denoted by h^bij (e.g., Collett, 2014). Because the logistic function is the inverse of the logit function (e.g., Raykov & Marcoulides, 2017), from Equation 5 it follows that

$$h^b{}_{ij} = 1/\left[1 + \exp\left(-a_j\right)\right] = \wedge\left(a_j\right) = \exp\left(a_j\right)/\left[1 + \exp\left(a_j\right)\right] \quad (6)$$

where $\Lambda(.)$ is the logistic function (see Equation 2) and 0 is the $k \times 1$ vector consisting of zeros only; that is, the baseline hazard is the logistic function at the value of the intercept in the model in Equation 5 ($i = 1, \ldots, n, j = 1, \ldots, J$).

An important model version results from the preceding DTSA model (Equation 5), which will turn out to play an instrumental role in the next section. This is the so-called proportional hazard odds (PHO) model, which is obtained from Equation 5 when in addition

$$b_1 = b_2 = \ldots = b_J \quad (7)$$

holds; that is, the effect of the covariates on the log-odds of the HF is constant over time, or time-invariant (e.g., Muthén & Masyn, 2005; as indicated earlier, this article uses the terms and references effect and predictor or predictive in their descriptive and noncausal meaning rather than as implying any causality relationship). The PHO model represents a potentially very useful parsimonious model, and its fit relative to the same model but without the restriction in Equation 7 (i.e., the model defined in Equation 5), or other models fitted to the same data set, can be evaluated, for instance, using the Bayesian Information Criterion (BIC; e.g., Raftery, 1995; see next section).

In a following step of an LVM application for DTSA, one can (a) consider each of the J observation periods under consideration as corresponding to observed variables, namely the earlier random variables E_{ij} that are defined as 0 or 1 for the ith subject depending on whether they have experienced or not the event of concern during the jth period; and then (b) assume their conditional independence given the values of the covariates under consideration, as well as (c) noninformative censoring; that is, the distribution of censoring times being independent of that of event times (given the covariates; a censoring time is defined as the last observation period in which a person was observed as not having experienced the event of concern; $i = 1, \ldots, n, j = 1, \ldots, J$; cf. Muthén & Masyn, 2005). For each censored subject, the values of this variable are declared missing after the last period he or she has been observed not to have experienced the event, and anyone who experiences it before the Jth period receives a missing value for all periods after the one of the event. We can then conceptualize the effect of the covariates on the ith individual at each observation period as transmitted through a latent variable, denoted u^*_i, and represent formally the model of Equation 5 in the constant covariate effect case as follows ($i = 1, \ldots, n$; see Equation 7; e.g., Muthén & Masyn, 2005):

$$P(E_{ij} = 1|x_i) = 1/\left\{1 + \exp[-(-\tau_j + u^*{}_i)]\right\} \quad (8)$$

where τ_j is a threshold associated with an assumed underlying latent variable reflecting the propensity of experiencing the event during the jth observation period (cf. Rabe-Hesketh & Skrondal, 2012), and u^*_i is the common factor (individual factor score) of these j underlying latent variables. In the context of DTSA, this common factor can be interpreted as the propensity for experiencing the event under consideration during the course of the empirical study (spanning the J observation periods), as we will do in the next section. We stress that the model in Equation 8 is a statistically equivalent representation of the PHO model defined by Equations 5 and 7, which permits various LVM-based extensions (Muthén & Masyn, 2005).

In the highly comprehensive LVM context underlying this article, it is worthwhile noting at this point the close connection of the model in Equation 8 to the well-known one-parameter logistic (1PL) model (Rasch model) in item–response theory (IRT; e.g., Raykov & Marcoulides, 2017). Specifically, using the popular in IRT notation of θ for a studied trait or ability underlying a given set of items or measuring instrument, and b for the item difficulty parameter, we can readily rewrite the right side of Equation 8 as follows:

$$P(U = 1|x) = 1/\{1 + \exp[-(\theta - b)]\} \quad (9)$$

In Equation 9, $\theta = u^*$, $b = \tau$, and $U = E$ is used as new notation, and for simplicity the individual person and item subindexes are dropped to emphasize this modeling framework connection. Equation 9 states that given the covariates, the probability of experiencing the event (during the jth observation period, or wave) equals the value of the logistic function at the difference between the overall propensity and pertinent threshold. Thereby, U is used as the event indicator flagging correct responses (denoted 1) if and only if the event occurred. The right side of Equation 9 is, however, precisely equal to the probability of correct response under the 1PL or Rasch model, when the variance of the underlying latent ability evaluated by the items under consideration is a free parameter and all items are postulated to have 1 as their common item discrimination parameter (e.g., Raykov & Marcoulides, 2017; this form of the 1PL-model is a reparameterization of the more popular expression of the probability of correct response under this model, with identical across items discrimination parameters and unit latent variance). We also note that the more general version of the model in Equation 8, allowing for time-varying (nonconstant) effects of the covariates on the event variables (denoted E_{ij} in Equation 8) as opposed to the assumption reflected in

Equation 7, corresponds similarly to the well-known and widely used two-parameter logistic model in IRT (in particular in settings with no guessing; e.g., Raykov & Calantone, 2014).

We apply next the discussed LVM approach based on the model in Equation 8 with several substantively important versions of it, after first attending to the vascular depression hypothesis—an increasingly prominent conjecture about the potential relationship between depression in middle and late life and stroke.

EXAMINING THE VASCULAR DEPRESSION HYPOTHESIS USING LATENT VARIABLE MODELING

The Vascular Depression Hypothesis

The VDH was advanced nearly two decades ago by Alexopoulos et al. (1997). It states that cerebrovascular disease might predispose, precipitate, or perpetuate some geriatric depressive syndromes. This potential relationship is especially relevant in aging research, psychology, gerontology, and geriatrics, as well as in the biomedical disciplines, because an increase in depression has been found to occur in late life (e.g., Mitchell & Subramaniam, 2005; Taylor, Aizenstein, & Alexopoulos, 2013). There is also evidence that depressed elderly are more likely to experience stroke; in addition, when this occurs they are more likely to die from it or related complications. If the VDH were to be confirmed, or substantially supported by empirical studies, then (a) impending strokes might be sensed by (sustained) elevated depression, and (b) appropriate treatment of affected adults can be undertaken to potentially prevent strokes from happening to them.

The VDH is potentially a rather complex phenomenon, with multiple aspects to it, and it is not the aim of this article to address all, many, or even more than one of them. Rather, as indicated earlier, we aim to shed light on one particular side of VDH, the predictive power of depression with respect to time to first stroke. To this end, we make use of several versions of the model in Equation 8 that permits evaluating the effect of certain covariates on the propensity for experiencing the event in question, in this case first stroke. For our purposes in this article, in the vector x of covariates whose effect on this propensity is to be studied we include (a) depression, as well as (b) a set of medical covariates and demographic measures, with all measures in (a) and (b) collected at the beginning of an empirical longitudinal study (in our case, the HRS). This permits us to address the following question: Once controlling for these covariates and demographic measures, can individual differences in baseline depression (for convenience, frequently referred to as depression in the remainder of this article) still explain a significant amount of individual differences in the propensity to experience stroke over the study period? To address this question, and by implication an important aspect of the VDH as discussed earlier, we use data from the HRS.

Examining the Relationship of Depression to Propensity for Experiencing First Stroke Using Data From the Health and Retirement Study

The HRS is a nationally representative, probability sample-based (e.g., Heeringa, West, & Berglund, 2010) panel investigation of older Americans that was started a quarter-century ago and involved collection from the participating respondents of an extensive set of variables at consecutive 2-year waves. The panel aims to provide one of the leading sources of information on the social, economic, and health status of this population, is sponsored by the National Institute on Aging, and is maintained by the University of Michigan. The data are publicly available at http://hrsonline.isr.umich.edu. The baseline interviews were carried out in 1992 with nearly 10,000 individuals who were born between 1931 and 1941; the respondents were reinterviewed every 2 years thereafter. We use data from all available 12 waves spanning 1992 to 2014 in a version harmonized by the RAND Corporation and published as Version P (RAND Corporation, 2016).

The sample for the following analyses is defined as persons born in the time period between 1931 and 1941 and thus aged 51 to 61 at Wave 1 (baseline). We exclude 402 persons who, at any wave during the study, disputed a prior report of stroke or were unsure whether they had stroke, as well as an additional 218 individuals who reported prior stroke at the baseline wave. As a result, a subset from the HRS data set that is of relevance for the following analyses consists of $n = 9{,}142$ individuals who had not experienced a stroke prior to Wave 1 (see also the conclusion section).

As indicated in a previous section, using the preceding LVM approach to SA, which is based on Equation 8 with possibly the constraint in Equation 7—that is, the PHO model or its more relaxed version without restriction (Equation 7)—we would like to address a particular aspect of the VDH. This aspect is concerned with the unique predictive power of baseline depression with respect to the propensity to experience a first stroke during the study, after controlling for a number of demographic and medical covariates from Wave 1 that are available in the HRS study.[1]

[1] The depression measure employed in this article is the overall score resulting from a short form of the widely used Center for Epidemiologic Studies Depression (CES–D) scale (Radloff, 1977). The CES–D measure used here includes seven indicators of a respondent's feelings over the week prior to the interview. Five negative indicators of it measure whether the respondent experienced feeling depressed, like everything is an effort, sleep is restless, felt alone, felt sad, and could not get going. The remaining two, positive indicators (reverse-coded) include having felt happy and enjoyed life. Response categories for all items were *all or almost all of the time, most of the time, some of the time*, or *none or almost none of the time*. The CES–D scale has high internal consistency, acceptable test–retest reliability, and excellent concurrent validity with clinical and self-report criteria across population subgroups, and thus is a useful tool for population studies of depression (Radloff, 1977). Acceptable validity and reliability have also been shown for the short forms of the CES–D scale such as that used by the HRS (Andersen et al., 1994; Livine, 2013).

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These are the time-invariant covariates (a) age, gender, and race or ethnicity (non-Hispanic Black, Hispanic, other, and non-Hispanic Whites, with the latter used as the reference group); (b) the binary indicators for marital status (married as reference), foreign-born (U.S.-born as reference), and educational level (years of formal education); (c) the binary indicators from Wave 1 for having been previously diagnosed with arthritis, cancer, diabetes, heart disease (including heart attack, coronary heart disease, angina, congestive heart failure, or other heart problems), high blood pressure, pulmonary disease such as chronic bronchitis or emphysema, as well as smoking status (current smoker or not); and (d) initial body mass index (BMI).

We commence with the PHO model defined in Equations 7 and 8, denoted in the remainder of the article as M0, which includes the last mentioned 14 covariates in addition to baseline depression. These 15 measures are used in M0 as explanatory variables of the unobserved propensity u^*_i to experience first stroke during the study (referred to as propensity for first stroke [PFS]; see Equation 8; i = 1, 2, …, 9,142; see the appendix for the pertinent M*plus* source code, and Example 6.19 in Muthén and Muthén, (2016), for a path diagram of the model). The fit statistics of this model are presented in Table 1, along with those of the following four models considered in this section.

In model M0, the unique effect of marital status is found to be nonsignificant: estimate = .025, with a standard error (*SE*) = .073, and associated (two-tailed) p value (p) of .729. We postulate next that effect of marital status on the PFS is 0 in the studied middle-age and older adults population and refit the model with the remaining 14 explanatory variables (including the depression measure), as described in the preceding paragraph. This model is denoted M1 in the rest of this section; we stress that due to the lack of significance of marital status in model M0 (even at the large sample size of 9,142 cases used), M1 is preferable to M0.

To examine next the main assumption in M1 of time-invariant effect of each explanatory variable on the PFS (i.e., the PHO stipulation; e.g., Muthén & Masyn, 2005), which is represented by Equation 7, we drop this constraint in the next model that is denoted M2. Its associated BIC is considerably higher than that of M1 (see Table 1), and so we consider M1 preferable also to M2. This result suggests that the PHO assumption does not appear to be seriously violated; that is, the assumption of time-constant covariate effect on the PFS during the course of the study (consisting of 12 waves, or 22 years) appears plausible.

To examine a possible nonlinear effect of depression, given the other 13 covariates in the model, we introduce its square (along with its linear effect) into the next model version fitted, denoted as M3. The quadratic effect of depression is found not be significant in M3: estimate = .001, *SE* = .002, p = .584.[2] We can thus consider model M1 also as preferable to M3.

As a final step in this multiple-model fitting process, instead of the quadratic depression effect (found as mentioned nonsignificant in M3) we include the age by gender interaction, along with the same other 14 covariates as used in M1 through M3 (including depression). The resulting model, denoted M4, is associated with a nonsignificant age by gender interaction: estimate = .023, *SE* = .036, p = .519. This finding suggests that M1 is preferable to M4.

The reported results obtained with the five models fitted in this section suggest that M1 can be selected from them all. Table 2 presents its estimates for the unique covariate effects on the PFS, which are of major interest for the aims of this article, along with their associated standard errors and p values.

Table 2 shows a number of interesting findings. Before we place trust in them, however, we need to address the issue of multiple testing that is involved in evaluating the p values associated with the 14 covariates in the selected model M1, leading to a total of 16 p values that are found in Table 2 (because the variable race is represented by three dummy variables in the fitted models, in particular M1, as indicated earlier). To respond to the query which of these p values can be declared significant, we use the increasingly popular Benjamini–Hochberg (BH) procedure that is based on the false discovery rate concept and has been shown to be more powerful than conventional multiple testing procedures (e.g., Benjamini & Hochberg, 1995; Benjamini & Yekutieli, 2001; see, for instance, Raykov, Lichtenberg, & Paulson, 2012, for a nontechnical discussion of the BH procedure; and Raykov, Marcoulides, Lee, & Chang, 2013, for an R-function facilitating its application in an empirical study). The BH procedure declares all p values that do not exceed .003 as significant, thus including baseline depression (see Table 2, and later for a discussion of other significant covariates).

The last finding suggests that, based on the analyzed HRS data, initial depression holds a significant unique predictive

TABLE 1
Fit Statistics for Models M0 Through M4

Model	*LL*	*q*	*BIC*
M0	−132,267.101	198	266,340.088
M1	−127,839.398	179	257,311.391
M2	−127,821.454	189	257,366.709
M3	−193,755.336	210	389,426.006
M4	−144,958.271	208	291,813.634

Note. See text for specific definition of models M0 through M4; LL = maximized log-likelihood; q = number of model parameters; BIC = Bayesian information criterion (Raftery, 1995).

[2] The linear and quadratic effects of depression were mean-centered in Model M3 to limit the potential impact of multicollinearity (e.g., Aiken & West, 1991).

TABLE 2
Parameter Estimates, Standard Errors, *t* Values, and *p* Values for Covariate Effect Estimates for Propensity to Experience First Stroke During Study in Preferred Model M1 (Software Output Format)

	Estimate	*SE*	*t Value*	*p Value*
AGE	0.047	0.014	3.481	.001
FEMALE	−0.266	0.069	−3.877	.000
BLACK	0.309	0.105	2.929	.003
HISP	0.162	0.132	1.230	.219
OTHER	−0.074	0.358	−0.206	.837
FOREIGN	−0.430	0.184	−2.335	.020
EDUYEAR	−0.022	0.016	−1.425	.154
BASE_DEP	0.032	0.010	3.325	.001
ARTHRITIS	0.196	0.081	2.402	.016
CANCER	0.281	0.193	1.452	.146
DIABETES	0.614	0.094	6.550	.000
HEART_DIS	0.518	0.142	3.645	.000
HIGH_BP	0.361	0.082	4.377	.000
LUNG_DIS	0.120	0.168	0.711	.477
CURRENT	0.609	0.056	10.785	.000
BMI_1	0.015	0.009	1.748	.081

Note. Variable names, unless self-explanatory, are as follows: FEMALE = binary indicator for female gender; BLACK = binary indicator for being non-Hispanic Black; HISP = binary indicator for being Hispanic (of any race); OTHER = binary indicator for not being White, Black, or Hispanic; FOREIGN = binary indicator for being born outside of United States; EDUYEAR = years of formal education; BASE_DEP = baseline depression score (at Wave 1); HEART_DIS = heart attack, coronary heart disease, angina, congestive heart failure, or other heart problems; HIGH_BP = high blood pressure or hypertension; LUNG_DIS = chronic respiratory disease except asthma such as chronic bronchitis or emphysema; CURRENT = binary indicator for current smoking; BMI_1 = body mass index at Wave 1.

power for the propensity to experience first stroke during the course of the study (encompassing a period of nearly a quarter-century), after accounting for (a) age, gender, race, education, the country of birth dichotomy (foreign born vs. U.S. born), smoking, and marital status; as well as (b) medical covariates such as suffering from arthritis, cancer, diabetes, lung disease, heart disease, high blood pressure, and also initial BMI. That is, even after controlling for these demographics and apparent medical risk factors (see also the conclusion section), the propensity to experience first stroke during the course of the study is enhanced significantly by an increase in baseline depression. Looking at its effect on the PFS, estimated at .032, across the entire scale of depression that encompasses 24 possible points (from 0–24), we realize that what one might call an "overall" unique effect of depression on enhancing the PFS is in fact higher than this unique effect of any other medical covariate, being 24 × .032 = .77. That is, an increase of baseline depression from very low to very high enhances substantially the propensity of experiencing a first stroke during the study, all other things being the same (according to M1), and in fact more than any single medical covariate after controlling for the remaining 13 covariates (including depression then).

In addition to these findings, we see from Table 2 that age holds significant unique predictive power, thereby increasing the PFS given constant covariates. Contrary to this effect, being female is associated with significantly lower PFS controlling for the remaining covariates, and being Black relative to White is associated with a significant increase in the PFS then. Diabetes, heart disease, high blood pressure, and smoking each also have significant unique predictive power for PFS, enhancing the latter after controlling for all remaining covariates. Being Hispanic or of other races (not Black or Hispanic), relative to White, is not associated with notable unique predictive power for PFS and does not enhance the latter significantly given the remaining covariates. Similarly, education, foreign born, arthritis, cancer, lung disease, and initial BMI are each associated with nonsignificant unique predictive power for the propensity to experience first stroke, and thus changes in the former do not affect notably the latter (after controlling for the remaining 13 covariates, including depression). We would like to stress in this connection that despite the fairly large sample of more than 9,000 analyzed persons, each of these eight last mentioned covariates (Black vs. White through initial BMI) is found to be associated with nonsignificant unique predictive power for PFS based on the analyzed data (and the preferred model M1).

DISCUSSION AND CONCLUSION

This article sought to discuss the potential of LVM when used to accomplish aims conventionally considered achievable utilizing DTSA, and thereby to employ the former approach to address the increasingly prominent VDH in gerontology, geriatrics, psychology, and aging research. Using data from the popular HRS, results were obtained that are consistent with the VDH. Specifically, baseline (initial) depression was found to hold significant unique predictive power with respect to the propensity to experience first stroke during the course of the study (available waves' data, spanning a period of 22 years), after controlling for a number of important demographics and medical covariates. These included (a) age, gender, race, education, marital status, foreign born versus U.S. born, as well as smoking and initial BMI; in addition to (b) suffering from arthritis, cancer, high blood pressure, heart disease, lung disease, and diabetes. These results appear to point to a potentially consequential relationship of depression to stroke, which is worth studying further.

In particular, the findings in Table 2 are generally highly consistent and expected when taking into account risks for stroke. For example, history of hypertension, diabetes mellitus, heart disease, and current cigarette smoking are well-established risks for stroke (Meschia et al., 2014). Arthritis, although not an established risk for stroke, could be a

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surrogate for systemic inflammation, which is an emerging risk for stroke (Elkind, 2010). Depression has more recently been recognized as an emerging risk for stroke, and the VDH is a prominent hypothesis signaling their likely interrelationship. People with depression might be at higher risk of stroke and other cardiovascular diseases based on being prone to tobacco use, poor compliance with medication, and possible street drug use (Carney & Freedland, 2016). In addition, patients with depression might be prone to develop a form of stroke, vascular dementia, in later life (Diniz, Butters, Albert, Dew, & Reynolds, 2013). Moreover, such patients might have asymptomatic subcortical vascular disease manifestations such as lacunar infarcts and white matter lesions, or so-called silent stroke findings, putting the patients at higher risk for subsequent stroke (Sachdev & Reutens, 2014). Thus, vascular depression is a plausible candidate factor to raise the risk of stroke, and this article's findings are entirely consistent with this possibility.

Although the results presented in this article enhance interest in the VDH and its further study, it is worthwhile explicating at this point several limitations of these analytic findings and their offered substantive interpretations. In their totality, these limitations lead us to the recommendation of exercising caution when interpreting the reported results in substantive terms, and that more trust could be placed on them and in particular their offered interpretations only after a replication study (studies) on an independent sample(s).

One limitation results from the fact that to achieve our substantive aims we had to focus on individuals who had not experienced stroke before the start of the study. To this end, we effectively removed persons with prior stroke from the general population that was to be sampled at the start of the HRS. It is unknown, strictly speaking, to what extent this could have affected the relevance of the design variables (in particular the weighting of the individual cases), which were used in the presented analyses (cf. Heeringa et al., 2010; see next). However, we hasten to add that only $n = 218$ respondents with stroke prior to the study beginning were excluded from the analyses reported in this article. In addition, these excluded individuals can, in our view, be reasonably considered a random subsample, and hence it might be conjectured that if the design variables (in particular individual weights) were to be affected in the resulting sample of 9,142 cases used in this article, then these effects might well be limited on the reported results. Given also the comparatively small number of excluded participants, relative to the analyzed 9,142 respondents, the findings and their interpretations in the last section arguably might not be notably or more seriously biased.

Further, as is commonly the case in contemporary applications of DTSA, the analyses conducted assume (a) data are missing at random (MAR), which as well known is less likely to be fulfilled in longitudinal studies, such as the HRS; and (b) noninformative censoring (NIC; e.g., Kleinbaum & Klein, 2011). To counteract possible violations of MAR, as well as of NIC, we used a substantial number of covariates, and so we are hopeful that by conditioning on them that we effectively conducted by including them in the reported analyses, the plausibility of MAR and NIC assumptions has been considerably enhanced and the potentially biasing effect of their violation reduced, particularly at later waves (e.g., Enders, 2010; the used covariates could also be considered in conceptual terms auxiliary variables; Little & Rubin, 2002). Beyond these helpful effects of the used covariates, it is unknown to what extent possible residual violations of MAR and NIC might have affected the given results and interpretations. (We mention in passing that similar to MAR, the routinely made NIC assumption in SA is not possible to examine; cf. Collett, 2014; Enders, 2010; see also Raykov, 2011).

In addition, the analyzed data included persons with a wide range of baseline depression scores, so it is unknown to what extent and how baseline depression that is low might be meaningfully related to PFS. Further analyses, particularly of this subpopulation of what might be considered nondepressed elderly, are needed to address this important question. We emphasize, however, that the original VDH envisaged only enhanced depression as possibly related to time to first stroke. Looking at Table 2, we can interpret, however, the effect of decreasing baseline depression as lowering of the PFS, controlling for the remaining covariates, which we alternatively find not to be inconsistent with the VDH. Relatedly, the article does not address the possibility (and does not exclude it) that higher levels of depression might have a stronger than linear effect on the PFS.

Similarly, this article is not concerned with the question of the immediate (lag-1) effect of depression, owing to the fact that we could only use baseline depression along with all other Wave 1 explanatory variables treated as time-invariant covariates. An extension of the DTSA model defined by Equation 8—with or without the constraint in Equation 7—to include time-varying covariates is possible (including depression; e.g., Muthén & Masyn, 2005) and goes beyond the confines of this article. We would like to point out, however, that this extension can still be carried out within the same LVM-based approach to DTSA that was used in this article.

As a further limitation, we would like to mention the fact that the analyses reported in this article were based on single-class modeling (e.g., Raykov, Marcoulides, & Chang, 2016). Future research is therefore encouraged that should be concerned with the examination of possible unobserved heterogeneity (e.g., Muthén & Masyn, 2005), specifically with respect to the VDH and its relationship to depression, which could not be pursued in this article. This examination of unobserved heterogeneity is also possible within the used LVM-based approach to DTSA, namely via using mixture discrete-time survival analyses that are going beyond the confines of this article.

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Moreover, it is worth mentioning that the target population from which the HRS sample was drawn comprised middle-aged persons between 51 and 61 years old in 1992. Hence, the suggested interpretations in the last section of this article, in particular in relation to the VDH, might not be applicable for older adults who are in their 90s and beyond (the cohort before that of the HRS participants). In this connection, it is not known to what extent if any the sampled population for the HRS is dissimilar to the current general population of middle-aged persons (say in their mid-50s through mid-60s), some quarter-century after the beginning of that study.

Finally, the article treated the depression score at baseline (Wave 1) as an effectively error-free measure (see also RAND Corporation, 2016, on the reporting of the depression scores). Dealing with potential violations of this assumption is only possible if individual depression item data were to be available, which is not the case here. We would like to add in this connection, however, that the baseline depression measure utilized in the HRS (and this article), which was based on a relatively limited number of items, has been found to be closely related to depression scores evaluated by longer instruments (Andersen, Malmgren, Carter, & Patrick, 1994; Livine, 2013). Thus, we are hopeful that possible biasing effects of measurement error are relatively limited.

Notwithstanding these limitations, we would like to conclude by stating that the discussed LVM approach to DTSA holds substantial potential for behavioral and social studies that involve discretely evaluated times to occurrence of events of substantive interest, and in particular to address various aspects of the VDH. Therefore, we are hopeful that the article contributes to this field also by stimulating future substantive and methodological research in relation to this important hypothesis about a likely highly consequential link between depression and stroke in middle and late life, which if better established could further contribute to preventing strokes and lead to enhancing quality of life of a considerable part of middle-aged and older adults.

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APPENDIX

M*PLUS* SOURCE CODE FOR FITTING MODEL M0

```
TITLE: MPLUS SOURCE CODE FOR FITTING MODEL M0
(see Example 6.19 in Muthén & Muthén, 2016).
DATA: FILE = < RAW DATA FILE NAME>;
VARIABLE: NAMES = id age92 female black hisp other foreign
    notmarrd eduyear cesd1 cesd2 cesd3 cesd4 cesd5 cesd6
    cesd7 cesd8 cesd9 cesd10 cesd11 cesd12 stroke1
    stroke2 stroke3 stroke4 stroke5 stroke6 stroke7
    stroke8 stroke9 stroke10 stroke11 stroke12
    bmi1 bmi2 bmi3 bmi4 bmi5 bmi6 bmi7 bmi8 bmi9 bmi10
    bmi11 bmi12 arth cancer diab heart hibp lung psych
    current former never normalw underw overw obese1
    obese2 stratum psu sampwght;
    MISSING = .;
    CATEGORICAL = STROKE2-STROKE12;
    STRA = STRATUM;
    CLUSTER = PSU;
    WEIGHT = SAMPWGHT;
    USEV = age92 female black hisp other foreign notmarrd
    eduyear CESD1 stroke2-stroke12 arth cancer diab heart hibp lung
    current bmi1;
DEFINE: PSU = 1000*STRATUM+PSU;
ANALYSIS: ESTIMATOR = MLR;
    TYPE = COMPLEX;
    INTEGRATION = MONTECARLO;
MODEL: S BY STROKE2-STROKE12@1;
S@0;
S ON AGE92-cesd1 ARTH-bmi1;
AGE92-cesd1 ARTH-bmi1;
```

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