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Effect of Demographic Risk Factors on the Change in Cognitive Function in the Presence of Non-Participation and Truncation due to Death

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Abstract

Missing data due to non-participation and death are two common problems in longitudinal studies of the elderly. The effect of socio-demographic variables on the decline in cognitive function after adjusting for non-participation and truncation due to death has not been well studied. This study is based on 6,105 subjects enrolled in the Chicago Health and Aging Project (CHAP), followed over four cycles of data collection approximately three years apart. Cognitive function was based on a standardized measure of mini-mental state examination. We will study the impact of non-participation and death on the decline in cognitive function with socio-demographic variables as risk factors, using four different modeling approaches: 1) a linear mixed effects model ignoring the missing data, 2) a pattern-mixture model using multiple imputation (MI) stratified by patterns of non-participation and death, 3) MI for non-participation stratified by patterns of non-participation and a pattern-mixture model stratified by the time of death, and 4) MI for non-participation stratified by patterns of non-participation and a pattern-mixture model with a categorical variable for time of death. The baseline association of socio-demographic variables with cognitive function was mostly unchanged among Blacks and Whites. However, the decline in cognitive function over a 10-year period had decreased by approximately 50% (Blacks coefficient changed from -0.544 to -0.285; Whites coefficient changed from -0.682 to -0.339) after accounting for non-participation and death. The effect of age on the change in cognitive function over a 10-year period had reduced by about 30% (Blacks coefficient changed from -0.033 to -0.010; Whites coefficient changed from -0.049 to -0.016). The trajectory of cognitive function for White males had reduced by approximately 45% (changed from 0.12 to 0.055) over a 10-year period. Education was significantly associated with the change in cognitive function among Blacks but not among Whites. Moreover, females showed a significant change in cognitive function among Whites, but not among Blacks. We found significant differences on the change in cognitive function between models that did not adjust for non-participation and death, and models that adjusted for them.

Introduction

The association of cognitive function with demographic variables has been established among the elderly [1-2]. Blacks have lower cognitive function compared to Whites, after adjusting for individual socio-economic status (SES) [3]. The racial differences, in part, can be attributed to indirect effects through education [4] and differential item function [5]. However, none of the demographic variables seem to exhibit any relationship with the change in cognitive function [6]. A closer look at the study revealed that a large fraction of respondents were lost to follow-up and were not given any special consideration. In order to make correct inferences, we will need to account for this large loss of follow-up in our longitudinal surveys.

Non-participation and death are the two main causes of loss to follow-up among aging population [7-9], and the analytic strategies need to appropriately account for this loss to follow-up [10]. Missing data can result in biased parameter estimation and incorrect inferences, when missing data mechanism is closely related to unobserved cognitive function [11]. A range of methodologies for handling cognitive function with non-participation and death have been proposed which accommodate general patterns of missing data. Most of these methods rely on likelihood-based theory, since the focus is on the subject-specific trajectories of study participants, in the presence of non-participation and death [12-14]. However, the observed cognitive function provides no means of verifying the different probability assumptions with regard to the distribution of non-participation and death. Consequently, sensitivity analysis under a range of assumptions about the missing process is to be undertaken.

Pattern-mixture models have gained wide popularity for handling data not missing at random. These models factorize the joint distribution into the conditional distribution of cognitive function given the time of event, and the marginal distribution of the time to event [15]. Multiple imputations have been rigorously developed to study the NMAR non-participation process [16]. Imputations can be performed in samples stratified by patterns of non-participation and the imputed datasets can be used to study the decline in cognitive function while stratifying on patterns of death [16-17]. Stratification by patterns makes it clear how the observed data lack information sufficient for estimating certain parameters while requiring a set of identifying constraints.

Our research is motivated by the Chicago Health and Aging Project (CHAP). One of the aims of the CHAP study was to study the effect of demographic variables on Alzheimer's disease and change in cognitive function. However, a large fraction of subjects were either deceased or did not participate in all follow-ups of the study. Thus, the primary aim of this article is to illustrate the use of missing data methods for analyzing longitudinal end of life research, in the presence of non-participation and death, among blacks and whites. In the next

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section, we will outline the likelihood-based approach for modeling observed data in the presence of independent and dependent missing mechanisms.

Mixed-Effects Regression Models

Let Y denote cognitive function, S the time of death, X the fixed-effects design matrix for Y, and β the vector of unobserved random subject-specific effects. Pattern-mixture models stratify the data according to patterns of non-participation and death, and provide a model for each pattern specific stratum [18]. The final estimate is a weighted average of the stratum specific estimates. After conditioning on the patterns, the missing data mechanism is ignorable within a stratum, and thus information from the complete cases can be borrowed to predict the incomplete cases. This implies the factorization

$$P(Y, S|X) = P(Y|X,\beta,S)P(\beta|X,S)P(S|X),$$

Where P(S | X) can be modeled as a multinomial distribution or a survival function based on whether we use missing data pattern or time to unobserved cognitive function, respectively.

Let subject i have n_i planned follow-up interviews. Using standard notation, a linear mixed effects model (LMEM) for cognitive function that implicitly imputes the data missing at random [19] is given by

$$Y_{in_i} = \alpha X_{in_i} + \beta b_i + \varepsilon_{in_i}, b_i \sim N(0,\Sigma_b), \varepsilon_{in_i} \sim N(0,\Sigma),$$

where X_{in_i} is the known design matrix for fixed effect and bi is the subject-level random effects for unobserved cognitive function Y_{in_i}. The missing at random assumption might hold for non-participation, however, there is little evidence to suggest that it would hold for the deceased.

Missing data can be classified into two types based on the time of non-participation and time of death. If the time of non-participation was one interview before death then this will be classified as missing due to death. If the time of non-participation was more than one cycle apart then they will be treated as missing due to non-participation. If missing data occurred among those who were not deceased then it is be treated as missing due to non-participation. Based on this definition, we will perform multiple imputations (c = 5) for non-participation and use pattern-mixture models with time to death in the imputed datasets.

In the second model, multiple imputations are performed on the missing data by stratifying on the patterns of non-participation and death. Let *k* denote the imputed data set. Then, the linear mixed effects model for the imputed data sets is given by

$$Y^k_{in_i} = \alpha X_{in_i} + \beta b^k_i + \varepsilon^k_{in_i}, b^k_i \sim N(0,\Sigma_b), \varepsilon^k_{in_i} \sim N(0,\Sigma),$$

where $Y^k_{in_i}$ denotes cognitive function from the k^{th} imputed data set. This model uses a stratification variable during imputations to capture the pattern effects of non-participation and death, and is similar to a pattern-mixture model (PMM). The estimates from the imputed datasets are combined using Rubin's combination method [20].

In the third model, multiple imputations are performed on the study population stratified by the patterns of non-participation. Let us define pattern *j* for those who were deceased. Then, a random pattern-mixture model (PMM-1) stratified on the patterns of death is used to capture the longitudinal trajectories for groups [21]. This model is represented as follows

$$Y^k_{ij} = X_{ij}\alpha + \beta b^k_i + \gamma u_j{}^k + \varepsilon^k_{ij}, b^k_i \sim N(0,\Sigma_b), u_j{}^k \sim N(0,\Sigma_u), \varepsilon^k_{ij} \sim N(0,\Sigma),$$

where the time of death depends on the pattern specific random effect u_j. Thus, the information of the deceased is modeled by the second component which imposes a constraint on the random patterns effect u_j.

Finally, a categorical time of death variable was added to capture the longitudinal trajectories for those deceased [22]. The random pattern-mixture (PMM-2) with the time of death variable is given by

$$Y^k_{ij} = X_{ij}\alpha + \beta b^k_i + \theta t_j{}^k + \varepsilon^k_{ij}, b^k_i \sim N(0,\Sigma_b), \varepsilon^k_{ij} \sim N(0,\Sigma),$$

where the time of death is used as a covariate to provide an accurate representation of cognitive function over time.

All models were fitted using SAS software with PROC MI, PROC MIXED and PROC NLMIXED procedures [23]. We used 5 imputations since this provides stable results [24]. In the next section, we describe the design of the CHAP study and the characteristics of CHAP participants.

Chicago Health and Aging Project

CHAP is a cohort of participants, 65 years and older, who have been followed for up to 15 years. This study was performed in three adjacent

Characteristic	Completers N=2035	Non-participants N=990	Deceased N=3080
Age (years)	72.1 (5.2)	72.2 (5.0)	77.6
Cognition score	0.31 (0.64)	0.22 (0.67)	-0.33 (0.99)
Physical function	11.05 (3.20)	9.00 (4.10)	6.7 (3.8)
CES-D score	1.42 (1.90)	1.38 (1.82)	0.97 (1.53)
Gender			
Females	1307 (64%)	607 (61%)	1796 (58%)
Males	728 (36%)	383 (39%)	1284 (41%)
Race			
Whites	735 (36%)	377 (38%)	1221 (40%)
Blacks	1300 (64%)	613 (62%)	1859 (60%)
Education (years)			
0-9	386 (19%)	195 (20%)	917 (30%)
10-12	826 (41%)	431 (44%)	1256 (41%)
13-16	632 (31%)	289 (29%)	716 (23%)
≥17	191 (9%)	75 (8%)	191 (6%)

Table 1: Descriptive measures of demographic and mental health at baseline among the completers, non-participants and deceased. Means and standards deviation are provided for age, cognition score, physical function and CES-D score. Number of participants and percentages are presented for gender, race, and education.

Pattern	Type of Pattern	No. of Participants	Average time in the study (Yrs.)	Mean cognition	Percent Black
Complete	CCCC	2035	9.32	0.314	64%
Non-Participation 1	CCCM	164	9.53	0.229	65%
2	CCMC	185	6.54	0.230	60%
3	CCMM	248	6.62	0.288	56%
4	CMCC	74	3.20	0.272	67%
5	CMMC	40	3.21	0.290	65%
6	CMMM	240	3.31	0.170	62%
7	CMCM	39	3.27	-0.002	77%
Deceased 1	CD	1423	2.73	-.525	62%
2	CMD	2	6.90	-.086	50%
3	CCD	1043	5.53	-.193	56%
4	CCCD	598	8.06	-.110	65%
5	CCMD	14	6.85	-.572	50%

Table 2: The characteristics of patterns defined for non-participation and death among the study sample, where "C" refers to completed observation, "M" refers to non-participants and "D" refers to the deceased.

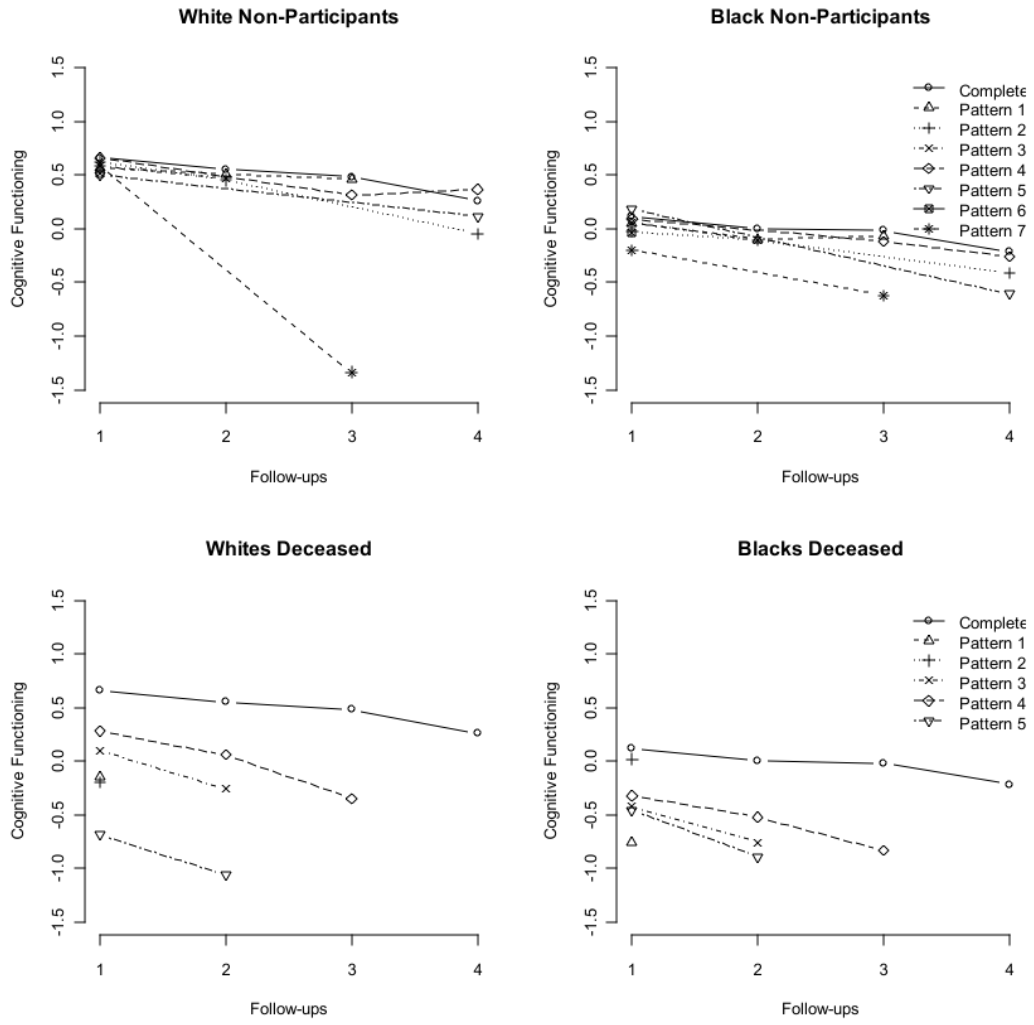

Figure 1: Trajectories of cognitive function by patterns of non-participation and death for Whites and Blacks.

neighborhoods on the South side of Chicago. In-home interviews were conducted three years apart to collect covariate and outcome data [25]. Cognitive function was evaluated using a battery of four tests and was summarized as a global standardized score. This score combines variables with different ranges and floor-ceiling effects by averaging the four tests together after centering and scaling to the baseline mean and standard deviation [26]. Thus, a participant whose performance matches the average participant at baseline has a composite cognitive score of 0, and a person who performs one SD better than average on every test has a composite cognitive score of +1. This article is restricted to the study participants from the CHAP cohort (N=6,105) with four cycles of data collection or truncated due to death.

The average age among study participants at baseline was 74.9 years (SD=7.13 years). In this CHAP cohort, 2679 (44%) participants completed the follow-up interviews and 3426 (56%) subjects did not participate or were deceased. The average time to follow-up from Cycle-1 to Cycle-2 was 3.29 years (SD=0.45) among those who completed the survey; the average time to follow-up from Cycle-1 to Cycle-3 was 6.37 years (SD=0.56); and the average time to follow-up from Cycle-1 to Cycle-4 was 9.35 (SD=0.55). The descriptive measures of the study cohort at baseline for those who completed, did not participate or died are shown in Table 1.

In this analysis, we considered study participants who had provided data at baseline and classified the missing data into two types: non-participation and death. We defined eight patterns of non-participation and five patterns of death. One of the missing data patterns had only two participants, hence, the two subjects were dropped from our analysis. Table 2 provides the definition of the patterns, the details of the follow-up, the average cognition score at baseline, and the percentage of Blacks. A large fraction of the participants had missing data and ignoring the patterns of missing data can cause severe bias in the parameter estimates. Figure 1 shows the average cognition score for study participants belonging to different patterns of non-participation and death by ethnicity. The average cognition score at baseline was different for the patterns ($p<0.001$). Also, the decline in cognitive function was different among the patterns. This suggests that a pattern-mixture model might be useful in studying the sensitivity of an underlying NMAR assumption.

Results from the CHAP Data

The mean cognitive function among the subjects at baseline was

Coefficients	LMEM	PMM	PMM-1	PMM-2
	Both Races Combined			
Intercept	0.323 (0.017)	0.286 (0.018)	0.303 (0.018)	0.365 (0.019)
Age	-0.047 (0.0013)	-0.049 (0.0014)	-0.048 (0.0014)	-0.046 (0.0014)
Male	-0.078 (0.018)	-0.081 (0.018)	-0.073 (0.020)	-0.067 (0.021)
Black	-0.472 (0.021)	-0.464 (0.023)	-0.475 (0.021)	-0.461 (0.022)
Education	0.072 (0.0027)	0.074 (0.0027)	0.072 (0.0027)	0.071 (0.0028)
Time	-0.593 (0.032)	-0.284 (0.033)	-0.355 (0.033)	-0.326 (0.038)
Age Time	-0.039 (0.0029)	-0.011 (0.0025)	-0.011 (0.0030)	-0.010 (0.0029)
Male Time	0.082 (0.035)	0.046 (0.034)	0.087 (0.036)	0.053 (0.032)
Black Time	0.014 (0.038)	0.028 (0.038)	0.058 (0.045)	0.055 (0.053)
Education Time	-0.006 (0.0049)	-0.007 (0.005)	-0.002 (0.005)	-0.006 (0.007)
Time of Death				-.128/-.164/-.202
	White Subjects Only			
Intercept	0.387 (0.018)	0.344 (.019)	0.354 (0.020)	0.424 (0.021)
Age	-0.046 (0.0019)	-0.049 (0.002)	-0.047 (0.002)	-0.045 (0.002)
Male	-0.150 (0.028)	-0.149 (0.029)	-0.144 (0.031)	-0.137 (0.030)
Education	0.049 (0.0042)	0.051 (0.004)	0.048 (0.0048)	0.050 (0.004)
Time	-0.682 (0.037)	-0.308 (0.032)	-0.355 (0.035)	-0.339 (0.055)
Age Time	-0.049 (0.004)	-0.009 (0.004)	-0.014 (0.004)	-0.016 (0.005)
Male Time	0.12 (0.051)	0.073 (0.057)	0.119 (0.050)	0.055 (0.050)
Education Time	0.014 (0.008)	0.002 (0.007)	0.003 (0.008)	0.0007 (0.008)
Time of Death				-.166/-.187/-.228
	Blacks Subjects Only			
Intercept	-0.158 (0.015)	-0.186 (0.016)	-0.182 (0.016)	-0.102 (0.018)
Age	-0.048 (0.0018)	-0.049 (0.001)	-0.050 (0.0018)	-0.047 (0.001)
Male	-0.0142 (0.024)	-0.014 (0.024)	-0.009 (0.026)	-0.0086 (0.026)
Education	0.087 (0.0034)	0.088 (0.003)	0.086 (0.004)	0.086 (0.0034)
Time	-0.544 (0.028)	-0.242 (0.027)	-0.313 (0.031)	-0.285 (0.035)
Age Time	-0.033 (0.0038)	-0.008 (0.003)	-0.012 (0.003)	-0.010 (0.005)
Male Time	0.050 (0.043)	0.017 (0.045)	0.027 (0.044)	0.010 (0.037)
Education Time	-0.017(0.0061)	-0.016 (0.0072)	-0.014 (.0078)	-0.017 (0.005)
Time of Death				-.104/-.162/-.198

Table 3: Parameter estimates and standard errors for the marginal random mixed model, linear mixed effects model, pattern-mixture model with multiple imputations, pattern-mixture model for deceased with multiple imputations for non-participants, and pattern-mixture model for deceased with time of death.

-0.0265 with a standard deviation of 0.8994. From Figure 1, the decline in cognitive function was dramatic among Whites who did not provided data at Cycle-2 and Cycle-4, when compared to Blacks. The decline in cognitive function was similar among complete-cases and patterns 1 through 6. However, the decline in cognitive function was different among patterns of the deceased. Cognitive function was lowest in the CCDD pattern among Whites. However, cognitive function was lowest in the CDDD pattern among Blacks. The decline in cognitive function had more variation among the Whites compared to Blacks. The change in cognitive function was shifted towards the null for Blacks.

We used the four modeling strategies described in the methods section to study the marginal change in cognitive function. The estimated mean decline over a 10-year interval using LMEM was -0.593, however, this estimate was -0.284 while accounting for the patterns of non-participation and death. Also, the estimate for decline in cognitive function based on baseline age reduced from -0.039 to -0.011, almost a third of the LMEM model estimate. The decline in cognitive function in terms of gender was almost half and no longer significant. The results from not adjusting for missing data are substantially different from adjusting for them. In other words, the estimate of change in cognitive function demonstrates minimal change among survivors compared to severe change among the deceased. Race is an important risk factor that can not only confound the decline in cognitive function but also other risk factors. Thus, we studied the decline in cognitive function among Blacks and Whites separately. Using LMEMs, almost all coefficients except the cross-sectional effect of age were different among Blacks and Whites. Males showed a slower decline in cognitive function among Whites, but not among Blacks. Education was significantly associated with decline in cognitive function among Blacks, but had no effect among Whites. The effect of education on the decline of cognitive function was not significant among Whites, but remained significant among Blacks.

The decline in cognitive function over 10-year period was -0.355 for PMM-1, whereas, the effect was -0.284 for PMM and -0.593 for LMEM. The change of cognitive function was slightly higher than PMM, but much lower than LMEM. The decline in interaction of age with time was consistent between the PMM and PMM-1 models. The value was about -0.011 for the two models. However, the attenuated effect of interaction of gender with time was no longer observed in PMM-1. The interaction of gender with time was 0.087 for PMM-1 and 0.082 for LMEM, whereas, 0.046 for PMM. Separately, among Blacks and Whites, the cross-sectional main effects were about the same for age, males, and years of education. However, the decline in cognitive function over a 10-year period was -0.355 for PMM-1, compared to -0.308 for PMM and -0.682 for LMEM among Whites, and -0.313 for PMM-1, compared to -0.242 for PMM and -0.544 for LMEM among Blacks. The effect of age on the decline of cognitive function had reduced from -0.049 for LMEM to -0.014 for PMM-1 among Whites, and from -0.033 for LMEM to -0.012 for PMM-1 among Blacks. These

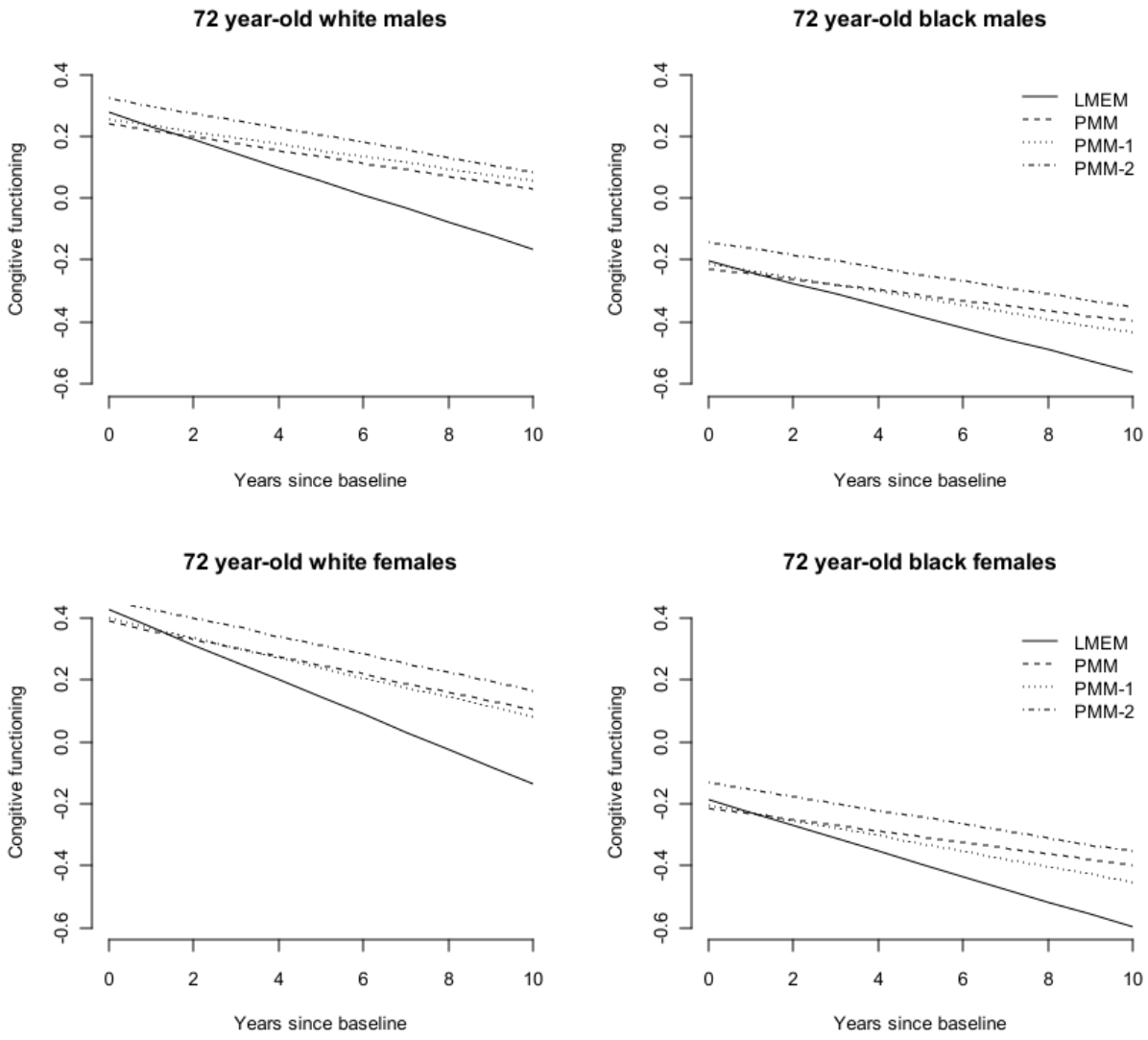

Figure 2: Decline in cognitive function of 72 year-old subjects using models linear mixed effect models and pattern mixture models by gender and race.

parameter estimates from the missing data models were significantly different from the LMEM models ($p<0.03$).

Finally, we fitted a pattern-mixture model with a categorical variable for time of death as one of the predictor variables. This approach allowed us to study the decline in cognitive function in terms of time of death. If a subject had not deceased or did not participate in the survey then they were classified into a different group. The model suggests that cognitive function was lower by 0.23 among those who were deceased at Cycle-4 in comparison to survivors. The average cognitive function at baseline among 75 year-old White females was 0.424 compared to 0.387, 0.344 and 0.354, for LMEM, PMM and PMM-1, respectively. This difference was significantly higher for PMM-2 model compared to other models. The intercept term attenuated towards the null for all models among Whites, but not among Blacks. The decline in cognitive function with respect to age was lower than PMM-1 and LMEM models. Using PMM-2, White males changed by an average of 0.055 over a 10-year period compared to females. However, this change was 0.12 using a LMEM model. Education was not associated with decline in cognitive function among Whites. However, education negatively impacted the decline in cognitive function among Blacks. Moreover, the effects of education on the decline were fairly stable across the different models.

The decline in cognitive function among 72-year old Blacks and Whites for the four models is shown in Figure 2. We can see from the figure that 72-year old Black males and females shown similar decline in cognitive function with LMEM exhibiting the most severe decline, where as PMM-2 showing the least severe decline. The decline among White females seems to be higher when compared to White males. The level of cognitive function was significantly higher among Whites when compared to Blacks. Figure 3 shows the decline in cognitive function among 80 year-old subjects. The figures suggest that 80 year-old White males and females have a higher decline in cognitive function compared to their counterpart Blacks. However, the effect of age on change of cognitive function was somewhat similar among the missing

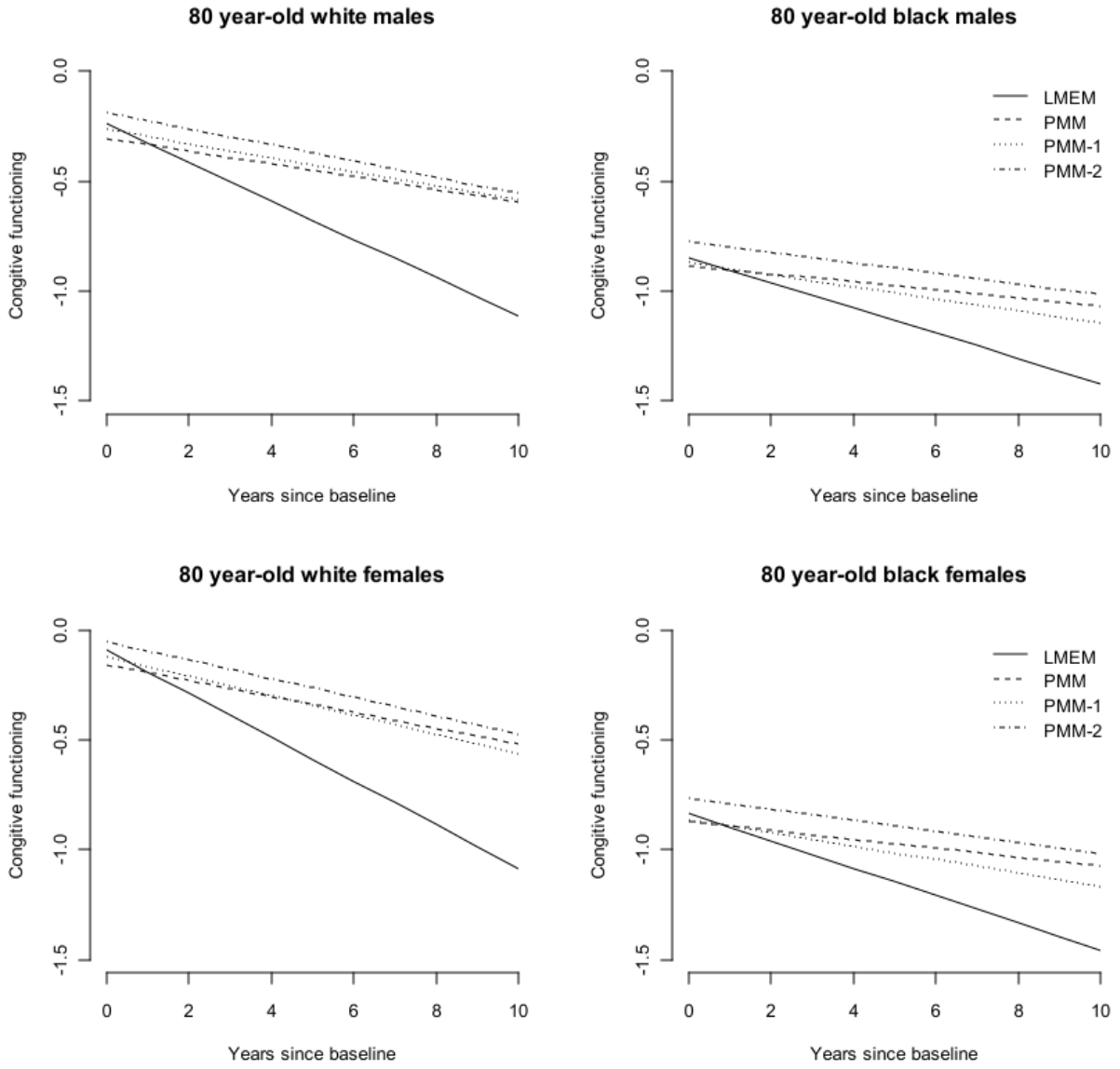

Figure 3: Decline in cognitive function of 80 year-old subjects using models linear mixed effect models and pattern mixture models by gender and race.

data models. The level of cognitive function was significantly lower among Blacks than Whites.

Discussion

In this article, we have illustrated the use of pattern mixture models for longitudinal studies with non-participation and death. The pattern mixture models borrow the fundamental idea of stratification from the traditional pattern mixture models, thus not requiring explicit specification of the non-participation and death mechanism. Unlike the traditional pattern-mixture model that fit a model for each pattern, we treat the pattern as nuisance parameters and explicitly model them as random. The parameters of interest are marginal after integrating out the random effects. This model avoids the over parameterization problem of the fixed pattern effects model while retaining the robustness.

The random pattern-mixture effects model assumes that conditional on the random effects the longitudinal outcome and the time to non-participation and death are independent. Considering this assumption, a pattern mixture model for the CHAP study was implemented and compared with our modeling approaches. We found substantial differences in the parameter estimates and inferences of these models. The change in cognitive function was significantly lower in LMEM models compared to pattern mixture models. If we used a fixed effect for time of death then we were able to describe the decline in cognitive function in terms of time of death and risk factors. The effect of patterns on the non-participation model and death was informative and accounted for the most differences in the study participants.

Some of the limitations of conducting such a sensitivity analysis cannot be ignored. We implemented fully conditional models to study the decline in cognitive function. However, partially conditional models using inverse probability weighted estimators can also be used to study the cognitive decline under missing at random assumption [27-28]. Implementing pattern mixture models can be time consuming and computationally difficult. The convergence of these models needs to be

carefully monitored and properly specified. Over specification of model can result in singularity issues and inefficient parameter estimates. Our models did not account for the fact that trajectories can be modified by time of death and other exogenous variables. In addition, in aging research one might want to model death separately, as death is usually an outcome of interest. The results of a study can vary significantly by the non-participation and death mechanism and one needs to take that into account while analyzing longitudinal aging data.

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