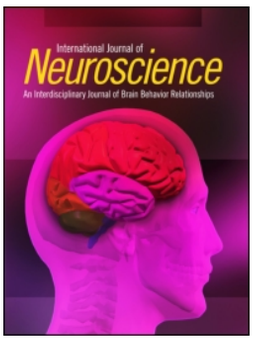

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Use, Maintenance, and Dose Effects of Cognitive Speed of Processing Training in Parkinson's Disease

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Abstract

Introduction: Recent research indicated that cognitive speed of processing training (SPT) improved Useful Field of View (UFOV) among individuals with Parkinson's disease (PD). The effects of SPT in PD have not been further examined. The objectives of the current study were to investigate use, maintenance, and dose effects of SPT among individuals with PD. **Methods**: Participants who were randomized to SPT or a delayed control group completed the UFOV at a six-month follow-up visit. Use of SPT was monitored across the six-month study period. Regression explored factors affecting SPT use. Mixed effects models were conducted to examine the durability of training gains among those randomized to SPT (n=44), and training dose effects among the entire sample (n=87). **Results**: The majority of participants chose to continue to use SPT (52%). Those randomized to SPT maintained improvements in UFOV performance. A significant dose effect of SPT was evident such that more hours of training were associated with greater UFOV performance improvements. The cognitive benefits derived from SPT in PD may be maintained for up to three months. **Conclusion**: Future research should determine how long gains endure and explore if such training gains transfer.

Key Words: Mixed effect models; non-pharmacological intervention; cognitive training

Use, Maintenance, and Dose Effects of Cognitive Speed of Processing Training in Parkinson's Disease

In addition to typical motor dysfunction, individuals with Parkinson's disease (PD) show deficits in various cognitive domains relative to healthy controls (e.g., 1, 2-5). Thus, recent interest has turned toward non-pharmacological interventions to improve cognitive performance, such as cognitive training.

Cognitive speed of processing and visual attention, as measured by the Useful Field of View Test (UFOV; 5), is impaired in PD. Among individuals with PD, poor performance is associated with reduced quality of life and independence due to driving impairments (5, 7, 14-16). Research with healthy older adults indicates that SPT can improve UFOV performance, and transfers to improved instrumental activities of daily living, driving mobility, and driving safety (17-20). Consequently, SPT has become of interest for persons with PD.

Various cognitive training programs have been investigated among those with PD, each focusing on different cognitive domains such as executive functioning (6), speed of processing (7), attention (8), or sequence production (9), with others training multiple cognitive domains (10-12). Results have been promising with immediate improvements observed in domains such as executive functioning (9, 12), memory (10, 12), speed of processing (7, 10), attention (10), visuospatial skills (10), and global cognitive function (11). However, few studies have examined longitudinal maintenance of training gains (13).

We examined SPT among people with PD in a randomized clinical trial (RCT) (7). Participants with PD were randomly assigned to either SPT, which was completed at-home, or a delayed treatment group (7). Immediately post-training, the SPT group showed significantly greater gains in UFOV performance than the control group. Although there is increasing evidence that cognitive training may be beneficial and many different programs are commercially available, the factors that affect individuals' use of cognitive interventions are unexplored. An objective of the present study was to examine use of SPT and determine

whether individual characteristics (e.g., demographics, cognitive status) affected such use. The second objective was to examine the durability of SPT gains among persons with PD. Although, recent longitudinal data indicate that SPT effects may last up to ten years in healthy older adults (21), no prior study has examined if SPT effects are maintained among persons with PD. A third objective of the present study was to examine dose effects of SPT in persons with PD. Previous research has found greater training gains with larger doses of SPT (22), but dose effects have not been examined in PD.

The objectives of the current study were to investigate use, maintenance, and dose effects of SPT among individuals with PD. We hypothesized that the majority of participants would continue to participate in the training program at home, that those randomized to SPT would maintain the improvements in UFOV performance previously observed at initial post-test (7), and that more hours of SPT would be associated with larger gains in UFOV performance.

Materials and Methods

Participants

Inclusion criteria and other study details including the CONSORT flow chart are published elsewhere (7). Ninety-three individuals were assessed for eligibility. Six of these individuals were not eligible. Eighty-seven participants were randomized to either SPT (n=44) ot the delayed control group (n=43). Participants had a mean age of 68.9 years, an average of 15.4 years of education. The sample was 62.1% male and 97.7% Caucasian. The University of South Florida Institutional Review Board approved the study, and written informed consent was obtained from all participants.

Procedure

Eligible participants completed a baseline testing visit and were randomized to either the SPT or delayed treatment condition (See Figure 1). The intervention, InSight, is a self-administered version of adaptive SPT, a computerized, process-based, cognitive training technique that involves perceptual practice targeting basic fluid abilities (23). InSight training

was completed at home by the participants. The program includes five exercises containing visual stimuli that progress from simple to complex in a gradual fashion as performance improves (i.e., adaptive in difficulty). See Table 1. As detailed elsewhere (7), participants were instructed to alternate between the daily recommended schedule, which included all five exercises, and choosing only the Road Tour exercise, which is most similar to a prior version of SPT that has shown substantial efficacy (18).

Immediately following the baseline visit, participants in the SPT condition were given the InSight software to take home and were instructed to begin with the goal of completing at least 20 hours over three months. Participants in the delayed control group were sent home after baseline as a no-contact control group. Post-test was scheduled 3 months after baseline for participants in both conditions (See Figure 1). Prior results of this RCT demonstrated greater gains in UFOV performance from baseline to three months among those randomized to training relative to controls (7).

After post-test, delayed control participants were given the SPT software and were instructed to complete at least 20 hours over the next three months. Participants in the SPT group continued to have access to the intervention, and were not provided specific instructions. All participants were invited to complete an additional study visit, six months after their baseline. See Figure 1. Therefore, all participants had access to the training prior to this six month follow-up visit. Participants' independent continued use of SPT was monitored to examine the likelihood of PD patients using the program. Participants completed the program at home, and hours of training completed were recorded by the software.

Measures

Mental status was assessed with the Mini Mental State Examination (MMSE). Scores of 24 or better were required for inclusion. Depressive symptoms were measured using the Center for Epidemiologic Depression Scale short-form (CES-D; 24). Participants indicated the number of days from the prior week that they felt or behaved in ways indicative of depression across 20

items with ratings ranging from 0 (less than one day per week) to 3 (5 to 7 days per week). Ratings were summed with a possible range of 0 to 60 with higher scores indicating more depressive symptoms.

Cognitive speed of processing for visual attention tasks was measured using the UFOV (25). This task has been well studied and is used in clinical practice among individuals with PD (5, 14-16). The UFOV includes three subtests of progressively increasing complexity. In each subtest, visual targets (cars and trucks) are shown on the computer screen at display durations ranging from 17 to 500 ms. Subtest 1 involves central target identification alone, measuring processing speed, while subtest 2 involves simultaneous identification of a central target and localization of a peripheral target, measuring divided attention. Subtest 3 is the same as subtest 2, except the peripheral target is embedded in distracters (triangles), measuring, selective attention. Scores for each subtest represent the briefest display durations at which the participant performed correctly 75% of the time, with higher scores indicating worse performance. Scores from all three subtests were summed with a possible range of 51 to 1,500ms. The UFOV has high reliability ranging from r=.74 -.81 (25).

Analyses

ANOVA and Chi-square analyses were conducted to determine if there were significant baseline differences between the SPT and control groups on depressive symptoms or descriptive characteristics: age, race, sex, and education.

Training Use. The average number of hours of training completed by each group at each time point was recorded. Regression analyses were performed to examine factors predicting training use including age, depressive symptomology, years of education, baseline MMSE score, and randomization group.

Two mixed effects models were used to investigate the hypotheses. An intent-to-treat approach was used in which all 87 participants randomized in the original study were included in analyses regardless of adherence to the training protocol or presence of missing data at any

time point. All 87 participants were included at all time points. Mixed effects models are an alternative to repeated measures ANOVA in modeling change over time(26). Similar to repeated measures ANOVAs, mixed effects models can statistically test main effects and interactions. Mixed models do not require complete data at all time points and can measure time as a continuous variable, making them commonly accepted for longitudinal data analysis (27, 28).

Maintenance of Training Gains. The first mixed effects model was conducted using only participants from the SPT group to investigate if the significant training gains previously observed in UFOV performance at initial post-test (7) were maintained at 6 months, with time as a predictor of cognitive performance. A no growth model with UFOV performance as the outcome was conducted first, including a fixed intercept, a random intercept, and a random residual as parameters. This model was followed by an unconditional growth model with time in weeks as the predictor and UFOV performance as the outcome, including the previous parameters, and adding a fixed effect of time as a parameter (See Table 2). A significant main effect of time would demonstrate that UFOV performance improved across the study period. Following a significant effect of time, planned contrasts were conducted using two paired sample t-tests to determine if there was a significant difference between baseline and post-test (confirming the previously observed training effect), as well as between initial post-test and follow up (to examine durability). No difference in UFOV performance between post-test and follow-up would indicate that the training gains endured.

Examination of Training Dose. A second mixed effects model was conducted among the entire sample to investigate whether the number of hours of SPT completed was a significant predictor of improved UFOV performance (i.e., dose effect). A no growth model with UFOV performance as the outcome was conducted, including a fixed intercept, a random intercept, and a random residual as parameters. This model was followed by an unconditional growth model with hours of SPT as the predictor and UFOV performance as the outcome including the previous parameters, and adding a fixed effect of hours of training as a parameter (See Table

2). A significant main effect of hours of SPT was expected, indicating that UFOV performance improved with increasing doses of training.

Results

Baseline Differences

Multivariate analysis of variance (MANOVA) indicated there were no differences between the SPT and control groups, Wilks λ=.99, $F(4,82)=.30$, $p=.88$, partial $\eta^2=.01$, in terms of age, $F(1,85)=.60$, $p=.44$, partial $\eta^2=.007$; education, $F(1,85)=.02$, $p=.09$, partial $\eta^2=.001$; depressive symptoms, $F(1,85)=.06$, $p=.81$, partial $\eta^2=.001$; or UFOV, $F(1,85)=.99$, $p=.32$, partial $\eta^2=.01$. Chi-square indicated the participants in the SPT and control conditions did not differ significantly in terms of sex, $\chi^2(1)=.09$, $p=.76$, or race, $\chi^2(1)<.001$, $p=.99$.

Training Use

At the end of the RCT, the SPT group had completed an average of 22.59 hours of training with an average of 10.98 of those hours spent specifically on the Road Tour exercise, while the control group participants had not yet completed any training. At the follow-up study visit, the SPT group had completed, on average, an additional 8.14 hours of training (30.73 hours total) with an average of 2.22 of the additional hours spent specifically on the Road Tour exercise (13.2 hours total of Road Tour). At follow-up, the control group had completed on average 23.45 hours of training, with an average of 10.48 of those hours spent specifically on the Road Tour exercise. Of those in the SPT group 52% completed additional training between post-test and follow-up on their own volition, 48% did not complete additional training. Among those in the control group 84% completed training between post-test and follow-up, and 16% did not complete any training.

MANOVA and Chi-square analyses compared the characteristics of the 52% of participants in the SPT condition who chose to complete additional training between post-test and follow up with those who did not. There were no significant differences at baseline between

these two groups on age, depressive symptomology, years of education, MMSE, UFOV performance, age at diagnosis, race, or sex, *p*'s>.05.

Multiple linear regression examined the association between hours of training completed and age, depressive symptoms, years of education, MMSE score and group assigned. This regression yielded non-significant results, $F(5,74)=0.82$, $p=.54$, $R^2=.06$, with neither age, depressive symptoms, years of education, MMSE score or randomization group being significantly associated with hours of training completed.

Training Maintenance

To examine the durability of training effects across six months, the first mixed effects model included only those randomized to SPT. Results are presented in Table 2. An unconditional growth model showed significantly better fit than an intercept-only model, Δ-2LL $\chi^2(1)= 23.53$, $p<0.05$. Findings indicated significant improvement in UFOV performance over time, $p<.001$. Fixed effects were estimated for both intercept and slope, but a random effect was estimated for intercept only, as the model failed to converge when a random effect for slope was included. Two planned contrasts were conducted using paired samples t-tests to determine if there was a significant difference between baseline and post-test, or between post-test and follow up. There was a significant difference between baseline and post-test, $t(32)=4.39$, $p<.001$, such that performance was better at post-test ($M=354.91$, $SD=285.47$) than at baseline ($M=497.06$, $SD=288.86$). However, the difference between post-test and second-post-test was not significant, $t(32)=.99$, $p=.33$, follow up ($M=333.70$, $SD=270.08$). This indicates that the training gains were maintained from post-test to follow up. See Figure 2.

Training Dose

Next, to examine the dose effect of the training, a mixed effects model was conducted that included all participants (N=87) from both SPT and control groups, as the control group completed training between initial post-test and follow up. Fixed effects were estimated for both intercept and slope, but a random effect was estimated for intercept only, as the model failed to

converge when a random effect for slope was included. A growth model using total number of hours trained as a predictor showed a significantly better fit than an intercept-only model, Δ-2LL $\chi^2(1)=53.11$, $p<0.001$, which indicated significant improvement in UFOV performance with greater hours of training, $p<.001$ (i.e., a dose-response effect). Among the entire study sample, more hours of SPT was associated with lower UFOV scores (i.e., better performance). Results are presented in Table 2.

Discussion

We examined use, maintenance, and dose effects of SPT among individuals with PD. The majority of participants continued to use SPT at home after the RCT. Our hypothesis that those randomly assigned to SPT would maintain the improvements in UFOV performance observed at initial post-test was supported. Our hypothesis that more hours of SPT would be associated with better UFOV performance was also supported. Our results showed that older adults with PD who were randomized to SPT longitudinally maintained the training gains observed at initial post-test. Further, larger doses of training were associated with greater performance gains.

It is encouraging that 52% of participants in the SPT group and 84% of participants in the control groups continued to use the program after the RCT ended. This provides real world evidence for the feasibility of and adherence to this program among persons with PD. However, there were no significant baseline differences between those who chose to continue using the program and those who did not. Further, none of our baseline demographics predicted number of hours completed. Thus, factors that significantly affect use of cognitive training remain yet unknown.

Prior work (7) showed that SPT is beneficial in those with PD. These finding extend this work by showing that the previously observed benefits from SPT are maintained 3 months after post-test. This is important because it suggests that the benefits of SPT do not immediately dissipate. The results are similar to other research with SPT in healthy and cognitively impaired

older adults, which suggests SPT training gains have lasting effects. Research from healthy older adults and those with mild cognitive impairment indicate that SPT gains may endure 5-10 years (21, 29). To our knowledge this is the first study to investigate whether cognitive training gains endure among persons with PD.

While there is a plethora of cognitive training literature, there is a relative dearth of research regarding the necessary dose or amount of training needed to see a benefit. There is even less information regarding necessary dose of cognitive training among those with PD. Our results show that increasing amounts of SPT were associated with better performance on the UFOV. Each hour of training was associated with 3.63 ms faster performance on the UFOV. If participants completed the instructed 20 hours of training, this would lead to an average 72.6 ms faster performance on the UFOV task, compared to the annualized declines of 15.6 ms slower performance on the UFOV task seen among healthy older adults (30). Future research should investigate if there is an optimal dose of cognitive training to see benefits. We did not observe plateaus of training gains in this study. In prior research among healthy older adults, we observed that during training participants commonly reached a plateau of performance at a display speed of 120 ms when simultaneous identification of a central target and localization of a peripheral target among distractors was required. The dose required to reach this threshold of performance varied among individuals.

Strengths and Limitations

A strength of the current study is its relatively large sample size. The original RCT to which this is a follow-up is the largest cognitive training trial in PD to date (31). The RCT provided sufficient evidence for the feasibility and efficacy of computerized cognitive training among individuals with PD. Further, our results demonstrate the durability of training gains after immediate post-test. Thus, cognitive training gains in PD do not immediately dissipate. Another strength of this study is its examination of training dose, an area which is understudied. Results show stronger effects with larger doses.

The current study does have limitations. The sample included primarily highly educated Caucasians in mild to moderate stages of PD; therefore, the results may not generalize to minorities, those with lower education levels, or those in later stages of the disease. Interestingly, prior research with healthy older adults suggests that race and education do not significantly impact SPT gains (19). The study was a field trial of effectiveness, so participants' access to the intervention was not prohibited. A RCT is needed to quantify maintenance effects. Although, it is not clear if the UFOV gains would have been maintained without continued access to the software, it is encouraging that more than 50% chose to continue use of the intervention on their own. Further our use of a delayed control group is a limitation. An active control group would be ideal. At the same time, other studies have found large effects of SPT relative to active control groups (e.g., 32). One final limitation is that participants and experimenters were not blinded as to condition.

Implications and Future Research

Future research should explore who is and is not likely to use cognitive training programs and why. Future research should also investigate if there is an optimal dose of cognitive training to see benefits, and if performance plateaus are evident with larger doses. SPT is a particularly unique cognitive training program in that it has shown transfer to everyday functional outcomes, such as driving (20). Future research should examine if SPT also transfers to everyday functional outcomes in PD and also include longer intervals of follow up to examine the long term durability of training gains in this population. SPT may be a viable non-pharmacological intervention option that can be self-administered by individuals with PD to improve their cognitive performance with potentially lasting effects.

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Authors' Roles: Drs. Valdés and Edwards contributed to the research project: conception, organization, execution; statistical analysis: design, execution, review and critique; manuscript: writing of the first draft, review and critique. Drs. O'Connor and Andel contributed to statistical analysis: design, execution, review and critique; manuscript: review and critique. Drs. Hauser and Uc contributed to the research project: conception, execution; statistical analysis: design, review and critique; manuscript: review and critique.

Disclosures of Interest:

J. Edwards worked as a limited consultant to Posit Science, Inc., the company that marketed InSight, from June to August 2008, and currently serves on the data safety and monitoring board of NIH grants awarded to employees of Posit Science.

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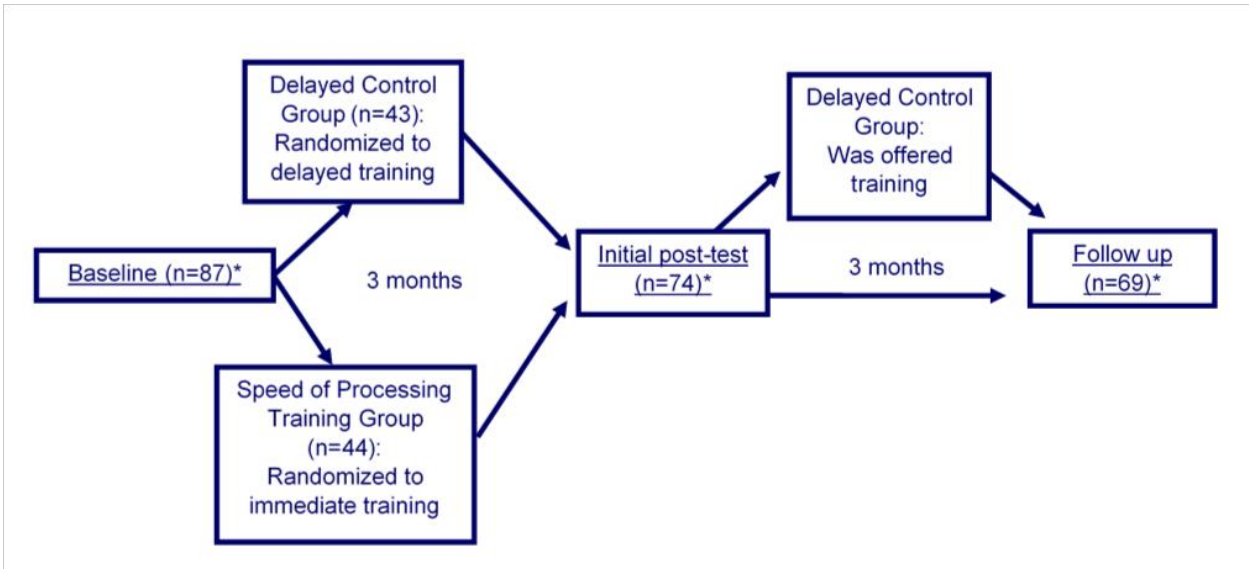
Delayed Control Group (n=43): Randomized to delayed training
Baseline (n=87)*
3 months
Speed of Processing Training Group (n=44): Randomized to immediate training
Initial post-test (n=74)*
Delayed Control Group: Was offered training
3 months
Follow up (n=69)*

Fig. 1.

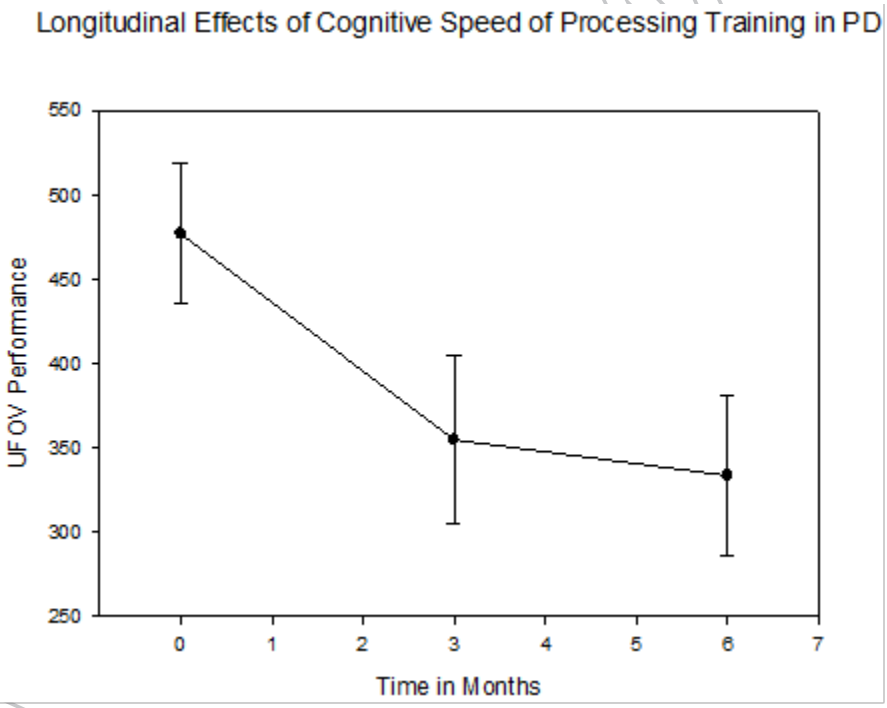
Longitudinal Effects of Cognitive Speed of Processing Training in PD
UFOV Performance
550
500
450
400
350
300
250
0
1
2
3
4
5
6
7
Time in Months

Fig. 2.

Table 1

Speed of Processing Training Program Exercises

Exercise	**Targeted Ability**	**Description**
Sweep Seeker	Visual processing	Identify order of visual sweeps; finer & faster sweeps
Bird Safari	Visual target identification	Visual discrimination of peripheral targets; degrading visual conditions & increasing speed of presentation
Jewel Diver	Visual tracking speed & memory	Track & remember visual targets; increasing number, speed, & background complexity
Road Tour	Visual attention	Discriminate center target & locate peripheral target; increasing speed & background complexity
Master Gardener	Visual speed & memory	Detect & remember targets; increasing speed & background complexity

Table 2

Mixed effects models: Training durability and effect of training dose on Useful Field of View performance.

	Analysis 1: Training Durability		Analysis 2: Effect of Training Dosage	
	No Growth Model	Unconditional Growth Model	No Growth Model	Conditional Growth Model
Value	Estimate *(SE)*	Estimate *(SE)*	Estimate *(SE)*	Estimate *(SE)*
-2LL	1508.82	1485.28	3167.34	3126.16
AIC	1514.82	1493.28	3173.34	3134.16
Parameters	3	4	3	4
Fixed Effects				
Intercept	401.59 *(38.80)***	460.48 *(40.40)***	391.83 (27.17)***	427.73 (27.95)***
Time	-----	-5.26 *(.99)***	-----	-----
InSightHours	-----	-----	-----	-3.63 (.64)***
Random Effects				
Intercept	57520.90 *(14200.30)***	60762.62 *(14295.61)***	57075.50 (9866.60)***	58906.38 (9914.22)***
Residual	20996.53 *(3627.50)***	14677.90 *(2544.82)***	19925.48 (2336.19)***	16352.48 (1924.85)***

Note. ***p<.001. Analysis 1, n = 44, only those randomized to immediate training. Analysis 2, n = 87, the entire sample regardless of randomization or adherence. Those with missing data were included in the models.