Citation:

Mercieca-Bebber, R. L., M. A. Price, M. L. Bell, M. T. King, P. M. Webb and P. N. Butow (2017). "Ovarian cancer study dropouts had worse health-related quality of life and psychosocial symptoms at baseline and over time." Asia Pac J Clin Oncol **13**(5): e381-e388.

Title: Ovarian cancer study dropouts had worse health-related quality of life and psychosocial symptoms at baseline and over time

Abstract

Aims

Monotone missing data, or study dropout is a major barrier to high-quality patient-reported outcome (PRO) data collection, particularly in patients with cancer as those with worsening health are more likely to drop out. To test the hypothesis that ovarian cancer patients with worse PROs would drop out earlier, we examined how patients differed by time of dropout on patient-reported health-related quality of life (HRQOL), anxiety, depression, optimism and insomnia.

Methods

This analysis included PRO data from 619 women with Stage II-IV ovarian cancer participating in the population-based Australian Ovarian Cancer Study (AOCS) – Quality of Life (QOL) sub-study, in which participants completed PRO questionnaires at three-monthly intervals for up to 21 months. For this analysis, participants were stratified by time of dropout. Mean scores of PROs at each timepoint were graphed and trends examined. Pearson r correlations were calculated to examine the relationship between time of dropout and each PRO variable.

Results

Participants who dropped out earlier had significantly worse baseline HRQOL ρ=.20,p<.0001,95%CI[0.13,0.28] and higher depression scores ρ=-.17,p<.0001,95%CI[-0.24,-0.09], which both declined at a faster rate over time than for participants who remained in the study longer. Similar patterns were evident for anxiety, and to a lesser extent, optimism, however results didn't achieve statistical significance. Insomnia appeared unrelated to dropout in this cohort.

Conclusions

Poorer HRQOL and greater depression were predictive of time of dropout. These results highlight the importance of collecting auxiliary data to inform careful and considered handling of missing PRO data during analysis, interpretation and reporting.

Keywords: quality of life, depression, ovarian neoplasms, patient outcome assessment.

Manuscript

Background

Patient reported outcomes (PROs) are patients' self-reports, usually completed by questionnaire, of symptoms, aspects of functioning or multi-dimensional constructs, including health-related quality of life (HRQOL) [1]. PRO measures have the potential to provide valuable information about the effects of disease and treatment on the patient, from the patient's perspective. However, a major barrier to high-quality PRO data collection is missing data; particularly unit non-response – when PRO data is missing for a whole time-point. Unit non-response at the patient level can further be classified into three groups: i) monotone missing data refers to patient dropout or attrition, i.e. a patient has completed initial PRO assessments but then drops out and is never observed again [2-4]; ii) intermittent missing data occurs where a patient is observed again after a missed assessment [2-6]; or iii) missing initial PRO data due to late study entry [4].

The focus of this article is monotone missing PRO data, in particular to illustrate the bias that can arise in data analysis and interpretation depending on how monotone missing data are addressed. Commonly used approaches such as excluding patients with missing data or using simple imputation can lead to biased interpretation [7]. For example, if patients who drop out have greater health decline, these approaches may lead to a false conclusion that the sample had better outcomes than was the true case. This is because PROs are often predictive of survival [8]. Experts recommend addressing missing PRO data using tailored imputation methods, based on scrutiny of individual data and consideration of why PRO data is missing (the 'missing data mechanism') [2, 9]. [For a detailed discussion we direct readers to the following sources [2, 6, 10]].

Predictors of missing PRO data have been studied in a range of research settings. In cancer clinical trials, patients with worse baseline HRQOL [6] and worse baseline symptom, emotional and physical functioning scores [5] exhibited higher rates of dropout. HIV-positive patients with higher depressive symptoms were more likely to drop out of a pain management study, regardless of their illness severity [11]. In a review of chronic headache, stress management and weight reduction studies, psychological variables were often predictive of attrition [12]. However, to our knowledge, the relationship between PROs and dropout in population-based cohort studies has not been studied.

PRO data may be missing for a diverse range of reasons in disease population-based cohort studies, owing to participant heterogeneity in disease stage or treatments, as well as difficulties in following up such large numbers of patients from diverse recruiting sites over the life of the study. Ovarian cancer provides a good example of the complexities inherent in assessing PROs longitudinally in population cohort studies. Approximately 75% of women with ovarian cancer present with advanced stage disease, due to limitations of effective screening methods for those at population risk and/or absence or vagueness of symptoms during earlier stages of the disease[13, 14]. Ovarian cancer treatment usually involves debulking surgery with neoadjuvant or adjuvant chemotherapy, and in many cases, maintenance therapy and therapy for recurrent disease[14]. The overall expected five-year survival rate is only 44% [15], however survival rates differ significantly depending on stage at diagnosis: with up to 95% of patients with Stage I disease surviving five years compared to <30% with advanced disease[13]. Thus, in a population-based cohort study of women with ovarian cancer, many enrolled participants will be expected to die during follow up, resulting in monotone missing PRO data. However monotone missing data may also result from reasons other than death, including health-and non-health related factors, further complicating decisions about how missing data should be handled for analysis [16]. To our knowledge, the relationship between PROs and dropout has not previously been studied in ovarian cancer population-based cohort studies.

Aims

Based on the expectation that patients with worse HRQOL would be more likely to drop out earlier than other patients, the primary aim of the present analysis was to compare the HRQOL of ovarian cancer patients in a population-based cohort study by time of dropout. Our secondary aim was to compare how patients differed by time of dropout on other key PROs, namely anxiety, depression, optimism and insomnia. These variables were chosen as we speculated they could impact a patient's willingness and ability to continue completing research-based PROs in the context of their illness. We hypothesised that patients who dropped out of the trial would have poorer HRQOL, higher anxiety, higher depression, lower optimism and more insomnia than those who continued to final assessment.

Materials and Methods

The Australian Ovarian Cancer Study (AOCS) and QOL sub-study

Existing PRO data from an ovarian cancer population-based cohort study: the Australian Ovarian Cancer Study (AOCS) QOL sub-study [17-19] was utilised for this analysis. Details of the parent AOCS [17] and QOL sub-study [18, 19] sampling and recruitment methods are detailed elsewhere. In brief, the AOCS recruited a population-based sample of women aged 18-79 years newly diagnosed with primary epithelial ovarian cancer (including fallopian tube and primary peritoneal cancer) between 2002 and 2006 through treatment centres and state cancer registries [17]. The QOL sub-study commenced in May 2005 and involved a total of 798 participants; including women already participating in the parent study and newly diagnosed patients. Participants with Stage II-IV disease completed PRO measures every three months for 21 months, or until death. Participants with Stage I disease completed PRO measures less frequently [19].

PRO measures

The PROs included in this analysis include the global HRQOL score of the Functional Assessment of Cancer Therapy - Ovarian Cancer (FACT-O version 4) questionnaire [20], anxiety and depression using the two sub-scales of the Hospital Anxiety and Depression Scale (HADS) [21]; optimism using the Life Orientation Test–Revised (LOT-R) [22]; and insomnia using the Insomnia Severity Index (ISI) [23].

Participants

AOCS QOL sub-study participants with confirmed Stage II-IV ovarian cancer who completed at least one PRO assessment are included in this analysis. We excluded participants with Stage I disease due to their different assessment schedule, and participants whose disease stage was unclear from available data.

Analysis

Participants were stratified into eight groups according to the number of PRO assessment time points completed. For example, participants who completed two PRO assessments, at study entry and three months later, were grouped together (T2 group), and participants who completed six consecutive assessments were grouped together (T6). There were 37 intermittent missing values in our dataset, which were imputed using a single imputation of the expectation-maximization algorithm. This represents less than 1% (37/3820) observations in our analysis.

For each PRO, the mean score for each group at each time point was graphed. We computed the Pearson's correlation between baseline score for each PRO variable and the time of participant dropout. All analyses were performed in SAS version 9.4.

Results

A total of 619 participants are included in this analysis and almost half 288 (47%) these participants had monotone missing PRO data. Table 1 shows the number of participants who dropped out after each scheduled

PRO assessment; forming the analysis groups for this analysis. Most women (87%) had Stage III/IV disease at diagnosis, n=159 (26%) participants' disease progressed during the study and n=243 (39%) died within the study period.

<<insert table and figures approximately here>>

HRQOL

Figure 1 shows that patients who dropped out of the study earlier had worse baseline HRQOL on average and more severe decreases in HRQOL over time, until they ultimately dropped out. The steepest declines in mean HRQOL occurred between the two final assessments for most groups. Participants who completed the fewest assessments (Group T1) entered the trial with lowest HRQOL. Participants who dropped out later in the study (Groups T7 and T8) entered the study with highest HRQOL. Mean HRQOL for the T8 group remained relatively stable across the study duration. Baseline HRQOL was significantly correlated with time of dropout: ρ=.20, p<.0001, 95% CI [0.13, 0.28].

Anxiety

Figure 2 shows mean anxiety scores for each dropout group. In all groups the mean anxiety score was in the normal range throughout the study, with the exception of the T6 group whose average anxiety score was in the subclinical range throughout. Figure 2 also shows that the T8 group experienced the least fluctuation in anxiety scores and maintained lower mean anxiety throughout the study, although this we did not test this claim statistically. Baseline anxiety score was not significantly correlated with time of drop out ρ=-.05,p=.24, 95% CI [-013, 0.03].

Depression

Figure 3 shows mean depression scores for each dropout group. The T8 group maintained lowest mean depression throughout the study. Groups T1, T2, T3 and T6 entered the study with higher depression scores, and continued to experience higher depression than other groups until their time of dropout. T6 was the only group where the mean score reached the HADS sub-clinical depression threshold, which occurred at 12 month follow-up. All groups experienced slight increases in depression over time, and most groups experienced steepest increases in depression between their final two PRO assessments. Pearson's correlation showed that baseline HADS depression score was correlated with time of drop out ρ=-.17,p<.0001, 95% CI [-0.24, -0.09].

Optimism

Figure 4 shows mean optimism scores for each dropout group. Groups T4, T5, T7 and T8 reported highest optimism, whereas Groups T2 and T6 reported lowest mean optimism. All groups but T8 experienced a decline in optimism between their final two assessments. Baseline optimism score did not correlate with time of drop out: ρ=.02,p=.70, 95% CI [0.06, 0.10].

Insomnia

Figure 5 shows mean insomnia scores for each group. All groups experienced fluctuations in insomnia, predominately within the 'no impairment' range. Group T4 had lowest insomnia (least impairment) on average. Baseline insomnia score did not correlate with dropout: ρ=.004,p=.92, 95% CI [-0.08, 0.08].

Discussion

This study examines the relationship between PROs and time of dropout in a large longitudinal cohort study of women with ovarian cancer, specifically examining the relationship between baseline PRO scores and dropout, and the change in PROs overtime between participants stratified by time of dropout. Participants who dropped out earlier had significantly worse baseline HRQOL and depression. They also had steeper declines in HRQOL and increases in depression overtime, particularly in the assessments prior to dropout, compared to those who completed more PRO assessments. Similar patterns were evident for anxiety, and to a lesser extent, optimism. Insomnia appeared unrelated to dropout in this cohort. These patterns may reflect a relationship between HRQOL, depression and dropout. The methodology used in this study to identify patterns in missing PRO data is one useful way to determine the potential missing data mechanism; which is a prerequisite to making a sensible choice of imputation method/s for missing PRO data.

As demonstrated by this study, not all PROs are predictive of drop out. The PROs that are predictive are likely to vary according to the clinical context of the population under study, and the study design and aims. The ability to predict participants at higher risk of dropping out based on baseline PRO scores can potentially assist researchers in developing strategies to improve PRO data completeness. Based on our finding that depression was predictive of dropout, we question whether earlier uptake of psychosocial referral options in patients with high baseline depression scores might improve PRO completion rates, as well as reducing symptoms of depression. This may be an interesting direction for future research.

As already noted, HRQOL has predicted survival in other studies [8], and in such cases, missing HRQOL data is not always preventable. Thus poor baseline HRQOL scores should prompt researchers to ensure auxiliary data is collected to assist in determining the missing data mechanism. Indeed we and others recommend that auxiliary data, such as clinician-rated Karnovsky or ECOG status, should be collected in all PRO studies [6]. Additionally, having site staff record reasons for incomplete PRO questionnaires using standardised forms can further inform choice of imputation method. Many examples of such forms have previously been published [4, 24, 25].

Although a large number of participants in our study experienced disease progression or died during the follow-up period, it is unlikely that all missing PRO data was due to worsening health status. Indeed, other cancer studies have reported logistic and administrative factors as a major cause of missing PRO data; variables often unrelated to patients' health [24]. Other variables may be influencing dropout. For example, despite remaining in the study for 15 months, the T6 group experienced negative symptoms across all domains tested over the study's duration. Possibly their lower optimism, and higher depression and anxiety at baseline was reflecting time since diagnosis, disease severity (86% had Stage 3 disease at diagnosis) and treatment status. These PRO domains also worsened overtime in the T6 group. While this may reflect a chance finding, it does underline the importance of not underestimating the influence of sampling, disease and treatment trajectory when examining missing PRO data.

The QOL study sample were recruited via an existing population-based cohort study involving women with ovarian cancer, at any stage of treatment, and the ensuing lack of a uniform time of entry into the study complicates data analysis and interpretation. However, it is ideal for the purpose of illustrating the importance of considering the way in which monotone missing PRO data is dealt with and interpreted. Thus our results showing large differences in PROs may be exaggerated compared to those observable in clinical trials or other designs with a more homogenous trial sample and baseline assessment point. Nevertheless, our results are similar to findings of a recent advanced stage renal carcinoma study, in which both the control and experimental group patients who dropped out earlier had worse baseline HRQOL [6].

Our findings cause us to echo the recommendations of others. Complete case analyses (without prior imputation of missing PRO data) should be avoided for PRO analyses, particularly in cancer research samples where a decline in PROs may be expected over the life of the study, or in studies with high missing data rates [2, 3, 6, 10, 25]. Using Figure 1 as an example, a complete case analysis would include only the Group T8 line,

thus missing all of the patients who dropped out and had worse HRQOL over the study duration. Apart from a significant reduction in sample size (n=331 compared to n=619) and statistical power, the results would falsely indicate that HRQOL was stable over time. We also recommend that imputation and analysis decisions are informed by close scrutiny of PRO data, including rates and reasons for missing data. These decisions should be reported and justified in research publications to facilitate interpretability and generalisability of findings.

In conclusion, baseline HRQOL and depression scores were predictive of time of dropout and trends in HRQOL, anxiety and depression overtime differed by time of dropout in this population-based cohort study of women with ovarian cancer. These results highlight the importance of careful and considered handling of missing PRO data during analysis, interpretation and reporting as well as the importance of implementing strategies to minimise the problem of missing PRO data, such as collecting auxiliary data and recording reasons for missing PRO data.

Acknowledgements

This study was funded by The Cancer Councils of New South Wales and Queensland (RG 36/05). Financial support for the parent study was provided by U.S. Army Medical Research and Materiel Command under DAMD17-01-1-0729; National Health and Medical Research Council (NHMRC) grants 400413, 400281, 199600; Cancer Councils of New South Wales, Queensland, South Australia, Tasmania, Victoria and Western Australia. RMB supported by funding from Sydney Catalyst and the Cancer Institute New South Wales. MK is supported by the Australian Government, courtesy of Cancer Australia. PW and PB are supported by the Australian Government through NHMRC Fellowships.

The Australian Ovarian Cancer Study gratefully acknowledges the women who participated in these research programs, study nurses and research assistants; Institutions and investigators represented within AOCS http://www.aocstudy.org ; clinical and scientific collaborators and New South Wales Hospitals: John Hunter, North Shore Private, Royal Hospital for Women, Royal North Shore, Royal Prince Alfred, Westmead and the NSW Cancer Registry; Queensland Hospitals: Mater Misericordiae, Royal Brisbane and Women's, Townsville, Wesley, and the Queensland Cancer Registry; South Australian Hospitals: Flinders Medical Centre, Queen Elizabeth, Royal Adelaide, Burnside War Memorial, and the South Australian Cancer Registry; Tasmania: Royal Hobart Hospital; Victorian Hospitals: Freemasons, Mercy Hospital for Women, Royal Women's, and the Victorian Cancer Registry; Western Australian Hospitals: King Edward Memorial, St John of God (Subiaco), Sir Charles Gairdner; and Western Australia Research Tissue Network (WARTN), Western Australian Cancer Registry.

References

1. FDA. Guidance for Industry: P*atient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*. In. 2009.
2. Fairclough DL, Peterson HF, Cella D, Bonomi P. Comparison of several model-based methods for analysing incomplete quality of life data in cancer clinical trials. *Statistics in Medicine* 1998; **17**: 781-796.
3. Troxel AB, Fairclough DL, Curran D, Hahn EA. Statistical analysis of quality of life with missing data in cancer clinical trials. *Statistics in Medicine* 1998; **17**: 653-666.
4. Curran D, Bacchi M, Schmitz SFH et al. Identifying the types of missingness in quality of life data from clinical trials. *Statistics in Medicin*e 1998; **17**: 739-756.
5. Moinpour CM, Lovato LC. Ensuring the quality of quality of life data: the Southwest Oncology Group experience. *Statistics in Medicine* 1998; **17**: 641-651.
6. Bell ML, Fairclough DL. Practical and statistical issues in missing data for longitudinal patient-reported outcomes. *Stat Methods Med Res* 2014; **23**: 440-459.
7. Bell ML, Fiero M, Horton NJ, Hsu C-H. Handling missing data in RCTs; a review of the top medical journals. *BMC Medical Research Methodology* 2014; **14**: 118.
8. Gotay CC, Kawamoto CT, Bottomley A, Efficace F. The prognostic significance of patient-reported outcomes in cancer clinical trials. *J Clin Oncol*. 2008; **26**: 1355-1363.
9. Rubin D. Inference and missing data. B*iometrika* 1976; **72**: 359-364.
10. Fielding S, Fayers PM, Ramsay CR. Investigating the missing data mechanism in quality of life outcomes: a comparison of approaches*. Health & Quality of Life Outcomes* 2009; **7**: 57.
11. Evans S, Fishman B, Haley A, Spielman LA. Predictors of attrition in HIV-positive subjects with peripheral neuropathic pain. *AIDS Care* 2004; **16**: 395-402.
12. Davis M, Addis M. Predictors of attrition from behavioral medicine treatments. *Annals of Behavioral Medicine* 1999; **21**: 339-349.
13. van Nagell JR, Jr., Pavlik EJ. Ovarian cancer screening. *Clinical Obstetrics & Gynecology* 2012; **55**: 43-51.
14. Jelovac D, Armstrong DK. Recent progress in the diagnosis and treatment of ovarian cancer. *CA: A Cancer Journal for Clinicians* 2011; **61**: 183-203.
15. American Cancer Society. Cancer Facts & Figures 2014. In. Atlanta: 2014.
16. Curran D, Bacchi M, Schmitz SF et al. Identifying the types of missingness in quality of life data from clinical trials. *Stat Med.* 1998; **17**: 739-756.
17. Jordan SJ, Green AC, Whiteman DC et al. Serous ovarian, fallopian tube and primary peritoneal cancers: a comparative epidemiological analysis. *Int J Cancer.* 2008; **122**: 1598-1603.
18. Price MA, Bell ML, Sommeijer DW et al. Physical symptoms, coping styles and quality of life in recurrent ovarian cancer: a prospective population-based study over the last year of life. *Gynecol Oncol*. 2013; **130**: 162-168.

19. Price MA, Zachariae R, Butow PN et al. Prevalence and predictors of insomnia in women with invasive ovarian cancer: anxiety a major factor. *Eur J Cancer.* 2009; **45**: 3262-3270.

20. Basen-Engquist K, Bodurka-Bevers D, Fitzgerald MA et al. Reliability and validity of the functional assessment of cancer therapy-ovarian. *J Clin Onco*l. 2001; **19**: 1809-1817.

21. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983; **67**: 361-370.

22. Scheier MF, Carver CS, Bridges MW. Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem): a reevaluation of the Life Orientation Test. *J Pers Soc Psych*ol. 1994; **67**: 1063-1078.

23. Morin C. *Insomnia: psychological assessment and management*. New York: Guildford Press 1993.

24. Bernhard J, Cella DF, Coates AS et al. Missing quality of life data in cancer clinical trials: serious problems and challenges. *Statistics in Medicine* 1998; **17**: 517-532.

25. Curran D, Molenberghs G, Fayers PM, Machin D. Incomplete quality of life data in randomized trials: missing forms. *Statistics in Medicine* 1998; **17**: 697-709.

List of Tables and Figures

Table 1: Analysis groups for all PROs, according to the number of PRO assessments completed

Analysis Group*	Months since study entry	Stage 2 disease		Stage 3 disease		Stage 4 disease		Total in each analysis group	
		N	%	N	%	N	%	N	% (cumulative)
T1	0	6	11.76	43	84.31	2	3.92	51	8.24
T2	3	3	6.52	39	84.78	4	8.70	46	15.67
T3	6	2	4.44	39	86.67	4	8.89	45	22.94
T4	9	6	11.11	42	77.78	6	11.11	54	31.66
T5	12	4	11.11	28	77.78	4	11.11	36	37.48
T6	15	3	10.34	25	86.21	1	3.45	29	42.16
T7	18	5	18.52	19	70.37	3	11.11	27	46.53
T8	21	50	15.11	246	74.32	35	10.37	331	100
Total	-	79	12.76	481	77.71	59	9.53	619	100

*Participants grouped according to the final PRO assessment completed prior to dropping out of the study. The T8 group did not drop out.

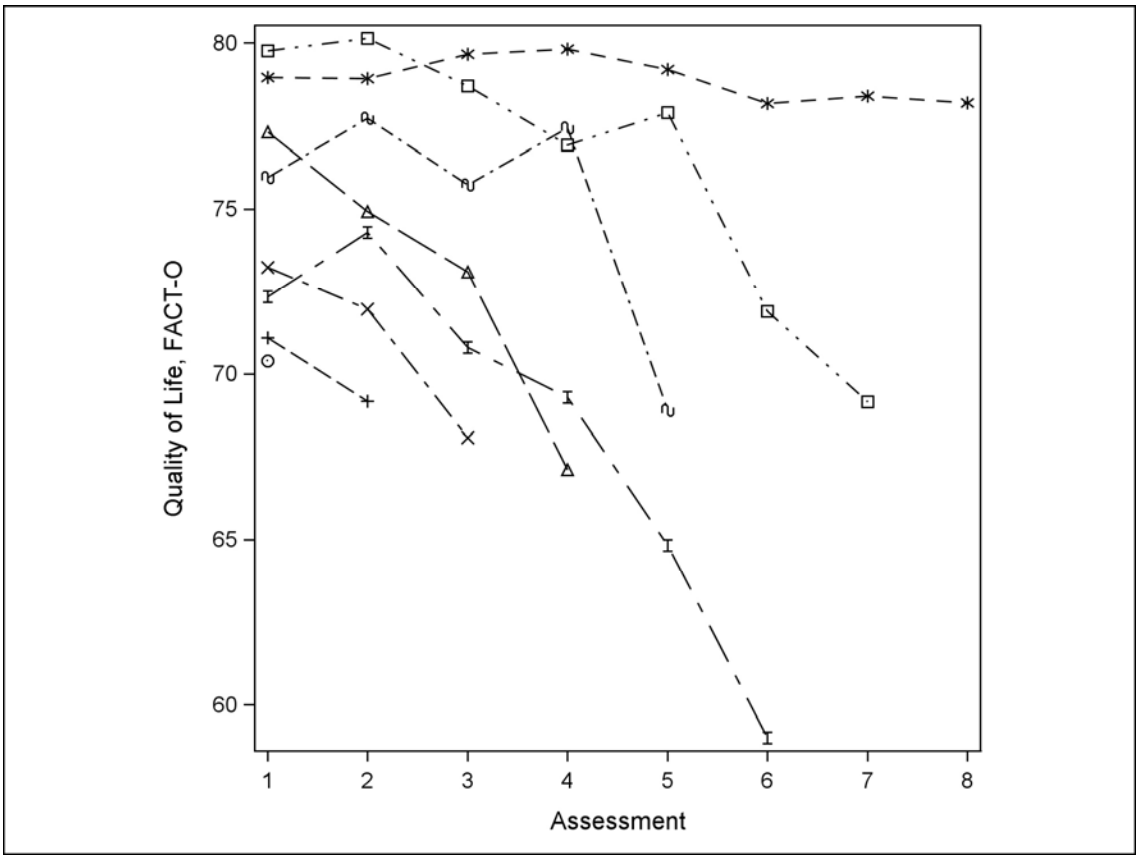


Fig. 1. Mean HRQOL (FACT-O) over time, stratified by time of participant dropout.
(Higher scores indicate better HRQOL).

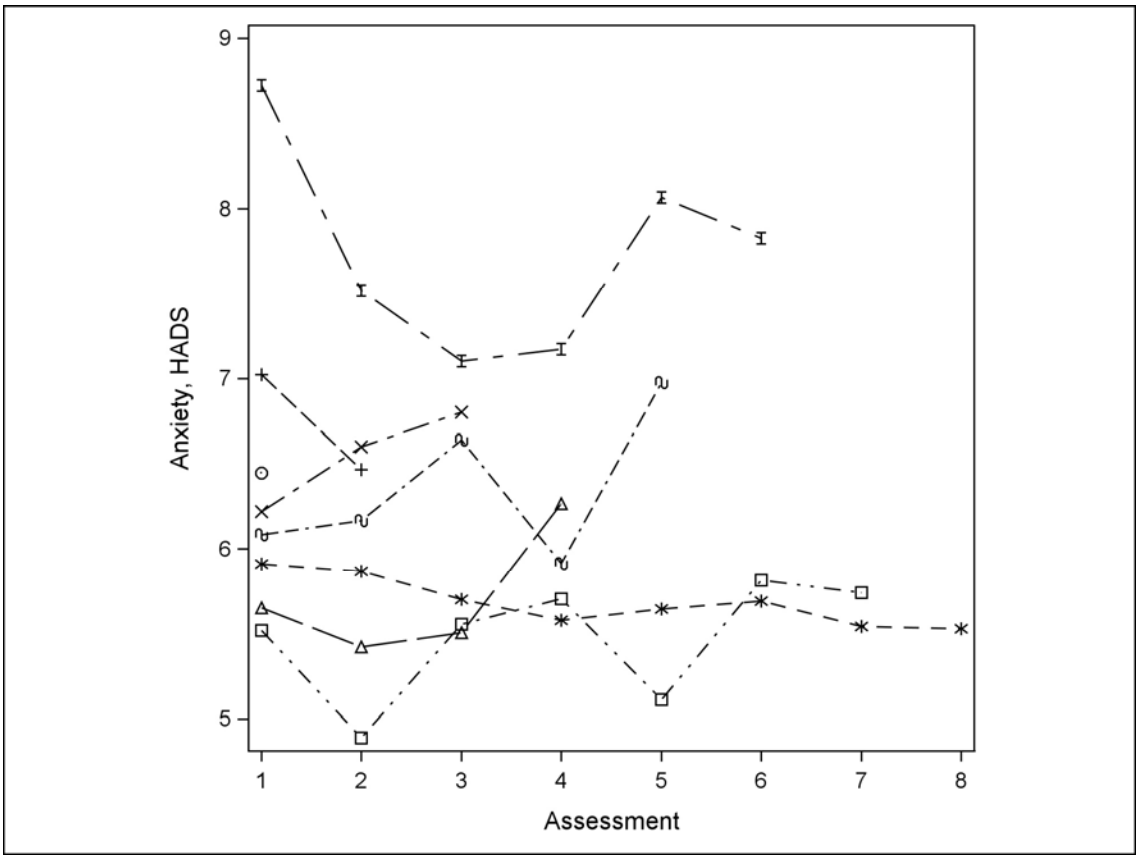


Fig. 2. Mean Anxiety (HADS) over time, stratified by time of participant dropout.
(Higher scores indicate higher [worse] anxiety)

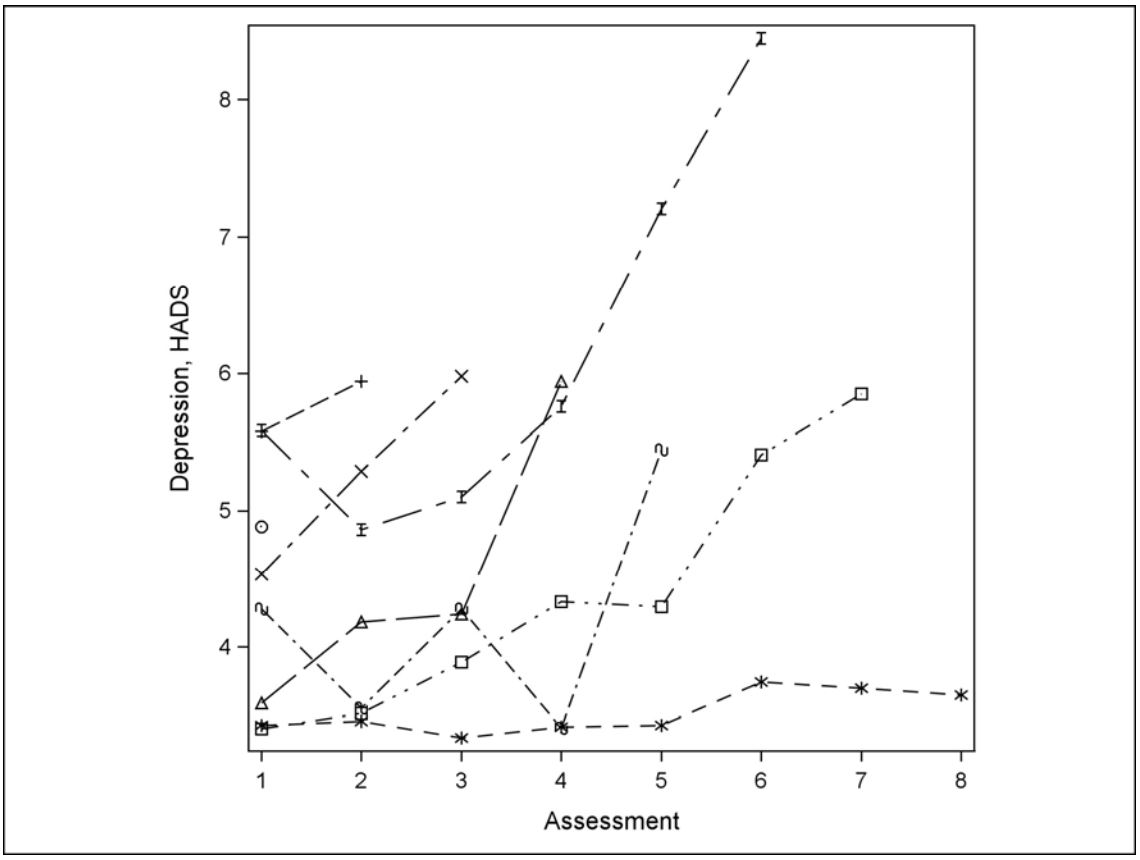
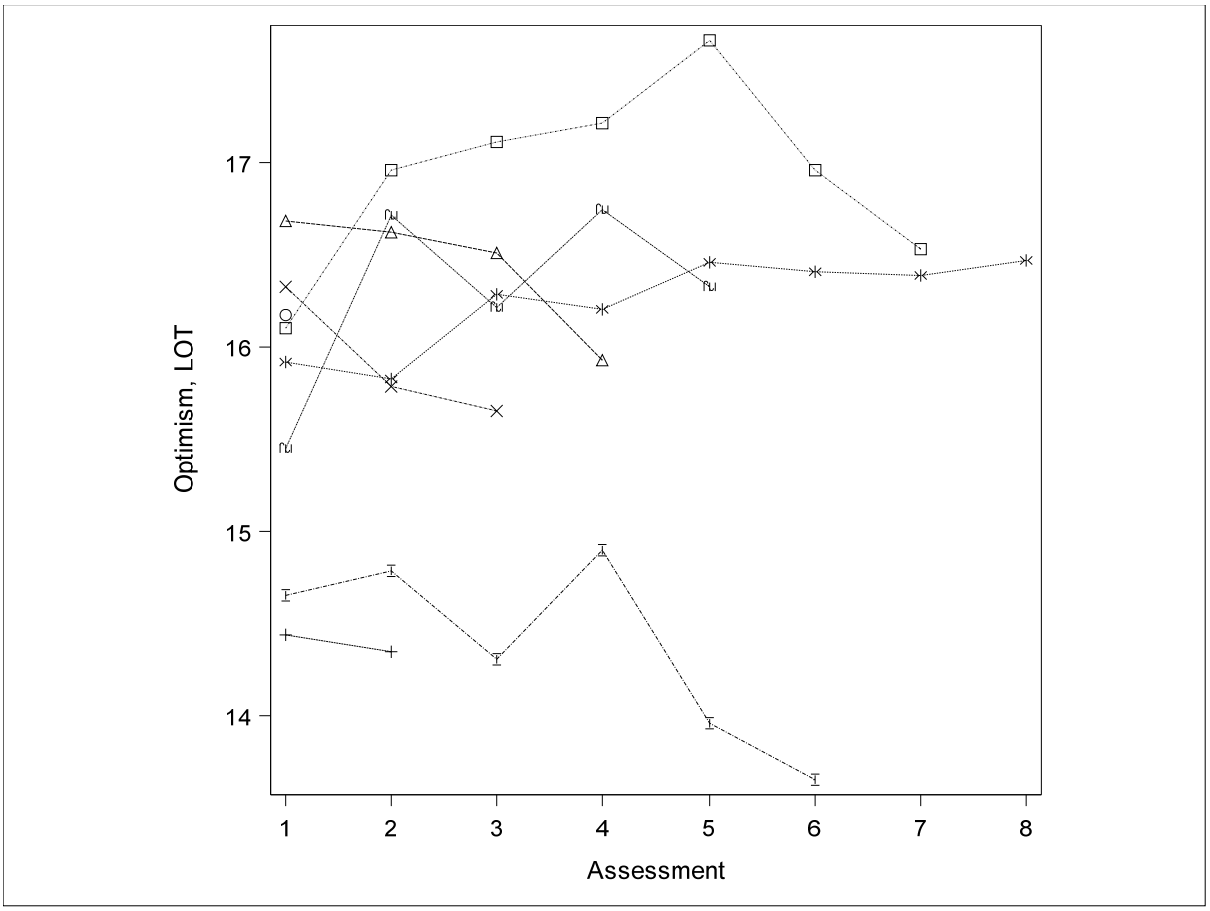


Fig. 3. Mean depression (HADS) over time, stratified by time of participant dropout.
(Higher scores indicate higher [worse] depression)


Optimism, LOT
17
16
15
14
1
2
3
4
5
6
7
8
Assessment

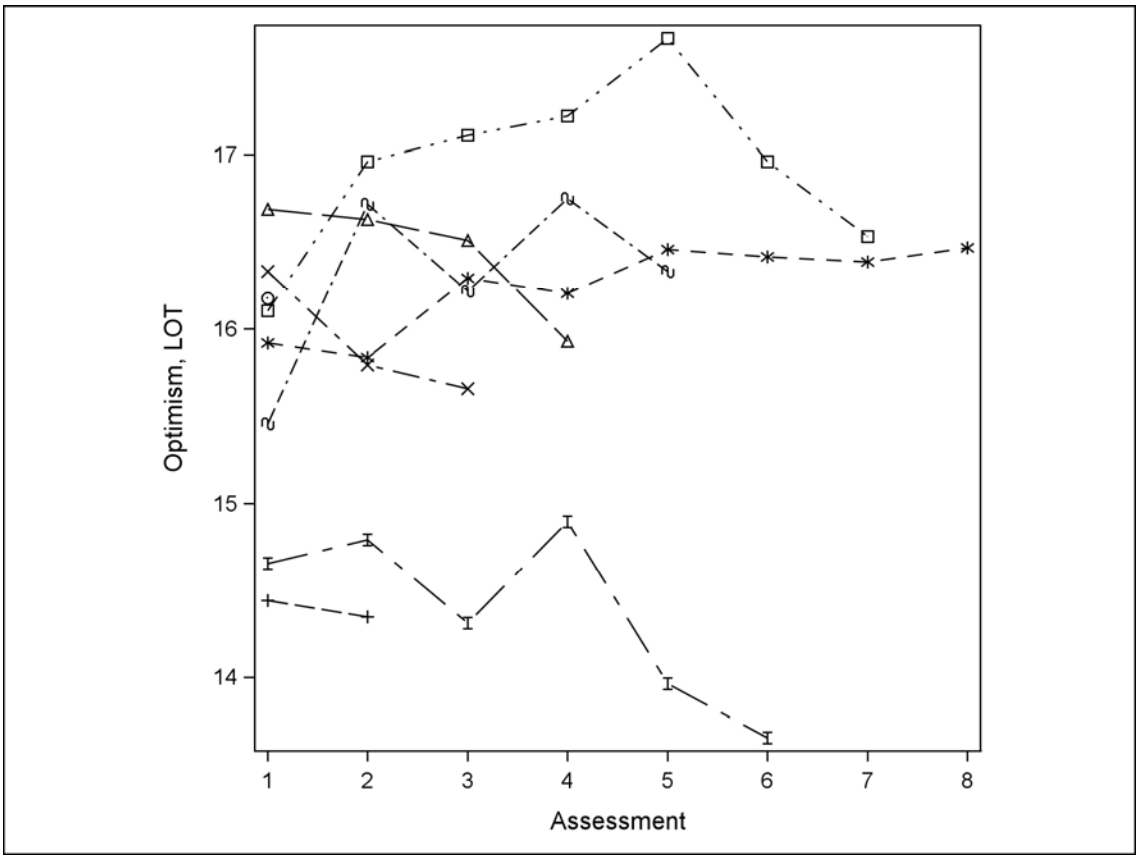


Fig. 4. Mean optimism (LOT-R) over time, stratified by time of participant dropout.
(Higher scores indicate higher [better] optimism).

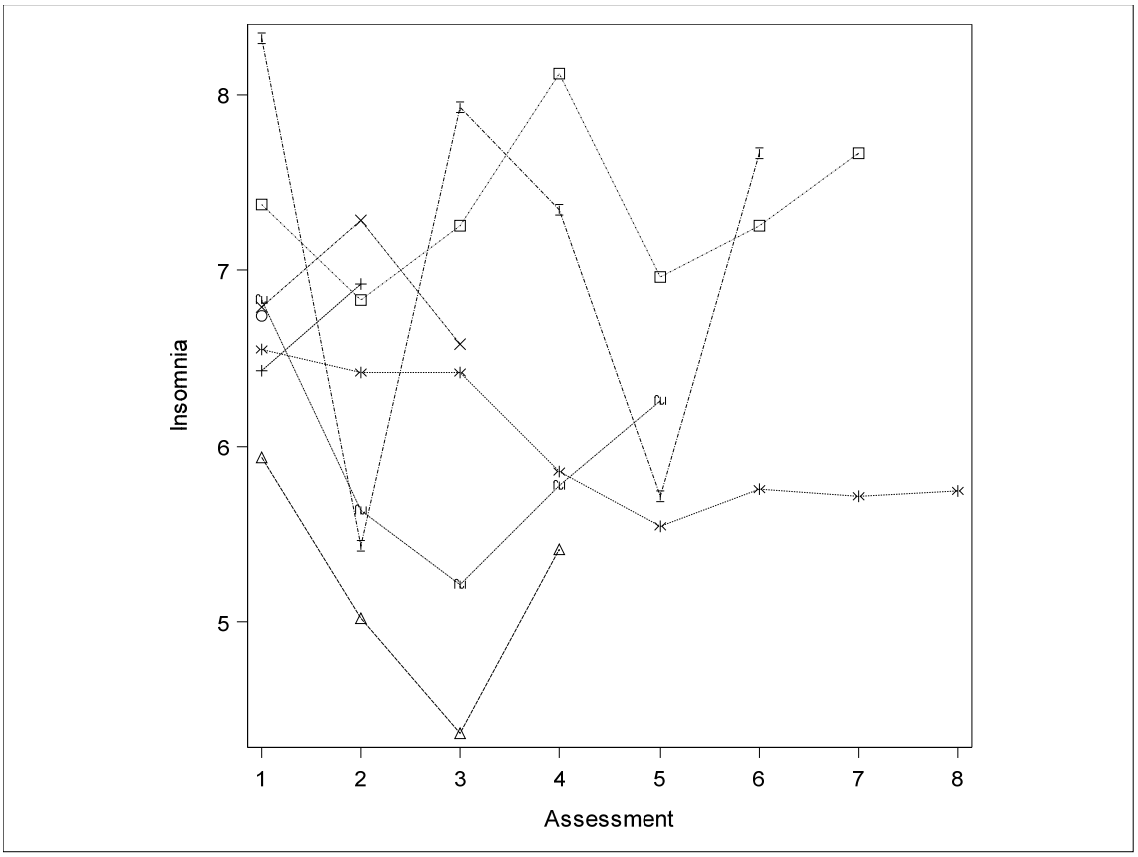


Fig. 5. Mean insomnia (ISI) over time, stratified by time of participant dropout.
(Higher scores indicate worse insomnia).