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Dropout from exercise trials among cancer survivors—An individual patient data meta-analysis from the POLARIS study

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Abstract

Introduction: The number of randomized controlled trials (RCTs) investigating the effects of exercise among cancer survivors has increased in recent years; however, participants dropping out of the trials are rarely described. The objective of the present study was to assess which combinations of participant and exercise program characteristics were associated with dropout from the exercise arms of RCTs among cancer survivors.

Methods: This study used data collected in the Predicting OptimaL cAncer RehabIlitation and Supportive care (POLARIS) study, an international database of RCTs investigating the effects of exercise among cancer survivors. Thirty-four exercise trials, with a total of 2467 patients without metastatic disease randomized to an exercise arm were included. Harmonized studies included a pre and a posttest,

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and participants were classified as dropouts when missing all assessments at the post-intervention test. Subgroups were identified with a conditional inference tree.

Results: Overall, 9.6% of the participants dropped out. Five subgroups were identified in the conditional inference tree based on four significant associations with dropout. Most dropout was observed for participants with BMI >28.4 kg/m^2, performing supervised resistance or unsupervised mixed exercise (19.8% dropout) or had low-medium education and performed aerobic or supervised mixed exercise (13.5%). The lowest dropout was found for participants with BMI >28.4 kg/m^2 and high education performing aerobic or supervised mixed exercise (5.1%), and participants with BMI ≤28.4 kg/m^2 exercising during (5.2%) or post (9.5%) treatment.

Conclusions: There are several systematic differences between cancer survivors completing and dropping out from exercise trials, possibly affecting the external validity of exercise effects.

KEYWORDS

cancer, decision tree, exercise oncology, individual patient data meta-analysis

1 | INTRODUCTION

Exercise has been associated with reduced cancer morbidity and mortality, improved physical fitness, reductions in fatigue, better management of treatment side effects, and better quality of life among individuals living with and beyond cancer, herein defined as cancer survivors.[1–5] The number of randomized controlled trials (RCTs) investigating the effects of exercise on a variety of outcomes among cancer survivors, spanning the pretreatment, treatment, and posttreatment phases has increased in recent years.[6] The exercise programs in such trials vary considerably in terms of the tested modality and delivery format, as well as frequency, duration, timing, and intensity of the exercise. Findings from these heterogeneous trials support statistically significant and clinically relevant benefits through participation in exercise programs.[7] However, evidence for the harms of exercise in some cancer populations is uncertain due to high risk of bias, poor reporting, and lack of trials.[8] A potentially higher risk of some harms during exercise interventions among cancer patients undergoing systemic treatment has recently been reported.[8] Systematic differences between participants who complete or drop out of RCTs may introduce bias to the findings and conclusions through missing data.[9,10] Participants dropping out may be underrepresented in the analyses, or their incomplete data can influence the size of observed effects. Consequently, findings may lack broad applicability and external validity if the missing data is not random. Reasons for not completing follow-up assessments could be withdrawal, not showing up to the study assessments, or exclusion. However, exercise intervention dropout, as defined by not completing follow-up assessments, does not provide insight into the intervention adherence.

The reported proportions of cancer survivors dropping out of exercise trials vary widely, ranging from none or only a few percent[11,12] to as high as 30%–45%.[13,14] The large differences in the number of participants dropping out of various exercise trials may partially be due to the difference in how these cases are defined and reported. While reasons are sometimes provided for why a participant did not complete study assessments, the type of missingness and how the missing data may bias the results are seldomly explained.[14,15] However, sample sizes of individual studies are often too small to identify associations with study dropout and rarely allow for comparisons of different exercise programs. If dropout is significantly associated with certain characteristics, the conclusions about intervention efficacy may be biased and the generalizability compromised. Identifying cancer survivors more likely to drop out from the exercise arms may further suggest targets where barriers and facilitators of trial completion must be identified.[13,16]

In the current study, we used individual patient data collected as part of the Predicting OptimaL cAncer RehabIlitation and Supportive care (POLARIS) study.[17] POLARIS is the largest set of individual patient data from RCTs investigating the effects of exercise in a mixed sample of cancer survivors. It thereby provides a unique opportunity to examine participants dropping out of the exercise arms across various trials. The objective of the present study was to assess which combinations of participant and exercise program characteristics were associated with higher levels of dropout among cancer survivors.

2 | MATERIALS AND METHODS

2.1 | Study design

The present study used individual patient data available via the POLARIS study, an international infrastructure and shared database of RCTs investigating the effects of exercise interventions in cancer survivors on a range of outcomes (registered in PROSPERO, CRD42013003805). A detailed description of the POLARIS study design, including the method of study identification and selection, and details on requested variables have been published elsewhere.[17] All individual studies in the database were conducted in line with the principles of the Declaration of Helsinki and received approval from their local ethics committees. Informed consent was obtained from all participants included in the individual studies. For the current analyses, we included cancer survivors who completed baseline assessments and were randomized to the exercise arms of the trials (34 RCTs, $n=2514$). We excluded participants with metastatic disease due to the small sample size, and the possibility of differential effects on dropout ($n=47$).

2.2 | Outcome assessment

The individual patient data contained two measuring points: Baseline and post-intervention. If trials included more than one post-intervention follow-up, the first follow-up after the intervention was finished, was included. Dropout was established when all data were missing at follow-up,[9] i.e., when participants did not complete any of the post-intervention assessments. All available variables in each original study were assessed for missing data post-intervention although only harmonizable variables related to the research question (participant and exercise intervention characteristics) were included. Information about exercise intervention adherence was not available, thus, the definition of dropout addressed missing data independent of adherence.

2.3 | Participant characteristics

Participant characteristics included age, sex, educational level, body mass index (BMI, kg/m^2), cancer type, and treatment. Educational level was dichotomized into low-medium (elementary, primary or secondary school, or lower or secondary vocational education) and high (higher vocational, college or university education).

Treatment with surgery, chemotherapy, radiotherapy, hormone therapy or stem cell transplantation were each dichotomized into previously or currently receiving this treatment versus not receiving this treatment. However, as numerous different combinations of treatment received were not feasible to assess, they were not included in the final model.

2.4 | Exercise intervention characteristics

Intervention characteristics included timing (during or posttreatment), exercise type (supervised aerobic, unsupervised aerobic, supervised resistance, supervised mixed, or unsupervised mixed), exercise intensity (low-moderate, moderate, moderate-vigorous, or vigorous), exercise session frequency (number of weekly exercise sessions), exercise session duration (≤30 min, >30 to ≤60 min, and >60 min), and intervention duration (≤3 months, >3 to ≤6 months, >6 months). Mixed exercise type included programs that had both an aerobic and a resistance exercise component. None of the included RCTs contained only unsupervised resistance exercise, and no intervention was carried out before treatment (Appendix S1).

Intervention timing was defined in line with previous POLARIS publications.[2] As hormone therapy for breast cancer may continue for several years posttreatment, women on hormone therapy who completed other primary cancer treatments were considered as being posttreatment. Men receiving androgen deprivation therapy for prostate cancer were considered as being during treatment.

2.5 | Missing data

For two studies, individual patient data on program duration were not available. One reported the median program duration (17 weeks, i.e., 3–6 months), which was added for this sample ($n=160$).[18] The other study reported an overall range for program duration, which spanned from <3 months to 3–6 months.[19] Thus, this sample ($n=40$) was randomly divided into two groups where <3 months was added for one half and 3–6 months for the other half. In the final dataset, there were some missing values for exercise program timing (0.1%), age (0.4%), session duration (2.8%), session frequency (5.3%), BMI (9.9%), exercise intensity (10.7%), and educational level (12.9%).

2.6 | Statistical analysis

Standardized effect sizes for the difference in or distribution of independent variables between participants dropping out or completing the exercise arms of the studies were reported with Cohen's d for continuous predictors, Cramer's V for nominal predictors, and Kendall's tau-b for ordinal predictors. Statistically significant *p*-values ($p < 0.05$) based on the independent sample *t*-test or chi square test were added.

With large sets of variables, complex, nonlinear and multilevel interactions can be challenging to assess and interpret through multivariable regression analysis.[20,21] As a parsimonious alternative, we applied the conditional inference tree (Ctree) to the dataset with dropout as the binary outcome. The Ctree algorithm can handle a large number of variables by performing multivariable assessments simultaneously and identifies the main and interactive effects explaining the most variability in the outcome.[22] The Ctree algorithm performs binary splits based on the predictors most strongly associated with the outcome, with a significance level of $p < 0.05$.[22] When splitting on continuous predictors, the splitting value is data driven and chosen based on the split that maximizes the statistical significance and "purity" of the new nodes, creating the most variability in the outcome. Cases with missing values on the split variable were allocated randomly to a node. The Ctree was conducted in R (version 4.1.1) with the "partykit" package.

3 | RESULTS

From the 34 original exercise trials (with a total of 4519 participants) included in the POLARIS database, 2467 participants without metastatic disease were randomized to an exercise arm. The number of participants included in the exercise arm of each original study varied from eight to 218, with a median of 53 (Appendix S1). Overall, 9.6% of the cancer survivors participating in the exercise arms dropped out but ranged from zero to 34.3% across the studies (Table 1).

Five subgroups of cancer survivors were identified based on four characteristics (Figure 1). These were BMI, with a split value of 28.4 kg/m^2 in the total sample, timing of the exercise intervention in the BMI ≤28.4 kg/m^2 subsample, and exercise type and educational level in the BMI >28.4 kg/m^2 subsample. The Ctree *p*-values for each split including all predictors with weaker but significant associations with dropout, hence not used for splitting, are presented in Appendix S2.

The lowest proportions of dropouts (5.1% and 5.2%, respectively) were observed for participants with BMI >28.4 kg/m^2, who performed aerobic or supervised mixed exercise and were highly educated, and participants with BMI ≤28.4 kg/m^2 who exercised during treatment (Figure 1). Among participants with BMI ≤28.4 kg/m^2 who exercised posttreatment, 9.5% dropped out. The highest proportions of dropouts (13.5% and 19.8%, respectively) were observed for participants with BMI >28.4 kg/m^2, who either performed aerobic or supervised mixed exercise and had a low-medium educational level or performed supervised resistance or unsupervised mixed exercise. Nine and four harmonized RCTs included only resistance exercise or unsupervised mixed exercise, respectively (≈38% of the RCTs).

4 | DISCUSSION

This study examined the characteristics of cancer survivors and exercise programs showing significantly higher levels of study drop out. While 9.6% of the cancer survivors dropped out overall, we observed large differences in dropout between identified subgroups, ranging from 5.1% to 19.8% across the five subgroups. Although BMI showed the strongest association with dropout in the total sample, with more dropout in the higher BMI subsample, the Ctree algorithm identified great differences within this subsample. Cancer survivors with high BMI who participated in resistance exercise interventions or unsupervised mixed interventions were more likely to drop out than those who participated in aerobic or supervised mixed interventions. However, among the participants of aerobic and supervised mixed interventions, the dropout rate was substantially higher among those with low educational levels.

Although there are currently few RCTs in the cancer population assessing resistance exercise only, more cancer survivors have been found to drop out of resistance exercise interventions relative to aerobic exercise interventions.[14,23] In the present sample, this appeared to apply only to cancer survivors with higher BMI. This could be related to being less familiar with performing resistance exercises, side effects from the exercise (e.g., soreness), or the need to travel to the facilities as all sessions were supervised. As there were no unsupervised programs with resistance exercise only in the present dataset, it is unclear whether unsupervised resistance exercise could result in a higher or lower probability of dropping out. Unsupervised mixed exercise did show higher dropout than supervised mixed in the higher BMI sample, suggesting that supervision of the exercise sessions increased the likelihood of completing the exercise arms of studies. However, this needs further exploration, as it may be dependent on the type of exercise performed. More complement of, and

TABLE 1 Characteristics of participants dropping out or completing the studies.

	Dropped out, $n=236$	Completed study, $n=2231$	Effect size
	Mean (SD)	**Mean (SD)**	**Cohen's d**
Age	53.9 (12.8)	54.8 (11.3)	−0.080
BMI	28.9 (5.6)	26.9 (4.9)	0.507**
Prescribed exercise session frequency (weekly)	3.0 (1.7)	3.2 (1.6)	−0.126
	n (%)	*n* (%)	**Cramer's V**
Total	236 (9.6)	2231 (90.4)	
Sex			
Female	184 (78.0)	1743 (78.1)	0.001
Male	52 (22.0)	488 (21.9)	
Educational level			
Low-Medium	130 (55.1)	1016 (45.5)	0.075**
High	70 (29.7)	933 (41.8)	
Missing	36 (15.3)	282 (12.6)	
Cancer type			
Breast	170 (72.0)	1574 (70.6)	0.044
Male genitourinary	34 (14.4)	280 (12.6)	
Gastrointestinal	10 (4.2)	131 (5.9)	
Hematological	13 (5.5)	186 (8.3)	
Other	9 (3.8)	60 (2.7)	
Timing			
During treatment	94 (39.8)	1160 (52.0)	0.069**
Posttreatment	140 (59.3)	1070 (48.0)	
Missing	2 (0.8)	1 (0.0)	
Type of exercise			
Supervised aerobic	10 (4.1)	253 (11.3)	0.085*
Unsupervised aerobic	35 (14.8)	384 (17.2)	
Supervised resistance	70 (29.7)	480 (21.5)	
Supervised mixed	76 (32.2)	732 (32.8)	
Unsupervised mixed	45 (19.1)	382 (17.1)	
			Kendall's tau-b
Prescribed exercise session duration			
≤30 min	63 (26.7)	840 (37.7)	0.054*
>30 to ≤60 min	146 (61.9)	1106 (49.6)	
>60 min	22 (9.3)	221 (9.9)	
Missing	5 (2.1)	64 (2.9)	
Prescribed program duration			
≤3 months	73 (30.9)	755 (33.8)	0.047*
>3 to ≤6 months	70 (29.7)	836 (37.5)	
>6 months	93 (39.4)	640 (28.7)	
Intensity			
Low-moderate	17 (7.2)	150 (6.7)	−0.007
Moderate	90 (38.1)	767 (34.4)	
Moderate-vigorous	87 (36.9)	898 (40.3)	
Vigorous	24 (10.2)	171 (7.7)	
Missing	18 (7.6)	245 (11.0)	

*$p<0.05$. **$p<0.001$.

Abbreviations: BMI, body mass index; SD, standard deviation.

Note: Low-medium–elementary, primary or secondary school, or lower or secondary vocational education; High–higher vocational, college or university education; Mixed exercise—participants performed both aerobic and resistance exercise.

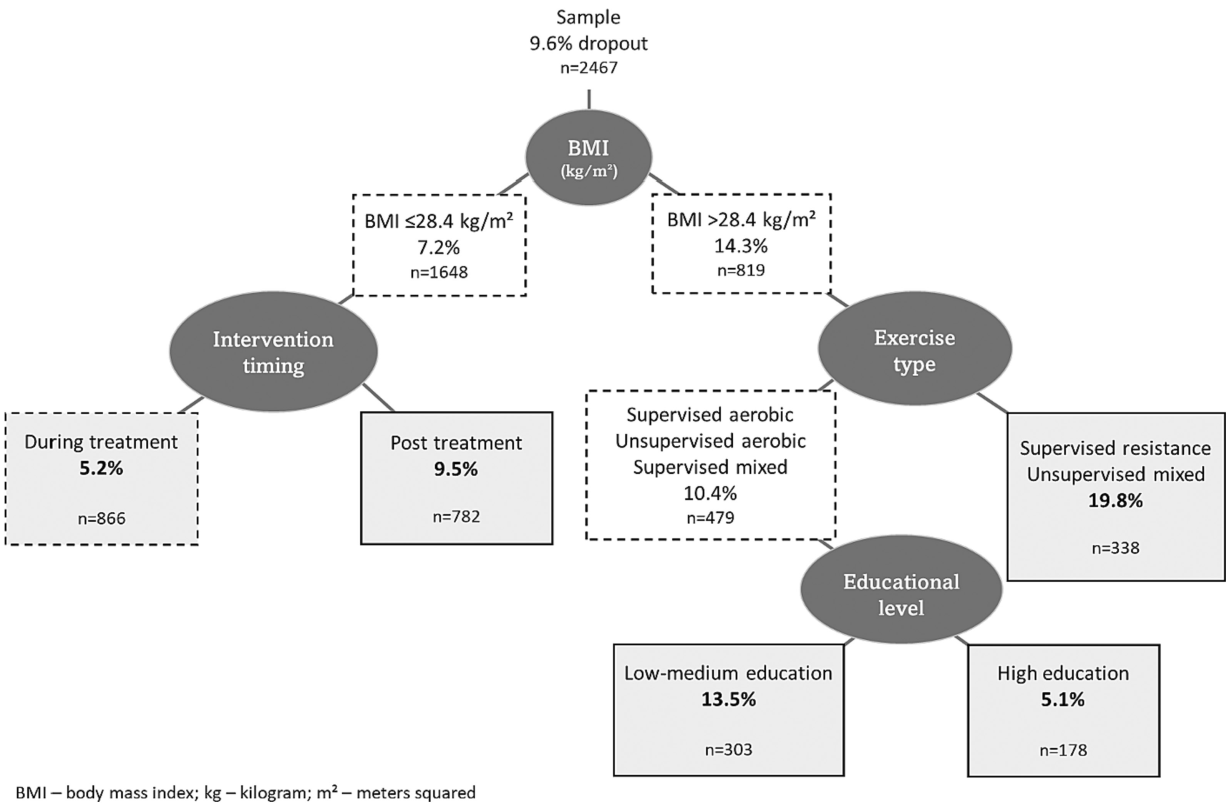

FIGURE 1 The conditional inference tree of associations with dropout. The circles represent variables with the strongest association with dropout in the total sample and subsamples. The dashed boxes represent subsamples where further associations with dropout were observed. The solid boxes represent the final subgroups where no further significant associations were observed. The percentages represent the proportions of participants dropping out in each subsample and subgroup.

compliance to, exercise interventions among cancer survivors have been previously reported for supervised compared to unsupervised programs.[14,24] Supervised exercise has also shown larger effects compared to unsupervised exercise for several outcomes.[1,25] Because cancer survivors with higher BMI were significantly more likely to drop out from resistance and unsupervised mixed exercise programs, they may be underrepresented when the effects of these interventions are assessed. Reasons for the higher dropout rate need further exploring, especially as resistance exercise is important for improving key health outcomes, including increased muscle mass, strength, and physical function.[26–28]

Having a high educational level was associated with a decreased probability of dropping out among participants with higher BMI who did not participate in resistance exercise intervention. A higher educational level has previously been associated with higher physical activity levels, decision-making abilities, health literacy, and a willingness to participate in exercise programs.[29–31] It is possible that a higher educational level was associated with factors increasing the probability of performing the interventions, leading to more completion of post-intervention assessments. Knowledge about exercise and exercise skills have previously been reported as predictors of exercise intervention adherence among cancer survivors,[32] and future studies should identify whether this or factors associated with knowledge and skills of exercise may also reduce dropout. Furthermore, it is possible that participants with a higher educational level were more motivated to exercise, and therefore endured the study period, due to more knowledge about benefits, higher levels of self-efficacy, more positive outcome expectations, and greater receptivity towards exercise.[33] However, there may have been other reasons for why cancer survivors with low-medium educational level in the higher BMI subsample were more likely to drop out. Factors such as other obligations, travel distance and transportation, comorbid health conditions, or lack of support may have influenced dropout.[32,34] Barriers for completing exercise trials should be further studied among cancer survivors with high BMI and low-medium education, as well as means to overcome these barriers.

In the subgroup of participants with lower BMI, we observed more dropout from exercise arms of trials conducted post cancer treatment compared to during cancer treatment. Although individuals undergoing cancer treatment are generally expected to be more ill due to treatment side-effects, they may also be more motivated to make healthy changes to their behavior and lifestyle, to actively contribute to the treatment outcome themselves, or to receive additional support or monitoring from their health care professionals.[35,36] Cancer survivors who had completed treatment may have prioritized their time differently, not wanting to focus on their cancer diagnosis, but rather return to their everyday life, and thus not prioritizing completing the study assessments. Other roles and responsibilities and lack of time have previously been reported by cancer survivors as barriers to physical activity participation.[34] In contrast to our findings, lower BMI has previously been associated with more dropout from exercise programs performed during cancer treatment.[37] However, it is likely that this association was related to the frailty of the participants, more advanced cancer, and possibly cancer cachexia.[37]

It is concerning that the reporting of adverse events in exercise oncology trials is poor and possibly subject to publication bias.[8] Adverse events caused by the exercise may impact study dropout and should be reported to inform future interventions and the need for tailored programs. In the present study, information about adverse events was not available, thus, we do not know whether adverse events were experienced by those dropping out.

The variables age, sex, cancer type, exercise intensity, and weekly number of exercise sessions were not significantly associated with dropout in any steps of the Ctree. Session duration was significantly associated with dropout in the total sample and the BMI >28 kg/m^2 subsample (Appendix S2), but BMI and exercise type yielded a stronger association, thus, session duration was not used for splitting.

4.1 | Strengths and limitations

Our study has a number of strengths. By analyzing individual patient data (i.e., utilizing information of each participant rather than relying on summary statistics), we could improve the accuracy of the estimated associations by preserving individual characteristics.[38,39] Pooling data from numerous exercise trials allows for assessments of dropouts, which may be too small of a sample size to assess in individual studies. It also allows for assessments considering exercise intervention design and modalities. Machine learning techniques, including decision trees, are better at identifying relevant subgroups and nonlinear interactions from a statistical perspective compared to more traditional statistical methods.[21,40] It may also provide more intuitive and easily interpretable results. The Ctree gave a more detailed overview of significant associations with dropout by showing how associations in the total sample remained significant in some subsamples and not in others (Appendix S2). Such data-driven approaches can discover patterns and associations that may be complex and not evident through pre-specified models, and can be used to generate hypotheses and guide further research. When the variable chosen for splitting the Ctree has many cases with missing values who are randomly allocated to one of the new nodes, the Ctree can change when repeated. Repeating the algorithm with the present data did not change the significant variables, although small changes in subsample size, dropout rates, and *p*-values were observed.

Our study also had limitations that should be noted. First, although the POLARIS database is a large collection of individual patient data, the number of included trials is still small compared to the available literature. The harmonized sample was also largely made up of breast cancer survivors followed by male genitourinary cancer, although we had no restriction on cancer type. This limits the generalizability of our results to all exercise trials and cancer populations. However, dropout rates did not appear significantly different between breast and prostate cancer survivors. The research design of the trials, such as whether it was a pilot trial, or an exploratory, pragmatic, or implementation study was not included in the assessments. Second, decision trees can be used to obtain (nearly) pure nodes that can be used to predict the outcome in new samples. We did not test the predictive ability of our Ctree; however, the purpose of the present study was to describe significant associations with dropout and show interactions between the variables, not to classify individuals or predict dropout in new samples. Nevertheless, data-driven approaches can be at risk of overfitting, which limits the generalizability to new data. Thus, interpretations of the present findings should consider the exploratory nature of the analysis. Third, relevant associations or underlying explanations for why participants dropped out were likely missed. We did not assess psychosocial factors related to stress, depression, anxiety, motivation, self-efficacy, or previous exercise habits, which could further add to our understanding of why some cancer survivors drop out of exercise trials. Cancer stage was also not included, as this information was not available for a large part of the sample. Due to the limited number of participants with distant metastasis we were only able to focus on patients treated with curative intent, the results can therefore not be generalized to all patients with cancer. Fourth, all possible interactions between included variables were not described in the Ctree because the variable with the strongest association was used for splitting in each subsample. Thus, splitting on variables with the second strongest association could have led to different interactions. Finally, we did not consider those declining intervention participation in the first place or assessed dropout in the control groups. Likely, there was already a bias in the initial sample caused by differences in characteristics between study participants and decliners, and the level of, and associations with, dropout could be different in the control groups. Further research should assess whether data missing not at random also occur among control groups.

4.2 | Perspectives

The present findings should be considered when designing, conducting, and generalizing results from exercise trials in the oncology setting. Further research is needed to understand the reasons for why specific subgroups of cancer survivors exhibit a greater tendency to drop out and to investigate possible facilitators to improve completion of the exercise arms. Future studies including different trials should also report and account for differences in study design when assessing dropout.

5 | CONCLUSIONS

Of the 2467 cancer survivors exercising in 34 RCTs, 9.6% dropped out. Five subgroups within the sample were identified, characterized by BMI, program timing, exercise type, and educational level, with dropout ranging from 5.1% to 19.8%. Participants most likely to drop out included those with BMI >28.4 kg/m^2 who either participated in resistance or unsupervised mixed exercise trials or had low-medium education and performed aerobic or supervised mixed exercise. These subgroups may require additional support to complete exercise interventions. Further research should explore possible reasons for why certain cancer survivors drop out and means to improve this.

AUTHOR CONTRIBUTIONS

LMB, MFK, and AEH contributed to the harmonization and handling of the POLARIS data. BW, LMB, SB, IV, and ID contributed to the conceptualisation and design of the present work. BW drafted the work, conducted and interpreted the present analyses, and revised the manuscript upon feedback from coauthors. AI made substantial contributions to the interpretation of the data and analyses. NKA, GR, MvB, MB, KC, AJD, DAG, RG, MMG, KAG, WHvH, SCH, FHR, MLI, EJ, MJK, HK, AL, AMM, AMC, WvM, NM, RUN, FN, HSO, RP, MES, KS, KHS, CES, GSS, KS, MMS, DRT, LT, MJV, JW, KMWS, JW, and LMB made substantial contributions to the design of the included RCTs, acquisition and handling of the data, and approved sharing of the data with the POLARIS database. All authors critically revised the work, contributed with valuable insight, and approved the final version of the manuscript.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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