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TOPIC REVIEW

Physical activity and exercise in adults diagnosed with primary brain cancer: a systematic review

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Abstract

Purpose The aims of this systematic review were to: (1) describe physical activity (PA) levels following diagnosis of primary brain cancer, (2) determine the relationship between PA levels and health outcomes, and (3) assess the effect of participating in an exercise intervention on health outcomes following a diagnosis of brain cancer.

Methods PubMed, EMBASE, Scopus and CINAHL were searched for relevant articles published prior to May 1, 2020. Studies reporting levels of PA, the relationship between PA and health outcomes, and exercise interventions conducted in adults with brain cancer were eligible. The search strategy included terms relating to primary brain cancer, physical activity, and exercise. Two independent reviewers assessed articles for eligibility and methodological quality (according to Joanna Briggs Institute Critical Appraisal Tools). Descriptive statistics were used to present relevant data and outcomes.

Results 15 studies were eligible for inclusion. Most adults with brain cancer were insufficiently active from diagnosis through to post-treatment. Higher levels of PA were associated with lower severity of brain cancer specific concerns and higher quality of life. Preliminary evidence suggests that exercise is safe, feasible and potentially beneficial to brain cancer symptom severity and interference, aerobic capacity, body composition and PA levels. However, the level of evidence to support these findings is graded as weak.

Conclusions Evidence suggests that it is likely appropriate to promote those with brain cancer to be as physically active as possible. The need or ability of those with brain cancer to meet current PA guidelines promoted to *all* people with cancer remains unclear.

Keywords Brain cancer · Physical activity · Exercise · Intervention · Survivorship · Glioblastoma

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Introduction

Brain and other central nervous system cancers are rare, accounting for approximately 1.5% of all cancers diagnosed, but their disease burden is high [1]. The most common malignant brain tumours in adults are gliomas, accounting for up to 80% of all primary brain cancers [2]. The 5-year relative survival rate for brain cancers is 22% [1], which is markedly lower compared to more commonly diagnosed cancers such as breast (91%) and prostate (95%), and considerably lower than all cancers combined (69%) [3]. While advances in treatments such as a combined radiotherapy and chemotherapy (temozolomide) have contributed to improvements in survival [4], treatment-related complications and side-effects that impact physical, cognitive and psychosocial functioning remain throughout all phases of survivorship (from cancer diagnosis until end-of-life) [5–8].

A recent meta-analysis quantified the relationship between post-diagnosis physical activity (PA) and disease-free and overall survival for all cancers combined, with findings showing reductions of 59% and 64% cancer-specific and all-cause mortality respectively, for those in the highest PA group compared with those in the lowest [9]. Further, the American College of Sports Medicine exercise prescription guidelines highlight that there is strong evidence for exercise in the management of anxiety, depressive symptoms, fatigue, quality of life (QoL), and physical function, and moderate evidence for bone health and sleep [10]. These findings contributed to the development and promotion of PA recommendations for cancer survivors, which state *all* cancer survivors should avoid inactivity and aim towards participating in 150 minutes of moderate intensity exercise, as well as at least two resistance exercise sessions, per week [10, 11]. However, the studies contributing data that support these guidelines predominantly involve common cancers with relatively good survival such as breast, colorectal and prostate cancers. Consequently, it remains unclear whether higher levels of PA are associated with improved health outcomes and survival, as well as whether exercise is safe, feasible and efficacious following a brain cancer diagnosis. Therefore, the aims of this systematic review were to: (1) describe PA levels following diagnosis of primary brain cancer, (2) determine the relationship between PA levels and health outcomes, and (3) assess the effect of participating in an exercise intervention on health outcomes.

Methods

This systematic review was conducted in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [12] and was registered with the international prospective register of systematic reviews (PROSPERO: CRD42019140001).

Search strategy

The systematic database search was conducted on PubMed, EMBASE, Scopus and CINAHL on 1 May 2020. A scientific librarian assisted with the development of the search strategy which included terms relating to brain cancer and exercise or PA, which were adapted to subject headings appropriate for each database (Supplementary Table 1). Where available, database specific limiters (Embase) were applied to identify publications in English, in adults, and by publication type. No restrictions were set on publication year. Additional articles were identified by searching reference lists of included articles.

Eligibility criteria

Peer-reviewed studies which contained information regarding levels of PA and/or exercise interventions (as assessed objectively or self-reported) in adults (age $\geq$ 18 years) with malignant, primary brain cancer (during or post-treatment) were included. Articles were excluded if they involved children and/or mixed interventions (e.g., exercise and psychological therapy). Observational studies contributed to answering aims one and two. Intervention studies contributed to answering aim three. Studies including participants with brain cancer which also enrolled benign or metastatic brain tumours were excluded, unless results for patients with primary malignant brain tumours were presented separately.

The results from database searches were imported to EndNote (X9) and duplicates were removed. One reviewer (MM) screened all titles/abstracts using the criteria described above. Full-text articles were assessed by two independent reviewers (MM, TJ). Any discrepancies were discussed and resolved by a third reviewer (CS). When two papers presented similar data from the same cohort, the paper with the most comprehensive information was used for data extraction.

Quality appraisal

Articles eligible for inclusion were assessed for quality using the Joanna Briggs Institute quality appraisal tools [13] specific to each study design. Two reviewers (MM, TJ)

conducted quality appraisal independently, the results were compared, and any discrepancies were resolved by consensus with a third independent reviewer (CS). Studies were not excluded based on quality. The level of evidence for each research question was then evaluated according to the NHMRC Guidelines for the development and implementation of clinical practice guidelines, where level I indicates the strongest and IV is the weakest evidence [14, 15].

Data extraction and statistical analysis

A data extraction spreadsheet collated relevant data from each included article, including: paper details, study design, sample size, sample information (e.g. age, cancer type, treatment status), study aims and primary outcome, PA measurements, PA levels, intervention details and outcomes.

A meta-analysis was not conducted due to small sample sizes, heterogeneity of study populations, study designs and the method of outcome assessment. PA levels, patient-relevant outcomes, and exercise interventions were summarised descriptively. PA levels were extracted as reported in the original papers (e.g., strenuous, moderate, mild exercise; or number of participants meeting guidelines). PA levels were grouped and summarised in tabular format according to assessment time point (i.e., pre-diagnosis, at diagnosis, during treatment, post-treatment, and follow-up $<$ or $\geq$ 12 months since diagnosis). Exercise intervention details were summarised according to the FITT principle (frequency, intensity, time, type), safety (number of adverse events) and feasibility (recruitment, retention, and adherence to exercise). For aims two and three, we report the outcomes which were found to have a statistically- and/or clinically-significant relationship with PA or exercise intervention participation. These were determined a priori based on previously reported literature (Table 1). A p value < 0.05 was considered statistically-significant unless otherwise specified in the included study.

Results

Study selection

Database searches yielded 5394 manuscripts, and after removing duplicates (n = 1469) and screening of titles and abstracts, 90 articles remained for full-text assessment (Fig. 1). Sixteen manuscripts (presenting findings from 15 studies) of varying quality (Supplementary Table 2) were identified as eligible [16–31] (Fig. 1), consisting of two randomised controlled trials (RCT; findings from one of these trials were presented in two manuscripts) [20, 29, 31], seven prospective cohorts [16, 18, 19, 24, 26–28], two cross-sectional [22, 23] studies, one case–control study [17] and three case-reports [21, 25, 30].

Sample characteristics

Sample sizes ranged from 1 (case-reports) to 243 (a prospective cohort study [28]), and included participants with an age range of 20–82 years. Seven studies almost exclusively included patients with high-grade glioma (HGG) (WHO grade III/IV) [19, 21, 22, 25–28, 30]. Other studies included mixed samples of low-grade glioma (LGG; WHO grade I/II) and HGG [16–18, 20, 23, 24, 29, 31], involving newly diagnosed brain cancer [19, 21, 24–27, 30] or recurrent brain cancer [22, 25, 28] (three articles did not specify [20, 29, 31]).

Aim one: PA levels in people with primary brain cancer

Level of evidence: III-2. PA levels were reported in six studies [19, 22–24, 27, 28] (Table 2), including two cross-sectional (n = 171,243) [22, 28] and four longitudinal (range n = 15 to 106) [19, 23, 24, 27] studies. Recruitment rates reported in four of six studies were $< 51\%$ (range: 28 [23] to 71% [27]), with common reasons for not participating being uninterested or time. Attrition rates ranged from 10 [24] to 61% [28], with four from six studies involving HGG reporting higher attrition rates due to disease progression and deaths (range: 38 [19] to 61% [28]). All studies used self-reported measures of PA (mostly the Godin Leisure Time Exercise Questionnaire [19, 22–24, 28]), with five studies reporting total PA in minutes per week (mins/wk) [19, 22–24], or MET-h/wk [28], and two of the four longitudinal studies involved retrospective collection of pre-diagnosis PA levels [23, 27]. One study categorised participants according to PA levels (i.e. almost completely inactive, some PA $<$ 3 h/week, regular PA, or regular hard physical training $>$ 4 h/week) [27] and four others categorised participants according to meeting PA guidelines ($\geq$ 150-mins of moderate aerobic exercise per week) [19, 22, 23, 28]. Timing of PA measurement varied from pre-diagnosis, during treatment and post-treatment (Table 2).

Mean PA during or post-treatment ranged from 134 ± 123 [24] to 177.2 ± 164.9 [19] mins/wk. Between 20 and 71% of participants pre- or at diagnosis [19, 23, 27], and 22–41% during or post-treatment met recommended PA guidelines. Longitudinal findings suggested that the proportion of 'regularly active' patients more than halved between pre- (59%) and post-diagnosis (25%) [27]. Participants reporting "no exercise" ranged from 24 to 44% [22, 23, 27, 28] (during or

Table 1 A priori definition of clinically-significant change for outcomes reported in brain cancer exercise interventions

Outcomes	Units of change	References
European organisation for the research and treatment of cancer quality of life	10	[48]
36-item short form survey	5	[49]
Edmonton symptom management system	1	[50]
MD Anderson symptom inventory brain tumour module	1	[51]
Brief fatigue inventory	1	[52]
Cardiorespiratory fitness	1-MET[a] (3.5 mL/kg/min)	[53]
Pittsburgh sleep quality index	3	[54]
Hospital anxiety and depression scale	1.5	[55]
30 s sit-to-stand	2 repetitions	[56]
Functional independence measure—total subscale	22	[57]
Functional independence measure—motor subscale	17	[57]
Functional independence measure—cognitive subscale	3	[57]

For outcomes that did not have established values for clinically-relevant differences, we applied the 0.5 standard deviation (SD) distribution method [58]

[a]1 MET is the amount of energy expended during one minute while at rest

post-treatment), and overall, most participants did not meet PA guidelines at any time from diagnosis to follow-up (approximately 60% categorised as insufficiently active or sedentary).

Aim two: PA and health outcomes

Level of evidence for any given outcome: III-3 to III-2. Five studies assessed the association between PA levels and cancer-related outcomes [19, 22, 24, 27, 28] (Table 2), including: survival [28], QoL FACT-G [19, 24], side-effects relating to brain cancer (FACT-Brain cancer subscale) [19, 24], physical function (6-min walk test [28], Karnofsky Performance Status [22]), anxiety (Hospital Anxiety Depression Scale [27]), muscular strength (lower-limb dynamometry [24]), and cardiopulmonary fitness (VO_{2peak} [24]).

Baseline PA (during or post-treatment) was shown to be an independent predictor of survival ($p = 0.008$) among patients with recurrent grade III/IV brain cancer in a cohort study (n = 243) [28]. Median survival was 22 months (95% CI 13.32–∞) for patients reporting ≥ 9 MET-h/wk compared to 13 months (95% CI 11.25–17.37) for patients reporting < 9 MET-h/wk. Two prospective cohort studies [19, 24] showed positive associations between total weekly PA levels and QoL (that is, higher PA levels were associated with higher QoL and fewer brain cancer specific concerns), but only one was supported statistically [19]. In a mixed (LGG and HGG) sample from a small (n = 35), prospective cohort study, increases in PA levels (from pre- to post-diagnosis) were associated with improvements in muscular strength, body composition, and cardiopulmonary function, although associations were not supported statistically [24]. Other studies failed to show an association between PA levels and physical function [22] or anxiety [27].

Aim three: effect of exercise interventions on cancer related outcomes

Nine studies (seven involving newly diagnosed patients [16–18, 21, 26, 30, 31]) evaluated the effect of an exercise intervention on cancer-related outcomes in patients with brain cancer (Table 3). These included three case-reports [21, 25, 30], three pre-post intervention studies (n: 5–24) [16, 18, 26], one case–control study (n = 43) [17] and two RCTs (n: 20–34) [20, 29, 31]. The case-reports related to three patients on treatment [21, 25, 30] and one post-treatment [25, 30]. Two studies evaluated exercise post-surgery (during inpatient rehabilitation) [16, 17], three studies during radiation and/or concurrent chemotherapy [18, 26, 31], and one evaluated exercise a minimum of 6-months post-treatment (surgery and/or adjuvant chemotherapy and/or radiotherapy) [20, 29]. The number of studies that evaluated any given outcome (objectively-assessed or patient-reported) ranged between one and six studies (Table 4).

Exercise intervention details

A summary of the intervention details is presented in Supplementary Table 3. Intervention studies included patients with grade I–IV disease (although most [17, 21, 25, 26, 30] involved patients with HGGs only), five studies included

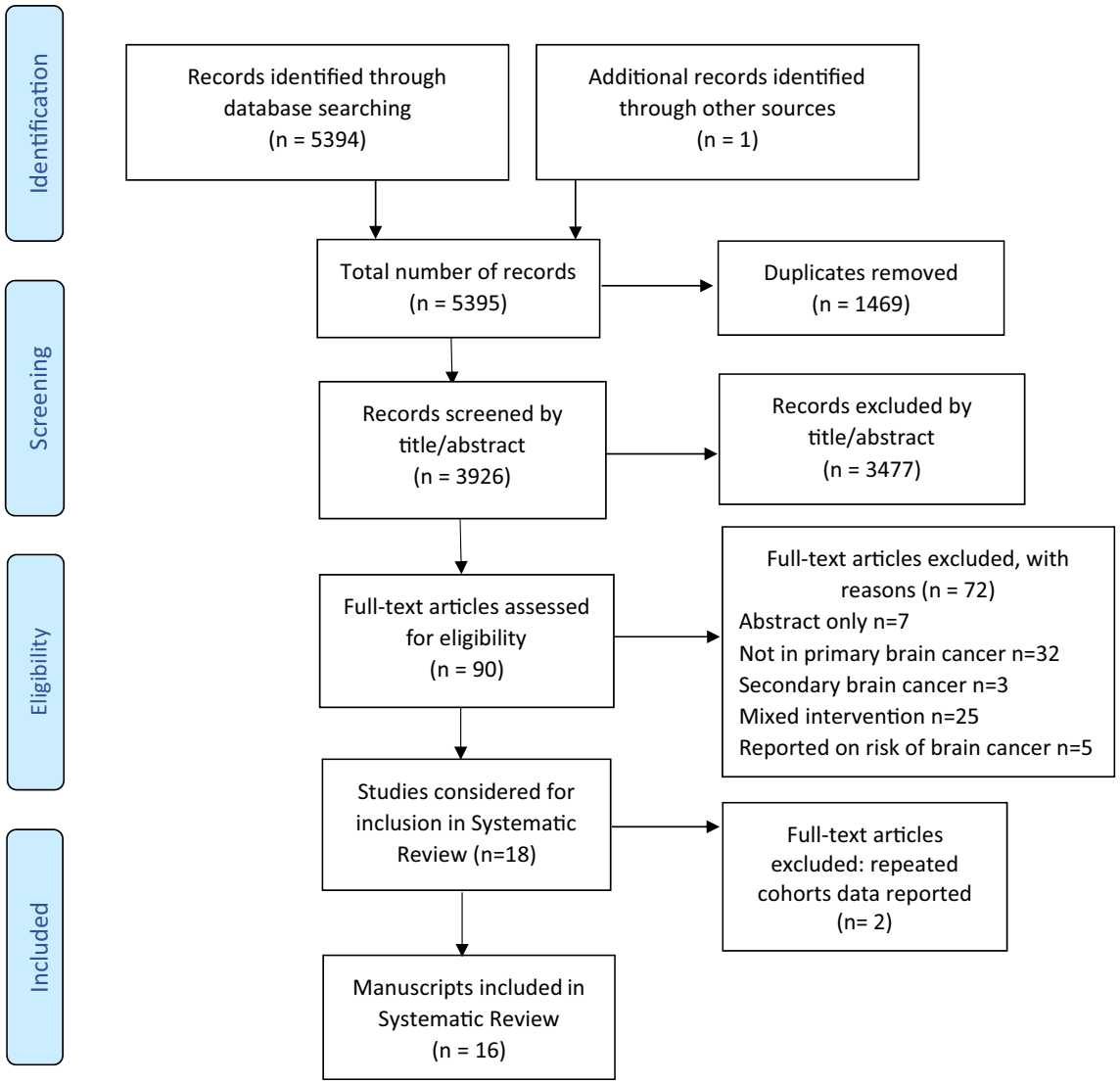

Fig. 1 PRISMA flow diagram

mixed Gliomas (e.g. astrocytoma, glioblastoma) [16, 18, 20, 25, 29, 31] and four studies involved glioblastoma only [17, 21, 26, 30]. Except for one case-report describing an 87-week intervention, the intervention period ranged from 4 to 24 weeks. Most investigated either aerobic exercise only (40%) or mixed-mode (aerobic and resistance exercise; 40%), while two studies (20%) evaluated yoga (Table 3). Frequency of sessions and session duration ranged between one to six days per week and 15–60 mins, respectively. Exercise intensity was moderate or higher as measured by rating of perceived exertion or age-predicted heart rate maximum. Most studies involved some degree of supervision with a qualified exercise professional. Only one home-based study evaluated a completely unsupervised intervention [20, 29]. The remaining studies were conducted either in a class/clinic setting, inpatient or combination of clinic and home-based.

Feasibility, safety and acceptability

Recruitment and retention rates (not including case-reports) ranged from 25 [20] to 83% [26] and 58 [18] to 100% [16, 17, 26], respectively (Supplementary Table 3). Reasons for not enrolling included being uninterested, lack of motivation, disease progression, physical limitations, and being too busy [16, 18, 20, 31]. Reasons for withdrawal or lost to follow-up included illness progression, travel, returning to work, and lack of motivation or time [16, 18, 20, 29, 31]. Safety was reported in all except two studies [17, 31], with one adverse event (participant lost balance and fell, reporting soreness to the head) recorded [18]. Intervention adherence (average number of sessions attended/sessions planned × 100%) ranged from 61 [18] to 100% [21, 25, 26]. Exercise adherence was reported in two studies as ≥ 75% of participants meeting exercise intensity and

Table 2 Summary of studies assessing physical activity levels in adults with primary brain cancer

Study details	Population at baseline: sample size (% female), age (mean ± SD or range in years), tumour type (tumour grade), time since diagnosis, treatment status; recruitment rate, attrition	Method of PA assessment and category of PA (as reported in the original paper)	Assessment time points						
			Pre-diagnosis	At diagnosis	During treatment	Post treatment	Follow up (< 12 months since baseline)	Follow up (≥ 12 months since diagnosis)	Association between PA levels and cancer related outcomes
Ruden et al. (2011) [28] USA Prospective cohort study (PA reported at one time point)	n = 243 (32%) 49 ± 11 years Recurrent glioma[a] (grade III/IV) Median 20 months (range 3–241) since recurrent diagnosis, 87% on treatment 65% recruitment rate 61% attrition	GLTEQ Mean ± SD MET h/week % meeting guidelines % no exercise			All 14 ± 19 Grade III: n = 76 16 ± 26 Grade IV: n = 167 14 ± 16 26% meeting guidelines 24% no exercise				☑* Survival ☐ Physical function
Jones et al. (2006) [23] USA Cross-sectional study (single survey)	n = 106 (51%) 44.8 ± 12 years Mixed[b] (grade I–IV) Mean 28 months (range 6–178) since diagnosis 47% on active therapy 28% recruitment rate Attrition not reported	GLTEQ Mean ± SD mins/week Total PA I: strenuous (heart beats rapidly, sweating) II: moderate (not exhausting, light perspiration) III: mild (minimal effort, no perspiration) % meeting guidelines % no exercise	160.8 ± 224.9 I 88.5 ± 134.6 II 27.5 ± 77.1 III 44.9 ± 88.2 42% meeting guidelines 41% no exercise		154.5 ± 222.2 I 67.9 ± 120.6 II 36.1 ± 72.8 III 50.5 ± 88.2 38% meeting guidelines 41% no exercise	177.0 ± 226.5 I 72.6 ± 109.4 II 48.1 ± 82.5 III 56.3 ± 86.1 41% meeting guidelines 31% no exercise			
Jones et al. (2009) [22] USA Cross-sectional study	n = 171 (32%) 49 ± 11 (range 20–77) years HGG[c] (grade III and IV recurrent disease) Mean 22 months (range 3–176) since diagnosis 85% on active therapy 45% recruitment Attrition not reported	GLTEQ Mean ± SD mins/week Total PA % meeting guidelines % no exercise			164 ± 201 25% meeting guidelines 26% no exercise				☐ Karnofsky Performance Status ☐ Physical function
Jones et al. (2010) [24] USA Prospective cohort study	n = 35 (40%) 47 ± 13 LGG (grade I/II), HGG (grade III/IV) New diagnosis (approx. 1 month), 10 ± 7 days post-surgery 51% recruitment 40% (HGG), 10% (LGG) attrition	GLTEQ Mean ± SD mins/week Total PA		LGG n = 7 48 ± 74 HGG: n = 13 82 ± 125		LGG: n = 7 167 ± 342 HGG: n = 13 134 ± 123	LGG: n = 7 141 ± 132 HGG: n = 13 192 ± 418		☑ Quality of life (brain specific subscale) ☑ Cardio-pulmonary function ☑ Muscle strength ☑ Body composition

Table 2 (continued)

Study details	Population at baseline: sample size (% female), age (mean ± SD or range in years), tumour type (tumour grade), time since diagnosis, treatment status; recruitment rate, attrition	Method of PA assessment and category of PA (as reported in the original paper)	Assessment time points						
			Pre-diagnosis	At diagnosis	During treatment	Post treatment	Follow up (< 12 months since baseline)	Follow up (≥ 12 months since diagnosis)	Association between PA levels and cancer related outcomes
Piil et al. (2015) [27] Denmark Prospective cohort study	n = 30 (37%) 60 (range 29–82) years HGG[d] (grade III/IV) New diagnosis 1 week post-surgery and diagnosis 71% recruitment rate 40% attrition	Leisure-time physical activity level Number (%) of participants I: almost completely inactive II: some physical activity < 3 h/week III: regular activity at least 3 h/week IV: regular hard physical training > 4 h/week	n = 17 I: 2 (11.8%) II: 3 (17.6%) III: 10 (58.8%) IV: 2 (11.8%)	n = 16 I: 8 (50%) II: 4 (25%) III: 4 (25%) IV: 0	n = 18 I: 4 (22.2%) II: 7 (38.9%) III: 6 (33.3%) IV: 1 (5.6%)	n = 16 I: 7 (43.8%) II: 9 (56.3%) III: 0 IV: 0	n = 18 I: 4 (22.2%) II: 13 (72.2%) III: 1 (5.6%) IV: 0	n = 18 I: 6 (33.3%) II: 10 (55.6%) III: 2 (11.1%) IV: 0	☐ Hospital anxiety and depression scale
Culos-Reed et al. (2017) [19] Canada Prospective cohort study	n = 15 (47%) 50.6 ± 3.7 years HGG (grade IV) New diagnosis receiving treatment 46% recruitment rate 38% attrition	GLTEQ Mean ± SD mins/week Total PA I: strenuous II: moderate III: mild exercise Number of participants meeting guidelines (%)		n = 15 155.8 ± 108.1 I: 14.7 ± 8.7 II: 38.8 ± 14.50 III: 102.4 ± 20.3 n = 3 (20%)		n = 9 177.2 ± 164.9 I: 16.7 ± 27.3 II: 63.9 ± 87.4 III: 96.7 ± 94.3 n = 2 (22%)	n = 2 125 ± 35.4 I: 0 II: 80 ± 56.6 III: 45 ± 21.2 n = 0 (0%)		☑* Quality of life (general and brain specific subscale)

Assessment time points for studies reporting multiple time points: Jones et al. [23] pre-diagnosis = before brain cancer diagnosis; during treatment = during active treatment; post-treatment = after the completion of treatment. Jones et al. [22] and Ruden et al. [28] participants had received or were receiving treatment. Jones et al. [24] at diagnosis = baseline, after post-surgical treatment consultation; post-treatment = approximately 6 weeks post-surgery for LGG, following the completion of adjuvant radiotherapy for HGG; follow up = approximately 24 weeks post-surgery. Piil et al. [27] pre-diagnosis = retrospectively reported 3 months prior to diagnosis; at diagnosis = baseline (after surgery and diagnosis); during treatment = during radiotherapy (6 weeks since baseline); post-treatment = after treatment (28 weeks since baseline); follow up = after treatment (40 weeks since baseline); follow up = after response scan (52 weeks since baseline). Culos-Reed et al. [19] at diagnosis = baseline (immediately prior to starting 6 weeks of concurrent Temozolomide chemotherapy with radiation); post-treatment = during the 4-week off-treatment period after concurrent therapy (i.e., approximately 2 months from T1); follow up = after 6 months of adjuvant Temozolomide (approximately 8 months from baseline)

C control group, *I* intervention group, *GLTEQ* Godin Leisure Time Exercise Questionnaire, *HGG* high grade glioma, *h* hour, *IPAQ* International Physical Activity Questionnaire, *LGG* low grade glioma, *MET* metabolic equivalent; 1 MET is the amount of energy expended while at rest, *MET-h/week* MET-hour per week, *mins/week* minutes per week, *NA* not applicable, *PA* physical activity, ☑ positive association reported, ☐ no association reported/found

[a]Glioma = glioblastoma multiforme, anaplastic astrocytoma, anaplastic oligodendroglioma

[b]Mixed tumour type = glioblastoma multiforme, anaplastic astrocytoma, astrocytoma, glioma, pilocytic astrocytoma, cerebellar medulloblastoma

[c]HGG = glioblastoma multiforme, anaplastic astrocytoma, anaplastic oligodendroglioma

[d]HGG = glioblastoma multiforme, primitive neuroectodermal tumour, glial cell sarcoma, anaplastic astrocytoma, anaplastic oligodendroglioma

*Statistically significant ($p < 0.05$)

Table 3 Summary of study details for exercise intervention studies

Authors	Sample size	Treatment status		Intervention details		Assessed			
		During treatment	Post-treatment	Aerobic exercise only	Aerobic and resistance exercise	Effect	Feasibility	Safety	Acceptability
Case-reports									
Levin et al. [25]	n = 2	x	x		x	x	x	x	
Hansen et al. [21]	n = 1	x			x	x	x	x	
Troschel et al. [30]	n = 1	x		x		x	x	x	
Pre-post intervention studies									
Capozzi et al. [18]	n = 24	x			x	x	x	x	
Ayotte & Harro [16]	n = 7		x	x			x	x	
Milbury et al. [26]	n = 5	x			Yoga	x	x	x	
Case–control study									
Bartolo et al. [17]	n = 43		x		x	x			
Randomised, controlled trials									
Gehring et al. [20]	n = 34		x	x		x	x	x	x
Milbury et al. [31]	n = 20	x			Yoga	x	x	x	
Gehring et al. [29]	n = 34		x	x		x			

duration (70 [20] to 100% [16]), mean distance cycled per session (6.27 ± 1.29 km) [16], and mean MET-hours completed per week (43.7 MET-h/wk) [30]. The most common reason for session absence was illness/disease progression [18, 20]. The one study that assessed acceptability, patient-reported satisfaction was rated as "good" to "excellent" by the majority (84%) [20].

Summary of exercise intervention outcomes

Level of evidence for any given outcome: III-4 to III-2. The effect of exercise on objectively-assessed outcomes and patient-reported outcomes are presented in Table 4. Evidence from one RCT supports clinically- and statistically-significant changes in overall symptoms severity [31]. Statistically-significant differences ($p < 0.05$) in aerobic capacity, body composition and PA levels were supported by individual RCTs [20, 31]. Outcomes that were found to have a clinically-significant improvement (although $p > 0.05$) included neurocognitive domains (particularly attentional inhibition, attention span and auditory select attention) [29, 31], mental health-related QoL and mood disturbance, all of which were supported by two, small sample (n = 20–34), RCTs [29, 31]. Symptom interference with daily life was measured in a single RCT and had a clinically-significant change [31]. Within the RCTs no consistent change was observed in self-reported physical functioning [29, 31]. Two RCTs reported improvements in fatigue and cognition, however these changes were only supported clinically in single studies [29, 31]

Preliminary evidence from case–control, pre-post intervention studies, and case-reports suggest that clinically-relevant improvements were observed in lower-body strength, balance, QoL [18], symptom severity and interference total score [26], symptom severity related to brain cancer [31], brain tumour symptoms interference to daily life [17, 31], fatigue [18], and sleep [26] following exercise. While upper-body strength, physical functioning, and shortness of breath have also been assessed, no changes were observed [17, 18, 21, 25, 26, 29, 31].

Discussion

Following a brain cancer diagnosis, persistently low PA levels were observed, with most patients failing to participate in PA levels recommended to cancer survivors [10, 32]. Yet, higher levels of PA post-diagnosis of brain cancer may be associated with better health outcomes, including higher QoL, fewer brain cancer specific concerns and potentially improved survival. Additionally, there is also preliminary evidence that suggests exercise interventions can be safe, feasible and beneficial for symptom management and improving aerobic capacity, body composition and PA levels. However, the strength of this evidence is weak.

Similar to what is observed in other cancer cohorts, this review suggests the proportion of insufficiently active patients increases during treatment [33–36]. After treatment, levels of PA are lower for patients with brain cancer (22–41% meeting guidelines) compared to more common cancers (e.g., mixed cohort of breast, colorectal, prostate cancer-54% meeting guidelines) [36]. This may be reflective of the unique challenges experienced by those with brain

Table 4 Summary of changes (either statistically- or clinically-significant) observed in objectively-assessed and patient-reported outcomes evaluated in exercise intervention studies involving patients with brain cancer

Authors	Aerobic capacity	Upper-body strength	Lower-body strength	Functional capacity (walk test)	Sitting balance	Standing balance	Gait	Body composition	Cognition
Objectively-assessed outcomes									
Case-reports[a]									
Hansen et al. [21]	☑cs	☑	☑cs	☑		☑cs		☐	
Levin et al. [25]	?	☑	☑	☑				?	
Troschel et al. [30]	☑cs								
Pre-post intervention studies									
Capozzi et al. [18]		☑ss	☑cs ss	☐				☑[b]ss ☐[c]	
Ayotte and Harro [16]									
Milbury et al. [26][d]									
Case–control studies									
Bartolo et al. [17]					☑cs	☑cs	☑cs		
Randomised, controlled trials									
Gehring et al. [20][d]	☑ss							☑ss	
Milbury et al. [31][e]									
Gehring et al. [29][e, f]									☑cs[g], ☑[h]☒[i]

Authors	Total score	Quality of life	Functional (social, emotional, occupational)	Mental health related quality of life[j]	Physical functioning	Symptom interference with daily life	Overall symptom severity	Mood disturbance	Cognition	Shortness of breath	Fatigue and tiredness	Sleep quality or insomnia	Physical activity
Patient-reported outcomes													
Case-reports[a]													
Levin et al. [25]				?	?			☑cs				☐	?
Hansen et al. [21]		☑	☐☒[k]		☑				☐	☑	☐	☑	
Troschel et al. [30]													
Pre-post intervention studies													
Capozzi et al. [18]		☑ss cs						☑ss cs			☑ss cs		
Ayotte and Harro [16]													
Milbury et al. [26][d,l]	☑ss ss[m]			☑cs	☐	☐	☐	☑			☐	☑ss cs	

Table 4 (continued)

Authors	Total score	Quality of life	Functional (social, emotional, occupational)	Mental health related quality of life[j]	Physical functioning	Symptom interference with daily life	Overall symptom severity	Mood disturbance	Cognition	Shortness of breath	Fatigue and tiredness	Sleep quality or insomnia	Physical activity
Case–control studies													
Bartolo et al. [17]	☑cs[n]				☑	☑cs[o]			☑cs				
Randomised, controlled trials													
Gehring et al. [20][d]													☑ss
Milbury et al. [31][e]				☑cs	☐	☑cs	☑ss cs	☑cs	☑cs		☑		
Gehring et al. [29][e,f]		☐		☑cs	☒			☑cs	☑		☑cs	☑	

☑ Positive outcome ☒ Negative outcome ☐ no change ? Varied results (case-reports only) cs = clinically significant ss = statistically significant

[a]Outcomes with changes of ≥ 20% were considered clinically-relevant for case-reports

[b]Decrease in total waist circumference measure

[c]No significant change in body weight, chest, hip or bicep circumference

[d]Within group analysis

[e]Between group analysis

[f]Presented effect sizes for outcomes. An effect size of ≥ 0.5 (medium or greater) were considered clinically-relevant

[g]Attention (attentional inhibition, attention span and, auditory select attention and working memory)

[h]Attention (information processing speed), memory (immediate verbal recall) and executive function (alternating attention/shifting, auditory working memory/shifting)

[i]Attention (sustained selective attention)

[j]Mental health component summary of the short form 36 (SF-36)

[k]Emotional functioning and role functioning remained stable; and social functioning decreased

[l]Statistical significance = $p \leq 0.1$ as specified by original paper

[m]MD Anderson symptom inventory core symptoms and interference—total score

[n]Functional independence measure (FIM) total score

[o]Functional Independence measure (FIM) activities of daily living subscale

cancer including disease- and treatment-related side-effects, such as instability and fatigue, which make engaging in PA and exercise particularly difficult [6, 8, 37]. Limitations of the reviewed studies include: weaker study design (mostly cross-sectional), high attrition rates, mixed cohorts (mostly newly diagnosed) and lack of objective PA measurement. These limitations likely influence our findings towards overestimates of PA levels rather than underestimates. This raises questions whether the PA targets [10, 32] set for all cancer survivors are realistic and achievable for the brain cancer population.

Consistent with the literature from other cancer cohorts [38], this review identified higher PA was associated with better QoL and lower brain cancer treatment-associated symptoms, although findings were supported statistically by only one prospective study. Further, we found preliminary evidence from exercise trials (including two RCTs) which supports exercise as beneficial to specific health outcomes, including overall symptom severity, aerobic capacity, body composition, neurocognitive domains, mental-health related QoL, mood and PA. However, limitations necessitate caution in the interpretation of these findings. Within the observational PA literature, limitations include small sample sizes, heterogenous samples within and between studies, high attrition rates and lack of objective PA assessment. Within the exercise trial literature, there is a lack of RCTs, limited number of studies contributing to the evidence-base for any given outcome and small and heterogenous samples.

Although exercise was deemed feasible, the wide range in recruitment and retention rates suggest that integrating exercise for brain cancer is complex. Participants were mostly newly diagnosed and those with comorbidities and significant side-effects (e.g., cardiac disease, neurological deficits) were deemed ineligible to participate [16, 18, 20]. This presents a potential recruitment bias which has been observed in other cancer populations (but is potentially exaggerated in brain cancer) [39], whereby only the 'more well' patient volunteers or is eligible to participate. Adverse events were few and mild suggesting exercise is safe. However, safety evaluation in exercise oncology has been identified as an area in need of improvement [40]. Therefore, it is plausible that risk of adverse events through exercise may be underestimated. Except for one study, all trials involved highly supervised exercise. As such, the safety of unsupervised exercise following brain cancer remains unclear. This is an issue as access to exercise services is inequitable, with lower socioeconomic status or those living in rural/regional areas less likely to have access to supervised exercise compared with their higher socioeconomic or urban counterparts [41–43]. The appropriateness of telehealth as an alternative to face-to-face supervision may be an important future research direction, particularly in the COVID-19 context [44].

Whilst acknowledging the numerous limitations, encouragingly, there are trends of improvement in health outcomes and exercise is safe and feasible. Further, viewed in the context of the robust and strong wider PA and exercise oncology evidence-base, findings presented in this review suggest that it is likely relevant and important to encourage those with brain cancer to be physically active from diagnosis through to post-treatment. It is also clear that the brain cancer cohort has unique challenges that may influence patient interest, acceptance and feasibility of engaging in PA: even if benefits can be derived through PA, brain cancer survivorship may make attaining these benefits only possible for a subgroup. There is a need for future research to inform what may constitute realistic PA targets for this cohort and whether these targets should differ according to brain cancer subtype and/or survivorship stage. Based on the current evidence, cautious interpretation of the potential benefits of PA and exercise is warranted.

Overall, higher quality, population-based, longitudinal studies investigating PA levels from time of diagnosis throughout treatment and post-treatment are needed to better understand rates and patterns of PA. Findings from higher quality research (e.g., larger RCTs) will better articulate who can benefit through exercise and in what way. Given brain cancer is rare, this will likely require multi-centre, national or international trials to ensure sufficient numbers for adequately-powered analysis of outcomes. Until findings from future trials become available, it is likely appropriate to promote and encourage those with brain cancer to be physically active in as many ways as possible. However, the need or ability of those with brain cancer to meet current PA guidelines promoted to *all* people with cancer remains unclear. In line with exercise prescription guidelines, a tailored, individualised approach to exercise prescription which accommodates fluctuating symptoms and unique circumstances (e.g. stage of diseases, functional capacity, treatment toxitcity) that present alongside brain cancer is necessary [45–47].

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Declarations

Conflict of interest The authors declare no conflict of interest.

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