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The relationship between social determinants of health and neurocognitive and mood-related symptoms in the primary brain tumor population: A systematic review

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Abstract

Social determinants of health (SDOH) impact cancer-related health outcomes, including survival, but their impact on symptoms is less understood among the primary brain tumor (PBT) population. We conducted a systematic review to examine the relationships between SDOH and neurocognitive and mood-related symptoms among the PBT population. PubMed, EMBASE, and CINAHL were searched using PROGRESS criteria (place of residence, race/ethnicity, occupation, gender/sex, religion, education, socioeconomic status, and social capital) on March 8th, 2022. Two individuals screened and assessed study quality using the NHLBI Assessment Tool for Observational Cohort and Cross-sectional Studies. Of 3006 abstracts identified, 150 full-text articles were assessed, and 48 were included for a total sample of 28 454 study participants. Twenty-two studies examined 1 SDOH; none examined all 8. Four studies measured place of residence, 2 race/ethnicity, 13 occupation, 42 gender, 1 religion, 18 education, 4 socioeconomic status, and 15 social capital. Fifteen studies assessed neurocognitive and 37 mood-related symptoms. While higher education was associated with less neurocognitive symptoms, and among individuals with meningioma sustained unemployment after surgery was associated with depressive symptoms, results were otherwise disparate among SDOH and symptoms. Most studies were descriptive or exploratory, lacking comprehensive inclusion of SDOH. Standardizing SDOH collection, reducing bias, and recruiting diverse samples are recommended in future interventions.

Keywords

mood | neurocognitive symptoms | primary brain tumor | social determinants of health

The World Health Organization and the Center for Disease Control and Prevention's *Healthy People 2030* have called for increased focus on the social determinants of health (SDOH).[1,2] The SDOH are broadly defined by the World Health Organization as the "conditions in which people are born, grow, work, live, and age that affect a wide range of health, functioning, and quality-of-life outcomes and risks."[2] The SDOH are important contributing factors to health inequities. Recent reviews of SDOH among a broad group of diseases, including cancer, have focused on objective outcomes such as mortality, survival, hospital readmissions, and health outcomes-including patient-reported outcomes.[3–6] Research within the field of Neuro-Oncology has focused on improving outcomes such as mortality and survival, and are driven by the fact that while the incidence of central nervous system tumors is low, they are the ninth leading cause of cancer-related deaths.[7] Studies exploring the impact of SDOH among individuals with central nervous system tumors, including primary brain tumors (PBTs), have similarly focused on cancer risk and the impact of SDOH on access to care or survival.[7–9] Key SDOH including, sex, race/ethnicity,[10] and access to Neuro-Oncology care all have been linked to survival among the PBT population.[11,12]

As a primary driver of survivorship and quality of life, patient symptoms are an important indicator of disease progression and may be influenced by the SDOH. Elements of SDOH, such as social isolation, disparities in education, and lower socioeconomic status, have been related to the risk of

developing cognitive decline and dementia among the general population.[13] Living in neighborhoods with higher levels of poverty have been associated with higher pain intensity among women with breast cancer.[14] Women and those with less social support are more likely to report fatigue among melanoma survivors.[15] The link between symptoms and SDOH are less studied among the PBT population. Individuals with a PBT experience neurologic, cognitive, and mood-related symptoms that occur with the development of a PBT or with subsequent treatment.[16] Mood disturbance, such as depressive symptoms, may affect an estimated 21% to 40% of individuals with a PBT.[17,18] These symptoms persist over time and have been linked to poorer quality of life and shortened survival.[19] Neurocognitive symptoms similarly impair quality of life and are distressing for individuals with a PBT.[20] Therefore, the aim of this systematic review is to examine the relationship between the SDOH and neurocognitive and mood-related symptoms among adult individuals living with a PBT. In addition, we aim to identify and quantify which SDOH were measured in studies focused on neurocognitive and mood-related symptoms of patients with a PBT. Exploration of SDOH with physical symptoms, including sleep-related symptoms and seizures, will be explored in a subsequent review.

Materials and Methods

A literature search of PubMed, EMBASE, and CINAHL was designed to identify relevant research studies that examined the relationships between the SDOH and symptoms of individuals living with a PBT. The search was conducted on March 8th, 2022. The SDOH were identified using the PROGRESS framework,[21] which serves as a guiding criterion for key SDOH, inclusive of socioeconomic factors, and has been used among other systematic reviews assessing intervention effects and the relationships between SDOH and symptoms, such as pain.[22] The PROGRESS criteria is a framework and acronym that serves as a guide to identify key SDOH factors. The individual letters of PROGRESS stand for place of residence, race/ethnicity, occupation, gender/sex, religion, education, socioeconomic status, and social capital.[21] Each of the PROGRESS criterion and key MESH terms, crafted by a research librarian (D. C.) and based on key symptoms patients with PBTs report,[23–25] were used to identify each study examining SDOH. These search terms are listed in Supplementary Table S1.

Included articles for consideration examined the relationship between at least 1 SDOH and symptoms among individuals 18 years or older with a PBT. Studies had to be published as peer-reviewed quantitative, qualitative, or mixed methods studies and written in English. No publication year limitations were set. Review articles, editorials, case studies, conference abstracts, and dissertations were not included. Publications that focused on non-human research, family caregiver reports of symptoms, childhood PBTs, or studies focused on symptoms reported during awake craniotomies and language mapping surgeries were not included. Publications focused on study samples including <50% PBTs, individuals with certain tumor types, including exclusively spine tumors, brain metastases, pituitary tumors, craniopharyngioma, chordoma, and esthesioblastoma tumors, were excluded from consideration.

The database search resulted in 2995 identified publications, with 11 other articles focused on symptoms identified through additional sources. Due to the large number of identified full-text articles and broad scope of SDOH meeting the review criteria ($n = 74$), this review reports only on studies reporting neurocognitive and mood-related symptoms. Figure 1 shows the PRISMA Flow Diagram detailing the article selection process for this systematic review and narrative synthesis.[26] Two screeners independently reviewed titles, abstracts, and full-text articles (M.S. and A.K.) using Covidence[27] with a third screener (T.A.) to review discrepancies in voting. Main outcomes extracted included the measurement and key findings related to SDOH and symptoms and information on sample characteristics, including tumor types, inclusion criteria, time period, the country where the study was conducted, and study design. The PRISMA 2020 Guideline is presented in Supplementary Table S2. The 48 included studies were assessed independently by 2 reviewers (M.S. and M.J.) for quality and bias using the National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool for Observational Cohort and Cross-sectional Studies.[28] Using the NHLBI Quality Assessment Tool, bias risk scores were calculated for each study based on 14 methodological quality items rated as "yes," "no," or with other nonscorable marks such as "not reported," "cannot determine," and "nonapplicable." Bias risk scores ranged from poor (<50%), fair (≥50%–≤70%), and good (>70%).

Results

Out of 3006 articles identified and screened, 150 full-text articles were assessed for eligibility, and 74 articles were identified as eligible for inclusion. Of these 74 articles, 48 articles published between 1996 and 2021 focused on neurocognitive and mood-related symptoms. All studies were of nonexperimental design or secondary analyses of trials with 27 cross-sectional studies, including 1 mixed-methods study, and 21 longitudinal studies. Most studies were conducted in the United States ($n = 12$), Germany ($n = 10$), or the Netherlands ($n = 5$). Thirty studies were from single institutions, 13 from multiple sites, and 4 used data from national databases. Most studies included <200 participants. Tumor types included in the sample were mixed: 26 studies listed broad inclusion criteria for brain tumors, PBTs, intracranial and mixed tumors; while others recruited those with specific tumor types, including glioma ($n = 15$), rare tumors such as adult-onset medulloblastoma ($n = 1$)[29] or ependymoma ($n = 1$),[30] and meningioma ($n = 5$).[31–35] Although publications focused on study samples including ≥50% PBT, most studies focused exclusively on PBTs. Six studies had samples consisting of <88% PBTs, and these studies instead consisted of PBTs with other lesions (ie, brain metastasis and a small number of vascular lesions).

Table 1 lists the pooled sample's sociodemographic characteristics. Gender or sex, marital status, educational

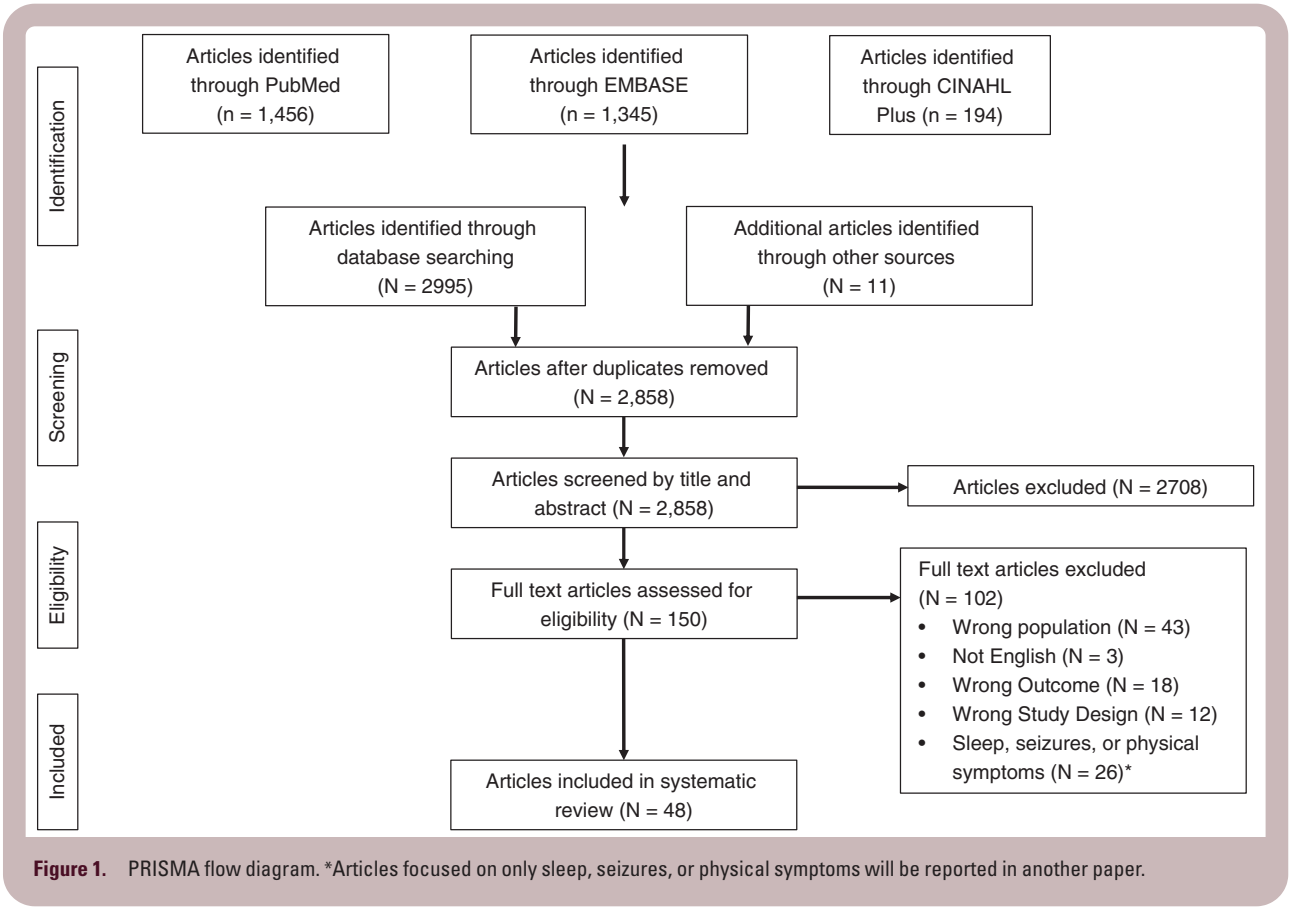

Figure 1. PRISMA flow diagram. *Articles focused on only sleep, seizures, or physical symptoms will be reported in another paper.

attainment, and race/ethnicity of the samples were reported as demographics in many of the studies, but not among all the studies: Information on marital status, which was categorized as 1 form of social capital in this review, was reported in 19 of the 48 included studies. Twenty-two studies reported educational attainment levels, with 8 reporting mean educational attainment levels on subsets of their sample. Of 6 studies detailing sample information on race/ethnicity, only 2 examined the relationship between these characteristics and symptoms in analyses.

Relationships of SDOH With Neurocognitive and Mood-Related Symptoms

None of the 48 included studies examined all 8, and nearly half ($n = 22$) of the studies examined the relationship with only 1 of the PROGRESS criteria. Table 2 details the number of PROGRESS criteria measured across the 48 studies: Including 11 studies examining neurocognitive symptoms, 33 examining mood-related symptoms, and 4 studies examining both neurocognitive and mood-related symptoms.[30,34,36,37] Figure 2 graphically presents the timing of patient recruitment to the included studies across the PBT trajectory. Twelve studies recruited patients across the disease trajectory, including patients from the time of diagnosis to either follow-up or survivorship and remission.[29,30,32,37–45] The majority (12/16) of cross-sectional studies targeted a specific recruitment time point either around the time of diagnosis or before completion of treatment, including chemotherapy or radiation. Among the longitudinal studies, studies assessing neurocognition at specific recruitment time points focused on assessing the effect of either surgery or radiotherapy on neurocognitive symptoms. Only 5 studies focused solely on clinically stable individuals with a PBT after the completion of therapy, and of which 4 measured neurocognitive symptoms.[36,46–48]

Study bias.—Bias assessment revealed that 61% of the studies were fair in quality, 31% poor, and only 8% good. Individual bias assessment scoring for the included studies is shown in Table 3. Of the 4 studies rated good, 2 examined mood-related symptoms (distress and mood disturbance),[38,49] 1 neurocognitive symptoms,[48] and 1 both mood and neurocognitive symptoms.[37] However, mood-related symptoms measured among the studies with good bias levels varied as the 2 measuring neurocognitive symptoms examined different SDOH, limiting the ability to draw conclusions from studies with limited bias.

Neurocognition.—All 15 studies examining neurocognitive symptoms measured some aspect of either neurocognition, cognition, or neuropsychological functions among a variety of tumor types including meningioma,[34] glioma[36,40,46,48,68,74,51,53] temporal lobe lesions,[54] medulloblastoma,[29] ependymoma,[30] and PBTs[37,45,47] (Supplementary Table S3). Sixty-seven percent

Table 1. Pooled Sample Characteristics

Study characteristic results (*N* = 48 studies)	Pooled	
Sample size, *Range*	28 454 (24–15320)	
Controls sample size, *Range* (*n* = 7 studies)	5285 (20–4765)	
Sample age, *Range*	18–90	
	N	%
Sex (*n* = 28 171) (*n* = 48 studies)		
Male	10 320	37
Female	17 851	63
Marital status (*N* = 3077 participants)* (*n* = 19 studies)		
Single	670	22
Partnered	2407	78
Race or Ethnicity (*n* = 1245 participants)* (*n* = 6)		
White/Caucasian	1127	91
Black/African American	59	5
Asian	5	<0.5
American Indian	5	<0.5
Other	23	2
Hispanic	26	2

*Sample demographic numbers were calculated from studies reporting the listed information. Control sample sociodemographic characteristics not included in totals for sex, marital status, or Race/Ethnicity.

were cross-sectional with sample sizes ranging from 24 to 203 (median = 70). The most measured SDOH with neurocognitive symptoms was gender/sex (73% of studies) and education (66% of studies). Most studies used objective measures in the form of formal cognitive assessment (73%), and 7 used subjective self-reported measures (47%). Three of the fifteen studies (20%) used both formal cognitive assessment and subjective measures. Generalizability of findings are limited by study quality, varied populations and timepoints of assessments, and use of varied measures.

Most studies using subjective measures of neurocognitive symptoms assessed self-reported cognitive function,[30,34,37,46–48] with 1 assessing neurocognition.[36] The most common subjective measure used was the Cognitive Functioning Scale,[36,46,48] followed by the functional assessment of cancer therapy-cognitive function (FACT-Cog),[37,47] and the cognitive failure questionnaire.[34,48] Studies using formal cognitive assessments reported on constructs such as objective cognitive functioning,[46,68,51] impairment[37] or dysfunction,[40] neurocognition,[29,45,53] neuropsychological functioning,[45,48] verbal and visual memory,[54] and parietal lobe higher-order deficits or cognitive deficits.[74] Seven of the 11 studies measuring neurocognition with objective measures consisting of test batteries made up of multiple tests such as the Wechsler Adult Intelligence Scale-Revised,[29,40,46,48] Rey-Osterrieth Complex Figure Test,[45,54] and Trail Making Tests[29,45] among others. Results are presented across the subjective and objective measures of neurocognitive symptoms below.

Among the 15 studies assessing neurocognitive symptoms, none examined race/ethnicity or religion. Disparate results were found between neurocognitive symptoms

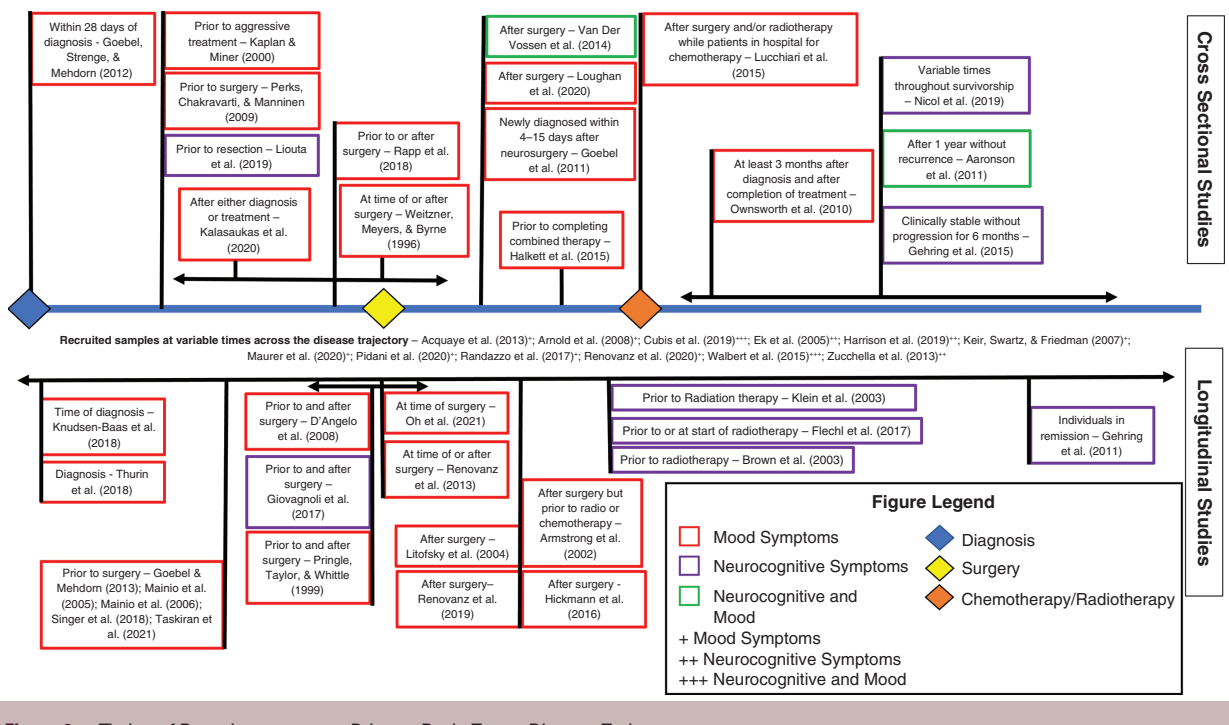

Figure 2. Timing of Recruitment across Primary Brain Tumor Disease Trajectory.

Table 2. Number of PROGRESS Criteria Assessed With Symptoms Among Included Studies

PROGRESS criterion	All studies *N* = 48	Neurocognitive studies *N* = 11	Mood-related studies *N* = 33	Both neurocognitive and mood-related studies *N* = 4
Place of residence	4	0	3	1
Race/Ethnicity	2	0	2	0
Occupation	13	2	10	1
Gender/sex	42	8	31	3
Religion	1	0	1	0
Education	18	8	8	2
Socioeconomic status	4	0	3	1
Social capital	15	0	13	2

and occupation, gender/sex, and social capital, with studies being limited by heterogenous or distinct sample populations,[34,37] small sample sizes,[37,40] and fair to poor study quality.[34,40,48] Socioeconomic status, measured as individual level income[30] and the impact of where care was received in relation to study participant birth country (ie, place of residence),[34] were each reported in only 2 studies among specific populations of individuals with either ependymoma and meningioma, respectively. Both studies were fair in quality which limited further generalizability (Supplementary Table S3).

Seven of the 10 studies measuring educational attainment found associations with higher education levels and either neurocognitive symptoms[29,40,46–48,53,54] or specific facets of neurocognition.[40,47] Overall, higher educational attainment was linked to better cognitive functioning,[29,40,46,53] including improved cognitive functioning,[48] postoperative visual memory,[54] and perceived cognitive abilities.[47] Four of these studies were exclusively in glioma populations.[40,46,48,53] Two studies found that after treatment patients with low-grade glioma and higher education levels reported better neurocognition.[46,48] Three studies reported no association between education level and aspects of neurocognitive functioning, but findings may have been impacted by sample diversity in terms of treatment or tumor type,[34,45] bias levels,[36] or descriptive analyses not accounting for confounding variables.[45]

Gender and sex were the most assessed SDOH with neurocognitive symptoms, with 8 of the 11 studies examining gender/sex finding no relationship.[29,34,45,47,48,68,74,51] However, 5 of the 8 negative studies were limited to cross-sectional design.[29,34,45,47,74] Of the 11 studies, 7 exclusively recruited individuals with gliomas, but synthesis of results were limited by the select study population inclusion criteria, measures, and mixed results across studies.

Mood.—Among the 37 studies assessing mood-related symptoms, depression was reported in 21 studies, anxiety in 14, and distress/stress in 11 (Supplementary Table S4). Thirty-two studies reported on patient-reported mood-related symptoms, while 5 studies reported on mood from other sources such as ICD codes or physician-reported diagnoses.[32,33,56,57,59] The most common mood-related measure was the Hospital Anxiety and Depression Scale,[31,34,35,70,60,72,63] followed by the NCCN Distress Thermometer,[41,43,44,49,72,65] and the Beck Depression Inventory.[21,58,67,55,50] Four studies used quality of life or symptom measures such as the EORTC QLQ,[64,61] SF-35,[36] or MDASI-BT[30] to report on emotional well-being or mood-related subscales. Since results were disparate between the broad group of mood-related symptoms and SDOH, the relationships between SDOH assessed and the subcategories of depression, anxiety, and distress/stress are further delineated below. Information on studies measuring other mood-related symptoms is listed in Supplementary Table S4.

Depression.—

Twenty-one studies examined depression among a variety of tumor types, including meningioma,[31–35] gliomas,[56,57,70] PBTs,[21,37,42,58] and mixed groups of intracranial[42,60,72] or brain tumors.[39,59,67,55,50,71] Fifty-seven percent were cohort or longitudinal studies, and sample sizes ranged from 28 to 15 320 (median = 109). The most measured SDOH with depression was gender/sex (90%), followed by social capital (52%), and race/ethnicity (10%). Religion and socioeconomic status were both evaluated in 1 study each. No association was found with religion; However, travel cost (but not socioeconomic status) was associated with more depression.[42,55] Disparate results were found between depression and place of residence, race, occupation, gender/sex, education, and social capital. Among the 2 studies examining either race or ethnicity with depression, Litofsky et al.[57] examined race while Arnold et al.[39] examined ethnicity in different tumor populations-limiting the generalizability of findings.

Among the 4 studies measuring place of residence and depression, 1 large cohort study reported a relationship between depression and rural residence among 4275 individuals with a brain tumor in Korea;[59]; However, this relationship was not sustained 1 year after surgery. The second study examining rural–urban residence found no relationship with rural residence among 15 320 individuals diagnosed with a meningioma in the United States.[32] Two studies found a relationship between place of residence, measured as residency and being born in the study host country, and depression.[34,42]

Table 3. Study Bias Assessment

Author & year	Q1	Q2	Q3	Q 4	Q 5	Q6	Q7	Q 8	Q 9	Q10	Q 11	Q12	Q13	Q14	# of Items free of bias	% of Items free of bias	Quali-tative rating
Observational cohort and Longitudinal Studies																	
Armstrong et al., 2002[50]	Yes	No	NR	Yes	No	No	Yes	Yes	Yes	No	No	CD	No	No	5	36	Poor
Brown et al., 2003[51]	Yes	No	NR	NR	No	Yes	Yes	Yes	Yes	No	Yes	CD	No	No	6	43	Poor
D'Angelo et al., 2008[52]	Yes	Yes	NR	Yes	No	No	Yes	NA	Yes	No	Yes	CD	No	Yes	7	50	Fair
Flechl et al., 2017[53]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	CD	No	No	8	57	Fair
Gehring et al., 2011[48]	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	CD	Yes	Yes	10	71	Good
Giovagnoli et al., 2017[54]	Yes	No	NR	No	No	CD	Yes	Yes	NR	No	No	CD	NR	No	3	21	Poor
Goebel & Mehdorn, 2013[35]	Yes	Yes	Yes	No	No	CD	Yes	Yes	Yes	No	Yes	CD	Yes	No	8	57	Fair
Hickmann et al., 2016[55]	Yes	NR	Yes	Yes	No	No	Yes	NR	Yes	No	No	CD	No	No	5	36	Poor
Klein et al., 2003[47]	Yes	NR	NR	NR	Yes	Yes	Yes	Yes	CD	CD	Yes	CD	NA	Yes	7	50	Fair
Knudsen-Baas et al., 2018[56]	Yes	Yes	CD	Yes	Yes	No	CD	NA	Yes	No	Yes	CD	NA	Yes	7	50	Fair
Litofsky et al., 2004[57]	Yes	Yes	CD	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	CD	NR	No	9	64	Fair
Mainio et al., 2005[19]	Yes	Yes	NR	Yes	No	Yes	Yes	No	Yes	No	Yes	CD	Yes	No	8	57	Fair
Mainio et al., 2006[58]	Yes	No	NR	Yes	No	No	Yes	No	Yes	No	Yes	CD	NR	Yes	6	43	Poor
Maurer et al., 2020[32]	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	No	No	CD	NR	Yes	7	50	Fair
Oh et al., 2021[59]	Yes	Yes	CD	Yes	Yes	Yes	Yes	Yes	No	No	No	CD	NR	Yes	8	57	Fair
Pringle, Taylor, & Whittle, 1999[60]	Yes	No	NR	No	No	Yes	Yes	Yes	NR	No	Yes	CD	Yes	No	6	43	Poor
Renovanz et al., 2013[61]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	NR	No	No	CD	CD	Yes	7	50	Fair
Renovanz et al., 2019[62]	Yes	Yes	NR	Yes	No	No	Yes	Yes	NR	No	No	CD	No	No	5	36	Poor
Singer et al., 2018[63]	Yes	Yes	No	Yes	No	No	Yes	No	Yes	No	Yes	CD	No	No	6	43	Poor
Taskiran et al., 2021[64]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	NR	No	CD	CD	NR	No	7	50	Fair
Thurin et al., 2020[33]	Yes	Yes	CD	No	Yes	No	Yes	Yes	Yes	No	Yes	CD	NR	Yes	8	57	Fair
Cross-sectional Studies																	
Aaronson et al., 2011[36]	Yes	Yes	Yes	No	CD	No*	No*	Yes	No	No*	No	CD	No*	Yes	5	50	Fair
Acquaye et al., 2013[38]	Yes	No	Yes	Yes	Yes	No*	No*	Yes	Yes	No*	Yes	CD	No*	Yes	8	80	Good
Arnold et al., 2008[39]	Yes	No	NR	Yes	Yes	No*	No*	Yes	Yes	No*	Yes	CD	No*	Yes	7	70	Fair
Cubis et al., 2019[37]	Yes	Yes	NR	Yes	Yes	No*	No*	Yes	Yes	No*	Yes	CD	No*	Yes	8	80	Good
Ek et al., 2005[40]	Yes	Yes	NR	Yes	No	No*	No*	Yes	Yes	No*	No	CD	No*	No	5	50	Fair
Gehring et al., 2015[46]	Yes	No	Yes	Yes	Yes	No*	No*	Yes	NR	No*	No	CD	No*	Yes	6	60	Fair
Goebel et al., 2011[65]	Yes	Yes	Yes	Yes	No	No*	No*	Yes	Yes	No*	Yes	CD	No*	No	7	70	Fair
Goebel, Strenge, & Mehdorn, 2012[66]	Yes	CD	No	Yes	CD	No*	No*	Yes	Yes	No*	No	CD	No*	No	4	40	Poor
Halkett et al., 2015[49]	Yes	No	Yes	Yes	Yes	No*	No*	Yes	Yes	No*	Yes	CD	No*	Yes	8	80	Good
Harrison et al., 2018[29]	Yes	Yes	Yes	Yes	Yes	No*	No*	Yes	No	No*	No	CD	No*	Yes	7	70	Fair
Kalasaukas et al., 2020[31]	Yes	No	NR	Yes	Yes	No*	No*	Yes	Yes	No*	Yes	CD	No*	No	6	60	Fair
Kaplan & Miner, 2000[67]	Yes	No	NR	NR	Yes	No*	No*	Yes	Yes	No*	Yes	CD	No*	No	5	50	Fair

Table 3. Continued

Author & year	Q1	Q2	Q3	Q 4	Q 5	Q6	Q7	Q 8	Q 9	Q10	Q 11	Q12	Q13	Q14	# of Items free of bias	% of Items free of bias	Qualitative rating
Keir, Swartz, & Friedman, 2007[41]	Yes	Yes	NR	Yes	No	No*	No*	Yes	Yes	No*	Yes	CD	No*	No	6	60	Fair
Liouta et al., 2019[68]	Yes	Yes	NR	Yes	No	No*	No*	No	NR	No*	Yes	CD	No*	No	4	40	Poor
Loughan et al., 2020[69]	Yes	Yes	Yes	Yes	No	No*	No*	Yes	No	No*	No	CD	No*	Yes	6	60	Fair
Lucchiari et al., 2015[70]	No	No	Yes	Yes	No	No*	No*	Yes	NR	No*	No	CD	No*	No	3	30	Poor
Nicol et al., 2019[47]	Yes	Yes	NR	No	Yes	No*	No*	Yes	No	No*	No	CD	No*	Yes	5	50	Fair
Ownsworth et al., 2010[71]	Yes	No	Yes	Yes	No	No*	No*	NR	Yes	No*	No	CD	No*	No	4	40	Poor
Perks, Chakravarti, & Manninen, 2009[71]	Yes	No	NR	No	No	No*	No*	Yes	NR	No*	No	CD	No*	Yes	3	20	Poor
Pidani et al., 2020[42]	Yes	Yes	CD	Yes	Yes	No*	No*	Yes	NR	No*	Yes	CD	No*	Yes	7	70	Fair
Randazzo et al., 2017[43]	Yes	Yes	NR	CD	No	No*	No*	No	NR	No*	No	CD	No*	No	2	20	Poor
Rapp et al., 2018[72]	Yes	Yes	Yes	No	No	No*	No*	Yes	NR	No*	Yes	CD	No*	Yes	6	60	Fair
Renovanz et al., 2020[44]	Yes	Yes	Yes	No	No	No*	No*	No	NR	No*	CD	CD	No*	Yes	4	40	Poor
Van Der Vossen et al., 2014[34]	Yes	Yes	Yes	Yes	No	No*	No*	No	Yes	No*	Yes	CD	No*	No	6	60	Fair
Walbert et al., 2015[30]	Yes	Yes	NR	Yes	No	No*	No*	No	Yes	No*	Yes	CD	No*	No	5	50	Fair
Weitzner, Meyers, & Byrne, 1996[73]	Yes	Yes	Yes	CD	No	No*	No*	Yes	NR	No*	Yes	CD	No*	No	5	50	Fair
Zucchella et al., 2013[45]	Yes	Yes	No	Yes	No	No*	No*	Yes	NR	No*	Yes	CD	No*	No	5	50	Fair

Abbreviations: CD, cannot be determined; NA, not applicable; NR, not reported; Q#, question #, etc.
*Questions 6, 7, 10, and 12 are only relevant to longitudinal studies. These questions were not counted towards the bias total among cross-sectional studies.
Q1, Was the research question or objective in this paper clearly stated?
Q2, Was the study population clearly specified and defined?
Q3, Was the participation rate of eligible persons at least 50%?
Q4, Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?
Q5, Was a sample size justification, power description, or variance and effect estimates provided?
Q6, For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?
Q7, Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?
Q8, For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?
Q9, Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
Q10, Was the exposure(s) assessed more than once over time?
Q11, Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
Q12, Were the outcome assessors blinded to the exposure status of participants?
Q13, Was the loss to follow-up after baseline 20% or less?
Q14, Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

Occupation was reported as employment status in the majority of included studies, with only Pidani et al.[42] measuring both occupation and employment status. Of the 8 studies examining the relationship between depression and occupation, 6 studies that included individuals with benign and malignant tumors did not find a relationship.[21,31,35,42,72,50] These negative studies included follow-up time points of 25 weeks,[35] 1 year,[19] or 6 years[50] after either surgery or treatment. Notably, 4 of the 8 studies examining employment included samples exclusively comprised of individuals with meningioma.[31,33–35] Among these, 2 found that being unemployed 1 year or later after surgery related to depressive symptoms[33,34]; however, worse depressive symptoms were not reported among meningioma patients in the immediate preoperative period.[31,35,55]

Nineteen studies measured gender/sex with depression, with 11 recruiting broad samples of patients with PBTs,[21,37,42,58] brain tumors,[39,59,55,71] and intracranial tumors.[59,72,71] Only 6 of the 19 studies found a relationship between gender/sex and depression.[32,39,59,60,50,52] Seven studies examined the relationship between depression and education[31,34,35,39,42,55,71]; however, only Arnold et al.[39] found a clear relationship between lower education level and higher levels of reported depression in a cross-sectional sample of 363 individuals with a brain tumor. Overall, studies examining education assessed small samples of patients with brain tumors (range = 28–194; median = 82), mostly through descriptive and exploratory analysis and at varying timepoints in the disease trajectory.

Of 11 studies measuring social capital, results were mixed as most studies did not find a relationship with marital or family status,[21,31,34,35,39,42,72] including 3 studies that recruited exclusively patients with meningioma.[31,34,35] However, relationships were found with social capital when the concept was measured as different types of support quality instead of the presence of support, as 3 studies found that loss of social group membership,[37] more marital difficulties,[67] and more family support was associated with worse depression.[50] One study found that better social support was related to less depressive symptoms in a small sample of patients 3 months after treatment.[71]

Anxiety.—

Fourteen studies examined anxiety among various tumor types, including meningioma,[31,32,34,35] gliomas,[56,70] PBTs,[37] and mixed groups of intracranial tumors,[52,60] lesions,[72] or brain tumors.[39,67,71,75] Sixty-four percent of the studies examining anxiety ($n = 9$) were cross-sectional with sample sizes ranging from 28 to 15 320 (median = 105). Of the studies examining anxiety, none examined the relationship between religion or socioeconomic status. No association was found between anxiety and occupation[31,34,35,72] or education level.[31,34,35,39,71] While race was not examined with anxiety, ethnicity was examined in 1 study, but no relationship was found.[39]

Disparate results were found between anxiety and place of residence, gender/sex, and social capital. Among 2 studies reporting on the relationship between place of residence and anxiety, neither found that either participant's birth country or rural–urban residence was related to participant anxiety.[32,35] Thirteen studies examined gender/sex in relation to anxiety, with 7 studies reporting significant findings.[32,37,39,52,56,60,75] Six of the seven studies reported higher levels of anxiety among women with PBT at various time points.[32,37,52,56,60,75] Negative reporting studies exhibited varied research methodologies, recruitment time periods, forms of measurement, cross-sectional study designs, and small sample sizes ranging from 28 to 194 (median = 62)-limiting generalizability of the findings.

Six of the eight studies measuring social capital (marital status,[34,35,39] relationship status,[72] family status,[31,35] or social support[71]) did not find a relationship with anxiety. Measured concepts related to social capital varied among the studies with marital status being the most common concept measured, and the majority of the studies exhibited poor to fair levels of study bias. Three of the 4 studies that examined marital status and found no relationship were cross-sectional, exhibited a fair level of bias, and recruited mixed tumor samples of either grade III/IV brain tumors,[67] mixed groups of brain tumor types,[39] or meningiomas.[34]

Distress.—

Eleven studies examined distress among various tumor types including meningioma,[31] gliomas,[49,63] intracranial tumors or lesions,[65,72] and PBTs,[41,43,73] brain tumors,[61,71] or brain cancer.[66] Eighty-two percent were cross-sectional with sample sizes ranging from 28 to 829 (median = 75). No studies examined the relationships between distress and place of residence, race/ethnicity, or religion. No relationship was found between distress and occupation. Only Halkett et al.[49] measured socioeconomic status as financial impact and found that it correlated with distress in a cross-sectional sample of patients with high-grade glioma. Disparate results were found between distress and gender/sex, education, and social capital. Of the 4 studies examining occupation (defined as employment status) and distress,[31,49,66,72] no relationships were reported; However, 2 were limited by small samples from single institutions and the exclusion of patients significantly ill or cognitively impaired who are less likely to be working.[31,72]

All 11 studies examined distress and gender/sex. Eighty-one percent of the studies assessing distress and gender/sex were cross-sectional, and more than half of the studies recruited samples smaller than 100.[9,41,63,66,71,73]The majority were in samples of mixed brain tumors, while 1 recruited solely individuals with glioma,[63]1 high-grade glioma[49] and 1 meningioma.[31]All but 2 focused on recruiting patients at the time of treatment.[41,43] Seven studies found no relationship.Two found that women with a PBT were more likely to report distress either at variable time periods throughout the illness trajectory or lower psychological distress scores during treatment.[43,73] Two studies found mixed relationships between gender/sex with distress: Gender/sex was not related to perceived stress scale scores[41] or distress on the Hospital Anxiety and Depression Scale[72]; however, women did report more higher distress[72] and more emotional concerns on the Distress Thermometer.[41]

Of 3 studies measuring educational attainment, only 1 found a correlation with distress among 116 individuals with high-grade glioma.[49] Social capital, including social support,[49,65] relationship[66] or marital status,[72] household status and family status,[31,66,76] was measured in 6 studies. Two studies reported relationships between distress and social support after surgery[65] and marital status or having children before surgery[72] among individuals with heterogeneous tumor types. Of the other 4 studies that did not find a relationship, 2 focused on heterogeneous groups of tumor types[71,72] or sample sizes smaller than 100.[31,66,71]

Discussion

To the best of our knowledge, this is the first systematic review examining the relationships between a variety of SDOH and PBT neurocognitive and mood-related symptoms. Table 4 presents the review of key findings

Table 4. Key Findings and Implications

Summary of key findings
1. Most studies were descriptive, exploratory, or cross-sectional with mixed tumor types and a lack of consistent operationalization of both social determinants and symptoms, limiting the ability to draw conclusions and generalize findings from the included studies-especially in relation to socioeconomic status and social capital.
2. Overall, gender and sex were the most frequently measured social determinants of health in this systematic review with education being reported almost as often only in studies exploring neurocognitive symptoms.
3. Religion was the least frequently measured social determinant of health. Key social determinants of health such as race and religion are underrepresented in PBT symptom research.
4. Higher educational attainment was an important predictor of lessened neurocognitive symptoms among individuals with a PBT.
5. Among individuals diagnosed with meningioma, sustained unemployment status was linked to depression after treatment.
6. The relationship between residence and mood should continue to be explored to further delineate contributing factors, whether related to cultural beliefs, access to care and distance traveled, the effect of supportive networks, comorbidities, and age on mood-related symptoms for individuals with PBTs.
Review implications
1. Less commonly measured SDOH should be further investigated to determine if they affect the symptoms of individual with a PBT.
2. Researchers should include social determinants of health identified by the PROGRESS criteria and clearly define social determinants of health measured in their studies.
3. Researchers should seek to reduce identified study biases including reporting of variable definitions used, recruiting diverse and representative sample populations, and collecting more longitudinal data.

and implications that are further contextualized below. Importantly, symptoms were the primary outcome in many of the reported studies, but SDOH were not. No study measured SDOH as a construct but instead focused on identifying key, but varying sociodemographic characteristics related to PBT symptoms. While most studies examined 1 SDOH according to the PROGRESS criteria, many SDOH coexist and compound health disparities. For example, previous literature has found that important SDOH, including educational attainment, marital status, and insurance status are all risk factors for delays in accessing care among brain tumor survivors.[76]

Place of residence can be an important factor related to *if and how* patients access health care. Among those with a PBT, geographic location is one of the most commonly reported barriers to clinical trial participation[77] and has been shown to be related to central nervous system tumor death.[78,79] Studies included in this review most commonly explored place of residence as the impact of rural–urban residence but with mixed results related to the occurrence of depression and anxiety.[32,59] This is not dissimilar to studies exploring the impact of rural–urban residence in the general population.[80,81] Our group recently published a systematic review evaluating distress and survival outcomes in those with a variety of cancers and found an association lending support to the potential impact of mood on outcomes such as survival.[82] **The relationship between residence and mood should continue to be explored to further delineate contributing factors, whether related to cultural beliefs, access to care and distance traveled, the effect of supportive networks, comorbidities, and age on mood-related symptoms for individuals with PBTs**.

Key SDOH such as race and religion are underrepresented in PBT symptom research. Race/ethnicity was reported among the demographic sample characteristics in only 6 studies, with samples overwhelmingly non-Hispanic and Caucasian. The relationship between symptoms of anxiety–depression and race/ethnicity were mixed and only explored in 2 studies in the United States or Canada, where the standard practice of reporting race and ethnicity is more common. The relationship between mood and race should continue to be explored as depression rates are higher among African Americans including among cancer survivors,[85,86] and studies in this review might have been underpowered to detect differences as samples were majority Caucasian. The inclusion of primarily Caucasian samples may reflect the higher incidence of PBTs in this population,[7,87] but also that minority groups are underrepresented in clinical trials in the United States due to issues related to historic mistrust of the health care system and also with clinicians being less likely to approach minority populations about enrollment in clinical trials.[88] Cultural differences may also be related to racial and ethnic differences among individuals with a PBT. Culture influences how cancer survivors report and perceive symptoms, perform self-care activities, and even the types of support they receive over the course of their illness trajectory.[83,84] More work is needed to understand if and how PBT symptoms differ among different racial and cultural groups.

Religion was the Least Measured SDOH. It was not assessed with neurocognition and found not to affect mood-related symptoms despite evidence that religion and spirituality contribute to better patient-reported physical health,[89] better quality of life,[90] overall distress, and anxiety.[91] Religion and spirituality are less commonly explored outside of end-of-life in the PBT disease trajectory[92]; although there is evidence that spirituality remains stable across the PBT trajectory and should be assessed early in the trajectory to address spiritual contributions to overall distress and anxiety.[91]

Inability to return to work is frequently seen in PBT patients, often from the time of diagnosis, with 40% or more

individuals unable to return to work.[93,94] Occupation, primarily measured as employment status, was only measured in 20% of neurocognitive studies and in 38% of studies examining depression.[19,31,33–35,42,50,72] Among a subset of 4 studies with samples of individuals with meningioma, depression was linked to unemployment status in the follow-up period after treatment.[33,34] Many individuals with a PBT report distress from their neurocognitive symptoms and how they both affect their ability to work[95] and contribute to depressive symptoms as time goes on; However, many studies in this review excluded patients with cognitive impairment scores at a certain threshold or those with functional impairments and other significant comorbidities. These excluded individuals might face increased risks for depressive symptoms since they may be less likely to continue working in the face of multiple cognitive impairments, functional limitations, and lack cognitive rehabilitation. Studies exploring this longitudinally in individuals with a PBT are needed.

Overall, Gender and Sex was the Most Frequently Measured SDOH in this Systematic Review. Gender or sex was measured in 92% of the studies examining mood and 73% of studies examining neurocognitive symptoms. Among the PBT population, women may report worse distress;[40] however, these reports vary by tumor type and grade. Ultimately, the relationship between gender/sex and symptoms was unclear as disparate results were reported among the included studies. This may be due in part to the diversity of included studies and the lack of reports on how gender and/or sex were measured. Biological sex is a variable mandated by most funding mechanisms as sex-based differences should be examined or accounted for in research studies. Since most studies did not define how they measured gender or sex, and none of the reviewed studies included non-binary categories for gender, we combined the terms under the umbrella of gender/sex in this systematic review. However, JAMA reporting guidelines clearly distinguish gender and sex and how they should be reported.[96] Future investigation into non-binary individuals' reported symptoms is needed to understand their experiences.

Socioeconomic status is often conceptualized to include educational attainment, income, and education. Since the PROGRESS criteria include educational attainment, education, and socioeconomic status as 3 separate criteria, we reported on the 3 separately. Among the included studies in this review, socioeconomic status was largely measured as individual income. However, there is increased interest in other measures of socioeconomic status at the neighborhood level and through measures of financial toxicity. Socioeconomic status was underreported compared to education among both neurocognitive[30] and mood-related symptom studies.[30,38,42,49]

Higher Educational Attainment was an Important Predictor of Lessened Neurocognitive Symptoms Among Individuals With a PBT. Education was measured in a minority (27%) of the studies examining mood and in 67% of studies examining neurocognitive symptoms. Categories of education attainment levels varied across studies, as well as reporting countries, and were not normalized. Among other cancer populations, including liver and prostate cancer, education levels have been associated with depression.[97,98] Education level is a common measure of cognitive reserve, which as outlined in a recent systematic review, has been related to cognitive outcomes among individuals with neurodegenerative and structural central nervous system diseases including tumors in cross-sectional studies.[99] While the relationship is less clear over time, most cross-sectional studies exploring neurocognitive symptoms mirrored this finding.

Social capital was the third most examined SDOH and included variables such as social support, family status, marital status, family support, relationship status, and social group membership. The included studies did not support a relationship with mood-related symptoms; although several studies pointed to a relationship between depression and specific measures of support quality such as social group membership, marital difficulties, family support, and social support. Other literature has found that social support has been linked to less anxiety among women[100] and lower reports of fatigue among melanoma survivors.[15] Among the PBT population, social connectedness has been linked to better quality of life.[101] One reason a relationship was not found might be that the measured concepts under the umbrella of social capital varied among the studies in this review and included concepts such as marital status, family status, or social support among others. Furthermore, the most measured variable of social capital was marital status, which was only examined in cross-sectional studies.

Limitations

This systematic review has several limitations. Most studies included in this review were descriptive, exploratory, or cross-sectional with mixed tumor types and a lack of consistent operationalization of both social determinants and symptoms, limiting the ability to draw conclusions and generalize findings from the included studies. Differing definitions of symptoms and constructs were used with different measures-including validated and unvalidated measures. Social Determinants of Health definitions across countries (ie, education) were not standardized, and the included studies may not have provided this context. Furthermore, our search terms related to the SDOH and patient symptoms may not be all-inclusive, especially as our understanding of how SDOH impact health outcomes continues to evolve. The PROGRESS criteria acronym was used as a guide in identifying key SDOH; however, we may have missed other important recognized SDOH, such as age and social isolation, as they were not reflected in our search terms. We believe the scope of this review is appropriate given the paucity of literature on SDOH among the PBT population, and it is an essential first step to identify which of the SDOH Neuro-Oncology has historically reported.

The SDOH listed in this review were reported as presented by study authors. Importantly, studies did not report on how gender or sex was defined; therefore, we presented them together in this review. Several studies had high sample attrition or did not report on key sociodemographic variables such as race. Many studies also used descriptive analyses with models not adjusted

for confounding variables. Only 8% of the included studies demonstrated good quality in relation to bias. Therefore, there is some risk of overinterpretation of results. Finally, most studies were descriptive and exploratory in nature which limited the ability of the authors to perform a meta-analysis on the data.

Conclusions and Implications for Future Research

While we were able to survey which SDOH were prioritized and measured with PBT symptoms, underreporting and a lack of consistent operationalization of symptoms and SDOH, as well as high levels of bias and the exploratory nature of many of the studies, limited our ability to draw conclusions on the relationships between SDOH and symptoms beyond the implications in Table 4. Future researchers should seek to reduce identified study biases, including reporting of variable definitions used and recruiting diverse and representative sample populations, while also collecting more longitudinal data, with clearly and consistently defined SDOH identified by the PROGRESS criteria.

Supplementary material

Supplementary material is available online at *Neuro-Oncology* (https://academic.oup.com/neuro-oncology).

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Conflict of interest statement

The authors declare no conflicts of interest.

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Data Analysis: MLS, MJ, ZK, DC, TSA, AK. Contributions to study design and interpretation of data: MLS, MJ, DC, TSA, AK. All authors read and approved the manuscript.

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