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REVIEW

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Factors associated with depression over time in head and neck cancer patients: A systematic review

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Abstract

Objective: To systematically review the literature on factors associated with a clinical diagnosis of depression or symptoms of depression (depression) among head and neck cancer (HNC) patients.

Methods: The search was conducted in PubMed, PsycINFO, and CINAHL. Studies were included if they investigated factors associated with depression among HNC patients, they were of prospective or longitudinal nature, and English full text was available. The search, data extraction, and quality assessment were performed by two authors. Based on the data extraction and quality assessment, the level of evidence was determined.

Results: In total, 35 studies were included: 21 on factors associated with depression at a single (later) time point, 10 on the course of depression, and four on both. In total, 77 sociodemographic, lifestyle, clinical, patient-reported outcome measures, and inflammatory factors were extracted. Regarding depression at a single time point, there was strong evidence that depression at an earlier time point was significantly associated. For all other factors, evidence was inconclusive, although evidence suggests that age, marital status, education, ethnicity, hospital/region, sleep, smoking, alcohol, surgery, treatment, tumor location, and recurrence are not important associated factors. Regarding the course of depression, we found inconclusive evidence for all factors, although evidence suggests that gender, age, chemotherapy, pain, disease stage, treatment, and tumor location are not important associated factors.

Conclusion: Depression at an earlier time point is significantly associated with depression later on. Several sociodemographic and clinical factors seem not to be important factors associated with depression. For other factors, further research is warranted.

KEYWORDS

depression, depressive symptoms, head and neck cancer, systematic review

1 | BACKGROUND

The prevalence of depression (clinical diagnosis or symptoms of depression) among head and neck cancer (HNC) patients is high and depends on type of measurement (diagnostic interview or patient-reported outcome measures [PROMs]) and time of assessment.[1] Over time, prevalence rates have been reported to vary from 13% to 40% at diagnosis, to 25% to 52% during treatment, to 11% to 45% in the first 6 months following treatment, and seem to decrease in the longer term (9%-27%).[2] The high prevalence at diagnosis and shortly after treatment might be due to HNC-specific symptoms, such as oral dysfunction and difficulties with speaking, eating, or swallowing, and facial disfigurement.[2-6]

Besides HNC-specific symptoms, general cancer-related symptoms and sociodemographic and clinical characteristics have been found to be associated with depression. Haisfield-Wolfe et al[2] conducted a systematic review including literature up to 2008 on factors associated with depression in HNC patients at different phases of the cancer trajectory. Based on 52 studies, they reported that several sociodemographic factors (male gender, younger age, lower education, less social support, smoking, unemployment, and being unmarried or living alone) as well as clinical factors (symptoms of depression before treatment, comorbidities, higher tumor stage) were associated with depression. However, information on which factors at what time points are significantly associated with (the course of) depression is scattered and remains unclear.

Since the review of Haisfield-Wolfe et al[2] new studies have been conducted, which warrants an update of the literature. The aim of this study was to systematically review available literature on factors associated with depression at a single time point or the course of depression among HNC patients. With this study, we aimed to generate an overview on factors that have been investigated in relation to depression in HNC patients. This overview may be used to focus further research to those factors which are currently understudied. In contrast to Haisfield-Wolfe et al[2] we focused our review on prospective and longitudinal analyses. Although randomized controlled trials are (if possible and ethical) needed to investigate causal relationships between factors and depression, data of observational cohort studies can be used to formulate hypotheses regarding such possible causal associations. Prospective and longitudinal analyses provide better hypotheses compared with cross-sectional studies, which is why we only included prospective and longitudinal analyses.

2 | METHODS

2.1 | Search strategy

A first literature search was conducted in PubMed (May 9, 2017) and in PsycINFO and CINAHL (February 9, 2018) using keywords, MeSH terms, and subject headings. As an update was warranted a search update of all three databases was performed up to August 20, 2018. The main keywords were as follows: "head and neck neoplasms," "depression," "depressive disorder," "distress," "depressive symptoms," "associat*," and "correlat*" (Appendix A). Reference lists of the included studies were searched for additional studies.

2.2 | Eligibility criteria

Studies were included if they (1) included a group of adult (greater than or equal to 18 years) HNC patients, (2) had depression as outcome, (3) reported on factors associated with depression at a single (later) time point (prospective analyses) or factors associated with the course of depression (longitudinal analyses), (4) were of a prospective (factors investigated in relation to depression were measured at an earlier time point than the measurement of depression) or longitudinal nature, and (5) full text was available in English. We excluded cross-sectional studies, randomized controlled trials, reviews, and case reports.

2.3 | Selection process and quality assessment

After eliminating duplicate studies, article title and abstract were screened by two reviewers (LK or BH and FJ) on eligibility and were either marked for further evaluation or excluded. In the second phase, the full text of the potentially relevant articles were assessed for eligibility based on the eligibility criteria. Disagreement between reviewers was resolved by consensus in each phase. If disagreement was unresolved, a third reviewer was consulted (IV).

Included studies were subjected to a quality assessment using a 12-item quality assessment scoring list (Appendix B). This list was adapted from Hayden et al[7] and has been used in previous studies.[8,9] The quality assessment comprised four aspects: study population, study attrition, data collection, and data analysis. All items were scored positive (score "1") or negative (score "0"). In case the necessary information was not provided or was unclear, also a negative score was provided. Two reviewers (LK or BH and FJ) independently performed the quality assessments. In case of disagreement between the two reviewers, a third reviewer (IV) was consulted. A total score per study was calculated by summing the scores resulting in a score of 0 to 12. Studies scoring greater than or equal to 70% of points were categorized "high methodological quality." Studies scoring less than 70% were categorized "low methodological quality." [9]

2.4 | Data extraction

The reviewers (LK or BH and FJ) extracted the following data: author, publication year, number of patients included, HNC sublocation, instrument used to measure depression, and factors investigated in relation to depression. If both univariate and multivariate analyses were used, the multivariate data were collected, since multivariate results are more likely to contain independent factors (factors that are still significant after correcting for potential confounding factors).

2.5 | Level of scientific evidence

We used a best-evidence synthesis to categorize the level of evidence of factors associated with (the course of) depression, as used in previous studies.[9,10] The levels of evidence were (1) strong if a factor was consistently supported by at least two high quality studies, (2) moderate if a factor was consistently supported by at least one high-quality study and at least one low-quality study or if a factor was consistently supported by at least two low-quality studies, and (3) inconclusive, if a factor was supported by only one study or results were inconsistent in multiple studies. A result was defined as consistent if greater than or equal to 75% of studies reported results into the same direction.

3 | RESULTS

3.1 | Identification and selection of the literature

The first literature search of PubMed, PsycINFO, and CINAHL yielded 1086 nonduplicate studies (Figure 1). A search update was performed up to August 20, 2018, which yielded 115 additional studies. All of these studies (n = 1201) were first screened based on title and abstract, of which 164 studies were selected for the full-text phase. In total 33 of these articles fulfilled the eligibility criteria. In addition, two studies were included after screening the reference lists, resulting in 35 articles.[11-45] These 35 articles provided results on 27 separate studies.

In Table 1, the characteristics of the 35 included studies are described. Twenty-one studies reported on factors associated with depression at a single time point,[11-28,42-44] 10 studies on factors associated with the course of depression[33-41,45] and four on both.[29-32] Results on factors associated with depression at a single time point and the course of depression are presented separately.

3.2 | Studies on depression at a single time point

Of the 25 studies that focused on factors associated with depression at a single time point, publication year ranged from 1999[18] to 2018.[27,32,42-44] Most studies focused on mixed HNC patients, while four studies focused on nasopharyngeal,[24,26] oropharyngeal,[42] or oral cancer.[20] The majority measured symptoms of depression, while four studies measured a clinical diagnosis of depression.[27,32,43,44] Symptoms of depression were measured using the Hospital Anxiety and Depression Scale (HADS) depression domain,[12,18-23,25,29-31,42] Center for Epidemiological Studies Depression Scale (CES-D),[13-16] Beck Depression Inventory (BDI),[11,12,17] self-rating depression scale (SDS),[24,28] and the Symptom Checklist (SCL) depression domain.[26] With respect to a clinical diagnosis of depression, two studies extracted data from an insurance database on the International Classification of Diseases (ICD) diagnosis on depression,[27,43] and two studies used a structured clinical interview to identify the presence of a Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV diagnosis of depression.[32,44] Of the included studies, nine measured depression less than or equal to 3 months,[12,18,21,24-26,28,29,44] 14 studies measured depression 3 to 12 months,[13-16,18,19,21-23,27-29,31,32] and nine studies measured depression less than 1 year after treatment[11,16,17,19,20,30,32,42,43] (some performed several analyses).

3.3 | Studies on the course of depression

Of the 14 studies that investigated factors associated with the course of depression, publication year ranged 1987[38] to 2018.[45] Studies mainly focused on mixed HNC patients; two studies focused on oral cavity[34] or laryngeal cancer.[36] Except for one study,[32] which used a clinical diagnosis of depression, all studies measured symptoms of

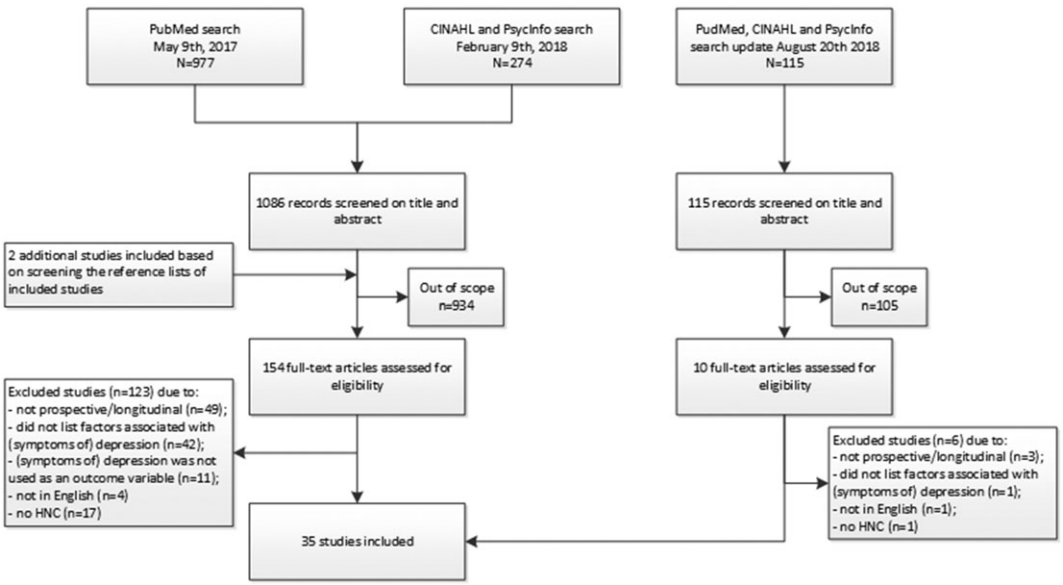

FIGURE 1 Flow diagram

TABLE 1 Characteristics of the included studies

Authors	Study Locale	Population	Used Measurement Instrument	Measuring Times
Depression at a single time point				
Aarstad[11]	Norway	Male HNC patients (n = 79). Results presented in this review focused on the 27 patients with follow-up data.	BDI	2 (during the first days of hospitalization and, on average, 6 ± 1 y after diagnosis)
Bozec[42]	France and Belgium	Oropharyngeal cancer patients treated with surgery (n = 58)	HADS	2 (before and at least 1 year after treatment [on average 4.5 y])
Chen[12]	USA	HNC patients undergoing (post-operative or primary) RT (n = 40).	HADS-D, BDI-II	3 (pre-RT, last day of RT, and first follow-up visit [generally 3 w after RT completion])
Derks[13]	Netherlands	HNC patients (n = 183) without distant metastasis. Results in this review focused on the 121 patients with follow-up data.	CES-D	2 (pretreatment and 1-y follow-up)
de Graeff[14]	Netherlands	HNC patients treated with curative intent and without recurrence or metastases (n = 153).	CES-D	3 (pretreatment and 6- and 12-mo follow-up)
de Leeuw[15]	Netherlands	HNC patients treated with surgery and/or RT and without recurrence or metastases (n = 155).	CES-D	3 (pretreatment and 6 and 12 mo after treatment)
de Leeuw[16]	Netherlands	HNC patients treated with surgery and/or RT with curative intent (n = 197). Patients with recurrence during follow-up were not excluded.	CES-D	5 (pretreatment and 6, 12, 24, and 36 mo)
Fan[43]	Taiwan	Newly diagnosed HNC patients (n = 48 548)	ICD diagnosis for depression	Depression in the time period following HNC diagnosis (on average 4.1 y).
Funk[17]	USA	HNC patients who survived at least 5 y (n = 337).	BDI	12, of which only baseline, 12-mo and 5-y follow-up data was used.
Hammerlid[18]	Sweden/ Norway	Newly diagnosed HNC patients (n = 357).	HADS-D	6 (at time of diagnosis and 1, 2, 3, 6, and 12 mo after treatment started) for this analyses only results at 3 and 12-mo follow-up were used.
Hammerlid[19]	Sweden	Newly diagnosed HNC patients (n = 232).	HADS-D	7 (6 times during the first year and once at 3-y follow-up). For these analyses only results at 1- and 3-y follow-up were used.
Hassel[20]	Germany	Advanced oral squamous cell cancer treated with CRT who were recurrence-free (n = 24).	HADS-D	2 (at least 3 y after treatment and 1 y later)
Henry[44]	Canada	Newly diagnosed HNC patients (n = 223)	Structured clinical interview for DSM-IV	2 (before treatment and 3 mo after baseline)
Humphris[21]	UK	HNC patients (n = 87).	HADS-D	2 (3- and 7-mo follow-up)
Llewellyn[22]	UK	Newly diagnosed HNC (n = 82).	HADS-D	3 (pretreatment, 1 mo after treatment, and 6-8 mo after treatment)

(Continues)

TABLE 1 (Continued)

Authors	Study Locale	Population	Used Measurement Instrument	Measuring Times
Llewellyn[23]	UK	Newly diagnosed HNC patients (n = 82).	HADS-D	3 (pretreatment, after treatment and 6-8 mo after treatment)
Mo[24]	China	Nasopharyngeal cancer patients treated with primary IMRT (n = 51).	SDS	2 (pre-RT and within a week after 6-7 w of RT [post-RT])
Neilson[25]	Australia	HNC patients (n = 102 of which 75 patients participated in the actual analyses).	HADS-D	2 (pre-RT and about 3 w after RT)
Qin[26]	China	Local-advanced nasopharyngeal cancer patients who completed RT and concurrent chemotherapy (n = 60).	SCL-90 depression	2 (pre-CRT and within 1 w after CRT)
Rieke[27]	USA	HNC patients (n = 3533) who were older than 67 y, and were linked to Medicare data.	ICD diagnosis for depression	Depression in the year following HNC diagnosis was abstracted from the medical file.
Sehlen[28]	Germany	Mixed HNC patients treated with RT (n = 81)	SDS	4 (the beginning of RT, the end of RT and 6 w and 6 mo after the completion of treatment)
Depression at a single time point and the course of depression				
Archer[29]	UK	Newly diagnosed HNC (n = 56)	HADS-D	4 (presurgery and 6-, 12-, and 24-w post-surgery)
Humphris[30]	UK	Newly-diagnosed HNC patients (n = 87)	HADS-D	4 (3, 7, 11, and 15 mo following initial treatment)
Kobayashi[31]	Japan	HNC patients treated with surgery (n = 58)	HADS-D	3 (presurgery, 7-10 d after surgery and at 6-mo follow-up)
Wu[32]	Taiwan	Newly diagnosed and untreated HNC patients (n = 106)	Structured clinical interview for DSM-IV	3 (pretreatment, 3- and 6-mo follow-up)
The course of depression				
Astrup[33]	Norway	HNC patients treated with radiotherapy (n = 133)	CES-D	5 (pre-RT, 1, 2, 3, 6 mo after start of RT)
Chen[34]	Taiwan	Newly diagnosed oral cavity cancer patients treated with postoperative RT or CRT (n = 76)	HADS-D	4 (pre-RT and 1-, 2-, and 3-mo follow-up)
de Graeff[35]	Netherlands	HNC patients treated with surgery and/or RT with curative intent (n = 107)	CES-D	5 (pretreatment and at 6-, 12-, 24-, and 36-mo follow-up)
Finizia[36]	Sweden	Laryngeal cancer patients (n = 26)	HADS-D	6 (baseline and 1-, 2-, 3-, 6-, and 12-mo follow-up)
Karnell[37]	USA	HNC patients (n = 235 for the cross-sectional analyses and n = 148 for the longitudinal analyses used in this study)	BDI, categorized into persistent depression (defined as scores of 10 or higher on two or more BDIs administered at least 6 mo apart) or no persistent depression	5 (pretreatment, 3-, 6-, 9-, and 12-mo follow-up)
Manuel[38]	USA	Newly diagnosed HNC patients (n = 35)	SCL-90 depression	3 (pretreatment, 4- to 6-w and 2- to 3-mo follow-up)

(Continues)

TABLE 1 (Continued)

Authors	Study Locale	Population	Used Measurement Instrument	Measuring Times
Neilson[39]	Australia	Newly diagnosed HNC patients treated with RT (n = 101)	HADS-D	3 (pre-RT, 3 w and 18 mo after RT)
Rhoten[40]	USA	Newly diagnosed HNC patients (n = 43)	CES-D	4 (pretreatment, after treatment and 6- and 12-w posttreatment)
Rhoten[45]	USA	Newly diagnosed HNC patients (n = 83)	CES-D	11 (before treatment, after treatment, every 6 w up to 48 w after the end of treatment, and 15- and 18-mo follow-up)
Van Liew[41]	USA	HNC patients, primary or recurrent diagnosis (n = 564)	BDI	5 (pretreatment, 3, 6, 9, and 12-mo follow-up)

Abbreviations: BDI, Beck Depression Inventory; SCL, Symptom Checklist; CES-D, Center for Epidemiological Studies Depression Scale; CRT, chemoradiotherapy; DSM, Diagnostic and Statistical Manual of Mental Disorders; HADS-D, Hospital Anxiety and Depression Scale depression domain; HNC, head and neck cancer; ICD, International Classification of Diseases; RT, radiotherapy; SDS, self-rating depression scale.

depression using the HADS-D,[29-31,34,36,39] CES-D,[33,35,40,45] BDI,[37,41] or SCL-90.[38]

3.4 | Quality assessment

Eleven of the 35 studies were of high methodological quality[16,18,22,24,26,27,33,34,39,43,44] (Appendix B). The majority of studies (23/35) did not have a baseline participation rate (the percentage of all eligible patients who wants to participate) of at least 80% or showed selective nonresponse (characteristics of participants differed from those patients who were not willing to participate).[11-14,17-21,23,25,28-30,32,33,37,39-42,44,45] Twenty-one studies included less than 100 patients[11,12,20-26,28-32,34,36-38,40,42,45] and about half (17/35) performed multivariate analyses.[14-17,22-27,29,33,37,39,42-44]

3.5 | Factors associated with depression at a single time point

From the 25 studies on depression at a single time point, 69 factors were extracted, of which 10 sociodemographic, four lifestyle, 22 clinical factors, 29 PROMs, and 4 inflammatory markers (Table 2). The only factor that was found to be significantly associated with depression was symptoms of depression at an earlier time point. Seven of the eight studies, which investigated this association, found that symptoms of depression measured before start of treatment,[12,14-16,25] 1 month after the end of treatment[20] or at least 1 month after the end of treatment[22] were significantly associated with a higher level of depression at a later time point. The only study that did not found a significant association was Aarstad et al[11] which investigated the association between symptoms of depression at time of hospitalization and depression at on average 6-year follow-up. As two studies were of high methodological quality,[16,22] the evidence on this association was rated as strong.

For all other 68 factors, inconsistent evidence was reported. However, based on at least two high-quality studies,[16,18,22,24,26,27,44] the evidence suggests that age, marital status, education level, ethnicity, treating hospital/region, and poor sleep are not important factors in relation to depression. Also, smoking history, alcohol use, (previous) surgery, type of treatment, tumor location, and cancer recurrence are hypothesized to be unimportant factors in relation to depression, because on all of these factors at least one high-quality study showed no significant association[16,22,27,43] or at least two low-quality studies showed no significant association.[12,15,17,19,23,25,28,32]

For 36 of the other 56 inconsistent factors, evidence was rated as inconsistent as only one study investigated this association. Of the remaining 20 factors, four factors were sociodemographic characteristics. One was a lifestyle characteristic; five factors were clinical characteristics, and 10 were PROMs. On the sociodemographic factors: gender, living alone, and income, some studies showed significantly higher depression among females,[14-16,24,27,43] people who are living alone,[12] or people with a lower income,[43] while other

TABLE 2 Overview factors associated with depression at a single time point (all)

	Factors Associated with Depression (all)						LoE[a]
	N	N+		N-		N0	
Sociodemographic							
Female gender	18	6	de Graeff et al[14](6 mo); de Leeuw et al[15](6 mo); de Leeuw et al[16](2 and 3 y); Mo et al[24]; **Rieke et al**[27]; **Fan et al**[43]	0		15	Chen et al[12]; de Graeff et al[14] (12 mo); de Leeuw[15] (12 mo); de Leeuw[16] (6 mo,1 y); Hammerlid et al[18]; Hammerlid et al[19]; Humphris et al[21]; Llewellyn et al[23]; Mo et al[24]; Neilson et al[25]; Qin et al[26]; Sehlen et al[28]; **Wu et al**[32]; Bozec et al[42]; **Henry et al**[44]	?
Younger age	19	3	Chen et al[12](HADS); Mo et al[24]; **Fan et al**[43]	1	**Rieke et al**[27]	16	Chen et al[12](BDI); Derks et al[13]; de Graeff[14]; de Leeuw et al[15]; de Leeuw et al[16]; Funk et al[17]; Hammerlid et al[18]); Hammerlid et al[19]; Humphris et al[21]; Llewellyn et al[23]; Neilson et al[25]; Qin et al[26]; Sehlen et al[28]; **Wu et al**[32]; Bozec et al[42]; **Henry et al**[44]	?
Being married	6	0		1	Chen et al[12]	5	Llewellyn et al[22]; Llewellyn et al[23]; **Rieke et al**[27]; Sehlen et al[28]; **Wu et al**[32]	?
Living alone	2	1	Chen et al[12]	0		1	Neilson et al[25]	?
Having children	1	0		0		1	Sehlen et al[28]	?
Being employed	5	1	Chen et al[12]	1	**Fan et al**[43]	3	Sehlen et al[28]; **Wu et al**[32]; Bozec et al[42]	?
Higher income	3	0		1	**Fan et al**[43]	2	Chen et al[12]; **Rieke et al**[27]	?
Higher education	9	0		1	Sehlen et al[28] (post, 6 w)	9	Chen et al[12]; Llewellyn et al[22]; Llewellyn et al[23]; Mo et al[24]; Qin et al[26]; **Rieke et al**[27]; Sehlen et al[28](6 mo); **Wu et al**[32]; Bozec et al[42]	?
Urbanization	1	0		0		0	**Fan et al**[43]	?
Ethnicity	3	0		0		3	Llewellyn et al[22]; Llewellyn et al[23]; **Rieke et al**[27]	?
Lifestyle								
Current smoker	2	1	Humphris & Rogers[30]	0		1	Bozec et al[42]	?
Smoking (history)	3	0		0		3	Chen et al[12]; Funk et al[17]; **Wu et al**[32]	?
History of addiction	1	0		0		1	Sehlen et al[28]	?
Alcohol use	4	1	Bozec et al[42]	0		3	Funk et al[17]; Neilson et al[25]; **Wu et al**[32]	?
Clinical								

(Continues)

TABLE 2 (Continued)

	Factors Associated with Depression (all)						LoE[a]
	N	N+		N-	N0		
Higher disease stage	15	6	de Leeuw[15]; de Leeuw et al[16] (6 mo, 3 y); Hammerlid et al[19] (3 y); Llewellyn et al[22]; **Rieke et al**[27]; **Henry et al**[44]	0	11	Chen et al[12]; de Leeuw et al[16](1 and 2 y); Funk et al[17]; Hammerlid et al[18]; Hammerlid et al[19](1y); Humphris et al[21]; Llewellyn et al[23]; Mo et al[24]; Qin et al[26]; Sehlen et al[28]); **Wu et al**[32]; Bozec et al[42]	?
(previous) surgery	5	0		0	5	Chen et al[12]; Funk et al[17]; Neilson et al[25]; Sehlen et al[28]; **Fan et al**[43]	?
Salvage surgery	1	0		0	1	Bozec et al[42]	?
Surgery approach	1	0		0	1	Bozec et al[42]	?
Chemotherapy	8	4	Neilson et al[25]; Qin et al[26]; Sehlen et al[28](6 mo); **Fan et al**[43]	0	5	Chen et al[12]; Funk et al[17]; Mo et al[24]; Sehlen et al[28] (post, 6 w); Bozec et al[42]	?
Radiotherapy	5	2	**Rieke et al**[27]; **Fan et al**[43]	0	3	Funk et al[17]; Humphris et al[21]; Bozec et al[42]	?
Treatment	6	1	**Henry et al**[44b]	0	5	de Leeuw et al[15]; de Leeuw et al[16]; Llewellyn et al[22]; Llewellyn et al[23]; **Wu et al**[32]	?
Treatment toxicity	1	0		0	1	Chen et al[12]	?
Performance (Karnofsky)	3	0		2	de Graeff et al[14]; Hammerlid et al[18](12 mo)	2	Hammerlid et al[18](3 mo); Sehlen et al[28]	?
Group[c]	1	1	de Graeff et al[14]	0	0		?
Tumor location	6	1	**Fan et al**[43d]	0	5	Funk et al[17]; Hammerlid et al[19]; Llewellyn et al[22]; Llewellyn et al[23]; **Rieke et al**[27]	?
Recurrence	2	0		0	2	de Leeuw et al[16]; Funk et al[17]	?
Comorbidity	3	1	**Fan et al**[43]	0	2	Funk et al[17]; **Rieke et al**[27]	?
Diet	1	1	Funk et al[17]	0	0		?
Dental status	1	0		0	1	Funk et al[17]	?
Treating hospital/region	2	0		0	2	Llewellyn et al[22]; **Rieke et al**[27]	?
Inpatient or outpatient	1	0		0	1	Sehlen et al[28]	?
Time since diagnosis	1	0		0	1	**Wu et al**[32]	?
Medical insurance	1	0		0	1	Sehlen et al[28]	?
Need for home care	1	0		0	1	Sehlen et al[28]	?
Grade	1	0		0	1	Sehlen et al[28]	?
Histology	1	0		0	1	**Henry et al**[44]	?

(Continues)

TABLE 2 (Continued)

	Factors Associated with Depression (all)							LoE[a]
	N	N+		N-		N0		
Patient-reported outcome measures or psychiatric diagnosis								
Symptoms of depression	8	7	Chen et al[12]; de Graeff et al[14]; de Leeuw et al[15]; de Leeuw et al[16]; Hassel et al[20]; Llewellyn et al[22]; Neilson et al[25]	0		1	Aarstad et al[11]	++
Symptoms of anxiety	3	0		1	**Henry et al**[44]	2	Aarstad et al[11]; Mo et al[24]	?
Anxiety disorder	1	1	**Henry et al**[44e]			1	**Henry et al**[44f]	?
Depression disorder	1	0		0		1	**Henry et al**[44]	?
Substance use disorder	1	0		0		1	**Henry et al**[44]	?
Sense of humor	1	1	Aarstad et al[11]	0		0		?
Childhood trauma	1	0		0		1	Archer et al[29]	?
Poor parental care in youth	1	0		0		1	**Henry et al**[44]	?
Number of life events	1	1	Archer et al[29](6 and 24 w)	0		1	Archer et al[29](12 w)	?
Received support	2	0		1	de Leeuw et al[16]) (6 mo, 1 and 3 y)	2	de Leeuw et al[15]; de Leeuw et al[16](2 y)	?
Available support	2	0		2	de Leeuw et al[15](12 mo); de Leeuw et al[16] (6 mo, 1 and 2y)	1	de Leeuw et al[15](6 mo); de Leeuw et al[16](3 y)	?
Social network	2	0		2	de Leeuw et al[15]; de Leeuw et al[16] (6 mo,1 and 3 y)	1	de Leeuw et al[16](2y)	?
Social support	1	0		0		1	Funk et al[17]	?
Satisfaction with social support	1	0		0		1	**Henry et al**[44]	?
Openness to discuss cancer in the family	1	0		1	de Leeuw et al[16](6 mo, 2 y)	1	de Leeuw et al[16](1 and 3y)	?
Higher self-esteem	1	0		1	Kobayashi et al[31]	0		?
Coping	4	2	de Leeuw et al[15g]; Llewellyn et al[23h]	1	de Leeuw et al[16i] (3y)	4	de Leeuw et al[15j]; de Leeuw et al[16] (6 mo, 1 and 2y)[i]; Llewellyn et al[23i]; **Henry et al**[44]	?
Locus of control	2	0		1	de Leeuw et al[16](1y)	2	de Leeuw et al[15]; de Leeuw et al[16] (6 mo,2 and 3 y)	?
Neuroticism	1	0		0		1	**Henry et al**[44]	?
Cancer-related symptoms	2	1	de Leeuw et al[16](3 y)	0		2	de Leeuw et al[15]; de Leeuw et al[16] (6 mo,1 and 2 y)	?

(Continues)

TABLE 2 (Continued)

	Factors Associated with Depression (all)						LoE[a]
	N	N+		N-	N0		
HNC-related symptoms	3	2	de Leeuw et al[16](6 mo,1 y); Hassel et al[20]	0	2	de Leeuw et al[15]; de Leeuw et al[16] (2 and 3 y)	?
Physical functioning	2	0		0	2	de Leeuw et al[15]; de Leeuw et al[16]	?
Illness perception	1	1	Llewellyn et al[23k]	0	1	Llewellyn et al[23j]	?
Beliefs about medicine	1	0		0	1	Llewellyn et al[23]	?
Satisfaction with cancer information	2	0		2	Llewellyn et al[22]; Llewellyn et al[23l]	1	Llewellyn et al[23m]	?
Optimism	1	0		0	1	Llewellyn et al[23]	?
Poor sleep	2	0		0	2	Mo et al[24]; Qin et al[26]	?
Pain	1	1	Funk et al[17]	0	0		?
Life stressors	1	0		0	1	**Henry et al[44]**	?
Inflammatory markers							
TNFα	1	0		0	1	Archer et al[29]	?
IL6	1	0		0	1	Archer et al[29]	?
C-reactive protein	1	0		0	1	Archer et al[29]	?
IFNγ	1	0		0	1	Archer et al[29]	?

Note. Studies on clinical depression are presented in bold.

Abbreviations: A, association; BDI, Beck Depression Inventory; IL6, interleukin 6; HADS-D, Hospital Anxiety and Depression Scale; HNC, head and neck cancer; IFNγ, interferon gamma; LoE, level of evidence; mo, month(s); N, total number of studies; N+, total number of studies that found a positive association, N-, total number of studies that found a negative association; N0, total number of studies that found no association; post, posttreatment; TNFα, tumor necrosis factor alpha; w, week(s); y, year(s).

[a]Level of evidence was defined as strong, moderate in conclusive.

[b]Patients who were treated with surgery only compared to all other treatments or treatment combinations.

[c]Based on site, stage and treatment.

[d]Reference category was larynx.

[e]Lifetime.

[f]Baseline.

[g]Avoidance.

[h]Self-blame and acceptance.

[i]Palliative coping, direction unknown.

[j]All other domains

[k]Timeline.

[l]Amount and content.

[m]Type, timing.

TABLE 3 Factors associated with the course of depression

	Factor Associated with the Course of Depression						LoE[a]
	N	N+		N-		N0	
Sociodemographic							
Female gender	4	1	de Graeff et al[35]	0		3	Astrup et al[33]; Karnell et a[37]; Neilson et al[39]	?
Younger age	4	0		0		4	Astrup et al[33]; de Graeff et al[35]; Karnell et al[37]; Neilson et al[39]	?
Being married	1	0		0		1	Astrup et al[33]	?
Living alone	1	0		0		1	Neilson et al[39]	?
Children living at home	1	0		0		1	Astrup et al[33]	?
Being employed	1	0		0		1	Astrup et al[33]	?
Higher education	1	0		0		1	Astrup et al[33]	?
Lifestyle								
Smoking	2	1	Humphris & Rogers[30]	0		1	Karnell et al[37]	?
Alcohol use	1	0		0		1	Karnell et al[37]	?
Clinical								
Higher disease stage	3	0		0		3	Astrup et al[33]; de Graeff et al[35]; Karnell et al[37]	?
Treatment intent (curative/palliative	1	0		0		1	Astrup et al[33]	?
Treatment	2	0		0		2	de Graeff et al[35]; Karnell et al[37]	?
Surgery (previous	1	0		0		1	Astrup et al[33]	?
Chemotherapy	3	0		0		3	Astrup et al[33]; Chen et al[34]; Neilson et al[39]	?
Performance (Karnofsky	1	0		0		1	Astrup et al[33]	?
Group[c]	1	0		0		1	de Graeff et al[35]	?
Tumor location	2	0		0		2	Astrup et al[33]; Karnell et al[37]	?
Recurrence	1	0		0		1	Karnell et al[37]	?
Comorbidity	1	0		0		1	Astrup et al[33]	?
Time since diagnosis	1	0		0		1	Astrup et al[33]	?
Weight loss	1	1	Van Liew et al[41]	0		0		?
Patient-reported outcome measures								
Symptoms of) depression	2	1	Karnell et al[37]	0		1	Astrup et al[33]	?
Childhood trauma	1	1	Archer et al[29]	0		0		?
Number of life events	1	1	Archer et al[29]	0		0		?
Social support	1	0		0		1	Astrup et al[33]	?
Higher self-esteem	1	0		1	Kobayashi et al[31]	0		?
Coping (low approach, low avoidance	1	1	Manuel et al[38]	0		0		?
Communication dysfunction	1	1	Finizia et al[36]	0		0		?
Nutrition	1	0		0		1	Astrup et al.,[33]	?
HNC-related symptoms	3	3		0		2		?

(Continues)

TABLE 3 (Continued)

	Factor Associated with the Course of Depression							LoE[a]
	N	N+		N-		N0		
			Wu et al[32c]; Karnell et al[37d]; Neilson et al[39]				**Wu et al**[32e]; Karnell et al[37f]	
Poor sleep	1					1	Astrup et al[33]	?
Pain	2	0		0		2	Astrup et al[33]; Neilson et al[39]	?
Body image/satisfaction with looks	2	0		1	Rhoten et al[40]	1	Astrup et al[33]	?
Neck disability	1	1	Rhoten et al[45]	0		0		?
Fatigue and energy	1	0		0		1	Astrup et al[33]	?
Inflammatory markers								
TNFα	1	0		0		1	Archer et al[29]	?
IL6	1	0		0		1	Archer et al[29]	?
C-reactive protein	1	0		0		1	Archer et al[29]	?
IFNγ	1	0		0		1	Archer et al[29]	?

Note. In bold the results of the studies on factors associated with clinical depression.

Abbreviations: N, total number of studies; N+, total number of studies that found a positive association, N-, total number of studies that found a negative association; N0, total number of studies that found no association; LoE, level of evidence; Assoc, association; HNC, head and neck cancer; TNFα, tumor necrosis factor alpha; IL6, interleukin 6; IFNγ, interferon gamma.

Studies on clinical depression are presented in bold.

[a]Level of evidence was defined as strong, moderate in conclusive.

[b]Based on site, stage and treatment.

[c]Sense problems, speech, sexuality, dry mouth, pain killers and nutritional supplements.

[d]Post eating, post social disruption.

[e]All other EORTC QLQ-H&N35 domains and items.

[f]Pre quality of life outcomes, post speech and post esthetics.

studies found no such significant association.[12,14-16,18,19,21,23-28,32,42,44] Regarding employment one study found a positive association with depression,[12] one study a negative association,[43] and three studies found no such association.[28,32,42] Of the lifestyle factor current smoking, one study found higher depression among those who currently smoked,[30] while another study found no such association.[42] Of the clinical factors, unclear findings were shown for disease stage, chemotherapy, radiotherapy, performance status, and comorbidity, with some studies showing significantly higher depression among HNC patients with a higher disease stage,[15,16,19,22,27,44] those treated with chemotherapy (versus no chemotherapy),[25,26,28,43] those treated with radiotherapy (versus no radiotherapy),[27,43] patients with a lower performance status,[14,18] or people with comorbidities.[43] However, other studies found no significant association.[12,16-19,21,23,24,26-28,32,42] Of the PROMs, unclear findings were reported on symptoms of anxiety, received and available support, extend of the social network, coping behavior (the strategy used to deal with stress and problems), locus of control (the degree to which people believe that they have control over the outcome of events in their lives), cancer and HNC-related symptoms, and satisfaction with information: some studies showed significantly higher depression among patient lower levels of anxiety,[44] with less received support,[16] less available support,[15,16] smaller social network,[15,16] with certain coping styles,[15,16,23] worse locus of control,[16] higher level of cancer-related[16] HNC-related symptoms,[16,20] and lower satisfaction with cancer information,[22,23] while others found no significant association.[11,15,16,23,24,44] Finally, physical functioning was not significantly associated with depression, as these two studies were performed in the same study population.[15,16]

To provide further insight into the 56 factors with rating "inconsistent," an overview was created in which we stratified for time period: less than or equal to 3 months (short), 3 to 12 months (medium), and greater than 12 months after treatment (long) (Appendix C).

3.6 | Factors associated with the course of depression

From the 14 studies on the course of depression, 39 factors were extracted, of which seven sociodemographic, two lifestyles, 12 clinical factors, 14 PROMs, and four inflammatory markers (Table 3). On all

these factors, inconsistent evidence was found. However, evidence suggests that gender, age, chemotherapy, and pain are not important factors in relation to the course of depression, as on all these factors at least two high-quality studies showed no significant association.[33,34,39] Also, disease stage, type of treatment, and tumor location may not be important factors in relation to the course of depression, since on these factors, one high-quality study[33] or two low-quality studies[35,37] showed no significant association.

For 28 of the other 32 inconsistent factors, evidence was rated as inconsistent as so far only one study investigated this association. The four other factors concerned smoking, depression at baseline, HNC-related symptoms, and body image/satisfaction with looks. Some studies showed a significantly worse course of depression among those who smoked,[30] had higher depression at baseline,[37] experienced (a higher level of) HNC-related symptoms,[32,37,39] and those who were less satisfied with their body image/looks,[40] while other studies did not.[32,33,37]

4 | CONCLUSIONS

The study aimed to systematically review available literature on factors associated with depression among HNC patients. Results presented in this systematic review show that depression at an earlier time point is significantly associated with depression at a later time point. For all other sociodemographic, clinical, PROMs, and inflammatory markers, results are inconsistent. However, results suggest that most sociodemographic and clinical factors are not important factors in relation to depression over time.

Regarding depression at a single time point, our finding that symptoms of depression at an earlier time point is significantly associated with depression at a later time point is consistent with the results of Cook et al,[46] which systematically investigated factors associated with distress among cancer patients in general. This previous review also supports our suggestion that age, marital status, education, type of treatment, and surgery (versus no surgery) seem not to be important factors in relation to depression and that findings on the association with other psychological outcomes, such as coping, are unclear. In our review, we identified three studies that assessed the prospective association between coping behavior and depression, showing conflicting results regarding the type of coping behavior that is associated with depression. One study showed that avoidance coping style was significantly associated with depression,[15] while other studies showed that palliative coping[16] and acceptance behavior and self-blame[23] were significantly associated with depression. In addition, the longitudinal study of Manuel et al[38] showed that patients who neither use approach nor avoidance strategies to cope with cancer have the worst course of depression (compared with those with low approach/high avoidance and high approach/low avoidance). A previous systematic review on the association between coping and psychological distress among HNC patients, which included cross-sectional and prospective studies, suggested that coping aimed at disengaging and distancing from cancer is associated with increased psychological distress, while such an association is less consistent for coping behavior aimed at actively changing, managing, or adjusting to cancer.[47] More prospective and longitudinal research is, however, needed to unravel the association between coping and depression.

Regarding the course of depression, the evidence of this systematic review suggests that sociodemographic and clinical factors are not important factors in relation to depression. This is in contrast to a systematic review in the general population, which found that female gender, younger age, lower social economic status, non-White race, and stressful life events are associated with a poor trajectory of depression.[48] In addition, our review shows unclear results regarding HNC-related symptoms. Three studies found evidence that HNC-related symptoms such as problems with senses and speech are significantly associated with higher depression.[32,37,39] However, because of the differences in measures used (EORTC QLQ-H&N35, HNCI, FACT-HN) no clear conclusion can be drawn, as to which symptoms are associated with depression. Further research is needed to provide better insight into this association as well as their interrelationship, as a previous systematic review provided evidence that depression is significantly associated with (HNC specific) quality of life.[49]

More research is also needed on the predictive factor of biomarkers, as so far only one study investigated biomarkers in relation to depression.[29] Although this study of Archer et al[29] did not found a significant association between TNFα, IL6, C-reactive protein, and IFNy and depression over time among HNC patients, they did show a significant association between TNFα and C-reactive protein, and depression among colorectal cancer patients. Also, other studies have hypothesized that these biomarkers may be associated with depression.[50-52] Further studies need to be performed on the association of such biomarkers and the course of depression among HNC patients. Also, further research is needed onto trajectories of depression, factors associated with depression in specific groups of HNC patients (eg, oropharyngeal cancer), and potential factors which have not yet been investigated, such as human papilloma virus, fear of cancer recurrence, and interpersonal factors (eg, social stigma). Finally, further insight is needed into moderators and mediators of relationships between associated factors and depression.

4.1 | Study limitations

An important limitation is that vote counting was used to summarize the findings of the included studies. The absence of a significant association may, however, be the consequence of limited power and may not represent an actual absence of an association. In order to provide more clear insight into the association of factors and depression meta-analyses should be performed (eg, regarding HNC-specific symptoms). We did not perform meta-analyses in this study, as we aimed to provide an overview on all factors investigated in relation to depression and we did not aim to focus on a specific association. Other limitations were the small proportion of studies with high methodological quality (eg, the majority had a sample size less than 100, did not report the baseline participation rate, and performed only univariate analyses). Also, heterogeneity regarding HNC sublocation measures used to

assess depression (eg, CES-D, HADS-D, and BDI), time point of measuring depression, definition of depression (symptoms of depression or a clinical depression) and investigated factors, and the focus on studies, which were written in English limited our study. Finally, we included studies that investigated factors associated with depression regardless of their depression status at time of HNC diagnosis. Further research is warranted that take these limitations into account.

4.2 | Clinical implications

The study provides insight into factors associated with depression in HNC patients. In further research, a model can be built that predicts the prognosis of depression and may help improve decision making for the management of depression in HNC patients. A major strength is that only prospective and longitudinal studies were included, while cross-sectional studies were excluded. By these studies, clearer hypotheses can be generated regarding potential causal relationships between factors and depression.

5 | CONCLUSION

Results show that depression at an earlier time point is significantly associated with depression later on. For all other sociodemographic, clinical, PROMs, and inflammatory markers, results are inconsistent. Results, however, suggest that most sociodemographic and clinical factors are not important factors in relation to depression. Further research is warranted.

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CONFLICT OF INTEREST

None.

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APPENDIX A

SEARCH STRATEGY

Search strategy PubMed

("Head and Neck Neoplasms"[Mesh] OR (("head and neck" OR larynx OR pharynx OR pharyngeal OR oral cavity) AND cancer))

And

("Anxiety"[Mesh] OR "Depression"[Mesh] OR distress OR "depressive disorder" OR "psychological functioning" OR "emotional functioning" OR depressive symptoms)

AND

(predict* OR associat* OR correlat* OR preval* OR inciden* OR facilitat* OR prognos* OR determinan* OR mediator*)

Search strategy CINAHL and PsycInfo

(MH "Head and Neck Neoplasms+" OR (("head and neck" OR larynx OR pharynx OR pharyngeal OR oral cavity) AND cancer))

AND

(MH "Anxiety+" OR MH "Depression+" OR distress OR "depressive disorder" OR "psychological functioning" OR "emotional functioning" OR depressive symptoms)

AND

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APPENDIX B.

QUALITY ASSESSMENT OF THE INCLUDED STUDIES

	Studies on Factors Associated with Depression										
	Aarstad[11]	Bozec[42]	Chen[12]	Derks[13]	de Graeff[35]	de Leeuw[15]	de Leeuw[16]	Fan[43]	Funk[17]	Hammerlid[18]	Hammerlid[19]
Study population and participation											
The sampling frame and recruitment are adequately described (setting and geographical location)	−	−	+	+	+	−	+	+	+	+	+
Description of inclusion and exclusion criteria	+	+	+	+	+	+	+	+	−	+	+
Positive if the participation rate at baseline was at least 80%, or if the nonresponse was not selective	−	−	−	−	−	+	+	+	−	−	−
Adequate description of baseline study sample for general characteristics (age, gender, cancer site, stage, and treatment)	−	+	+	+	+	−	−	−	−	+	+
Study attrition											
Provision of the exact number of participants at each follow-up measurement	+	−	+	+	−	−	+	+	+	+	+
Provision of exact information on follow-up duration	+	+	+	+	+	+	+	+	+	+	+
Number of patients included in the analysis >100	−	−	−	+	+	+	+	+	+	+	+
Positive if the response at first follow-up was at least 80%, or if the non-response at first follow-up was not selective	−	−	+	−	−	−	+	+	−	+	−
Data collection											
Depression was measured by a reliable and valid tool	+	+	+	+	+	+	+	−	+	+	+
Data analysis											
Multivariate analysis techniques were used	−	+	−	−	+	+	+	+	+	−	−
Results were presented as point estimates (mean differences/betas/correlation coefficients) and measures of variability (SD, standard error or CI)	−	−	+	−	−	−	−	+	−	−	−
Positive if number of samples is at least 10 times the number of independent variables	−	+	−	+	+	−	−	+	+	+	+
Total score	4	6	8	8	8	6	9	10	7	9	8

	Studies that Investigated both Factors Associated with Depression and the Course of Depression				Studies on Factors Associated with the Course of Depression									
	Archer[29]	Humphris[30]	Kobayashi[31]	Wu[32]	Astrup[33]	Chen[12]	de Graeff[35]	Finizia[36]	Karnell[37]	Manuel[38]	Neilson[25]	Rhoten[40]	Rhoten[45]	Van Liew[41]
Study population and participation														
The sampling frame and recruitment are adequately described (setting and geographical location)	+	+	+	+	−	−	−	−	+	−	+	+	−	−
Description of inclusion and exclusion criteria	+	−	+	+	+	+	+	+	−	+	+	+	+	+
Positive if the participation rate at baseline was at least 80%, or if the non-response was not selective	−	−	+	−	−	+	+	+	−	+	−	−	−	−
Adequate description of baseline study sample for general characteristics (age, gender, cancer site, stage and treatment)	−	+	+	−	+	+	+	+	+	−	−	+	+	+
Study attrition														
Provision of the exact number of participants at each follow-up measurement	+	−	−	+	+	+	−	+	+	−	+	−	−	+
Provision of exact information on follow-up duration	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Number of patients included in the analysis >100	−	−	−	−	+	−	+	−	−	−	+	−	−	+
Positive if the response at first follow-up was at least 80%, or if the non-response at first follow-up was not selective	+	+	−	+	+	+	−	+	−	+	−	+	+	−
Data collection														
Depression was measured by a reliable and valid tool	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Data analysis														
Multivariate analysis techniques were used	+	−	−	−	+	−	−	−	+	−	+	−	−	−
Results were presented as point estimates (mean differences/betas/correlation coefficients) and measures of variability (SD, standard error or CI)	−	+	+	+	+	+	−	−	−	−	+	−	+	+
Positive if number of samples is at least 10 times the number of independent variables	−	+	+	−	−	+	+	+	+	+	+	+	+	+
Total score	7	7	8	7	9	9	7	8	7	6	9	7	7	8

	Studies on Factors Associated with Depression									
	Hassel[20]	Henry[44]	Humphris[21]	Llewellyn[22]	Llewellyn[23]	Mo[24]	Neilson[25]	Qin[26]	Rieke[27]	Sehlen[28]
Study population and participation										
The sampling frame and recruitment are adequately described (setting and geographical location)	+	+	−	+	+	+	+	+	+	+
Description of inclusion and exclusion criteria	+	+	−	−	+	+	+	+	+	+
Positive if the participation rate at baseline was at least 80%, or if the nonresponse was not selective	−	−	−	+	−	+	−	+	+	−
Adequate description of baseline study sample for general characteristics (age, gender, cancer site, stage, and treatment)	+	+	+	+	−	+	−	+	+	+
Study attrition										
Provision of the exact number of participants at each follow-up measurement	+	+	+	+	+	+	+	+	+	+
Provision of exact information on follow-up duration	+	+	+	+	+	+	+	+	+	+
Number of patients included in the analysis >100	−	+	−	−	−	−	−	−	+	−
Positive if the response at first follow-up was at least 80%, or if the non-response at first follow-up was not selective	+	−	+	+	+	+	−	+	+	+
Data collection										
Depression was measured by a reliable and valid tool	+	+	+	+	+	+	+	+	−	+
Data analysis										
Multivariate analysis techniques were used	−	+	−	+	+	+	+	+	+	−
Results were presented as point estimates (mean differences/betas/correlation coefficients) and measures of variability (SD, standard error or CI)	−	+	−	−	−	+	−	+	+	−
Positive if number of samples is at least 10 times the number of independent variables	+	+	+	+	−	−	+	+	+	−
Total score	8	10	6	9	7	10	7	11	11	7

APPENDIX C.

OVERVIEW FACTORS ASSOCIATED WITH DEPRESSION AT A SINGLE TIME POINT (PER TIME PERIOD)

	≤3 mo after the end of treatment						3 to 12 mo after the end of treatment						>12 mo after the end of treatment					
	N	N+		N−		N0	N	N+		N−		N0	N	N+		N−		N0
Sociodemographic																		
Female gender	8	0		0		8	Chen et al[12]; Hammerlid et al[18]; Humphris et al[21]; Mo et al[24]; Neilson et al[25]; Qin et al[26]; Sehlen et al[28]; **Henry et al**[44]	11	3	de Graeff et al[14]; de Leeuw et al[15] (6 mo); **Rieke et al**[27]	0		9	de Graeff et al[14]; de Leeuw et al[15] (12 mo); de Leeuw et al[16]; Hammerlid et al[18]; Hammerlid et al[19]; Humphris et al[21]; Llewellyn et al[23]; Sehlen et al[28]; **Wu et al**[32]	4	2	de Leeuw et al[16]; **Fan et al**[43]	0		2	Hammerlid et al[19]; Bozec et al[42];
Younger age	8	2	Chen et al[12] (HADS); Mo et al[24]	0		7	Chen et al[12](BDI); Hammerlid et al[18]; Humphris et al[21]; Neilson et al[25]; Qin et al[26]; Sehlen et al[28]; **Henry et al**[44]	11	0		1	**Rieke et al**[27]	10	Derks et al[13]; de Graeff et al[14]; de Leeuw et al[15]; de Leeuw et al[16]; Hammerlid et al[18]; Hammerlid et al[19]; Humphris et al[21]; Llewellyn et al[23]; Sehlen et al[28]; **Wu et al**[32]	5	1	**Fan et al**[43]	0		4	de Leeuw et al[16]; Funk et al[17]; Hammerlid et al[19]; Bozec et al[42]
Being married	2	0		1	Chen et al[12]	1	Sehlen et al[28]	5	0		0		5	Llewellyn et al[22]; Llewellyn et al[23]; **Rieke et al**[27]; Sehlen et al[28]; **Wu et al**[32]	0	0		0		0	
Living alone	2	1	Chen et al[12]	0		1	Neilson et al[25]	0	0		0		0		0	0		0		0	

(Continued)

	≤3 mo after the end of treatment					3 to 12 mo after the end of treatment					>12 mo after the end of treatment				
	N	N+		N−	N0	N	N+		N−	N0	N	N+		N−	N0
Having children	1	1		0	1 Sehlen et al[28]	1	0		0	1 Sehlen et al[28]	0	0		0	0
Being employed	2	1	Chen et al[12]	0	1 Sehlen et al[28]	2	0		0	2 Sehlen et al[28]; **Wu et al**[32]	2	0		1 **Fan et al**[43]	1 Bozec et al[42]
Higher income	1	0		0	1 Chen et al[12]	1	0		0	1 **Rieke et al**[27]	1	0		1 **Fan et al**[43]	0
Higher education	4	0		1 Sehlen et al[28]	3 Chen et al[12]; Mo et al[24]; Qin et al[26]	5	0		0	5 Llewellyn et al[22]; Llewellyn et al[23]; **Rieke et al**[27]; Sehlen et al[28]; **Wu et al**[32]	1	0		0	1 Bozec et al[42]
Urbanization	0	0		0	0	0	0		0	0	1	0		0	1 **Fan et al**[43]
Ethnicity	0	0		0	0	3	0		0	3 Llewellyn et al[22]; Llewellyn et al[23]; **Rieke et al**[27]	0	0		0	0
Lifestyle															
Current smoker	0	0		0	0	1	1	Humphris & Rogers[30]	0	0	2	1	Humphris & Rogers[30]	0	1 Bozec et al[42]
Smoking history	1	0		0	1 Chen et al[12]	1	0		0	1 **Wu et al**[32]	1	0		0	1 Funk et al[17]
History of addiction	1	0		0	1 Sehlen et al[28]	1	0		0	1 Sehlen et al[28]	0	0		0	0
Alcohol use	1	0		0	1 Neilson et al[25]	1	0		0	1 **Wu et al**[32]	2	1	Bozec et al[42]	0	1 Funk et al[17]
Clinical															
Higher disease stage	7	1		0	6 Chen et al[12]; Hammerlid et al[18]; Humphris et al[21]; Mo et al[24]; Qin et al[26]; Sehlen et al[28]	10	4	de Leeuw et al[15]; de Leeuw et al[16] (6 mo); Llewellyn et al[22]; **Rieke et al**[27]	0	7 de Leeuw et al[16](1 y); Hammerlid et al[18]; Hammerlid et al[19]; Humphris et al[21]; Llewellyn et al[23]; **Wu et al**[32]; Sehlen et al[28]	5	2	de Leeuw et al[16] (3 y); Hammerlid et al[19]	0	5 de Leeuw et al[16] (2 y); Funk et al[17]; Bozec et al[42]; **Fan et al**[43]
previous) surgery	3	0		0	3	1	0		0	1	1	0		0	1 Funk et al[17]

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	≤3 mo after the end of treatment					3 to 12 mo after the end of treatment					>12 mo after the end of treatment				
	N	N+		N−	N0	N	N+		N−	N0	N	N+		N−	N0
					Chen et al[12]; Neilson et al[25]; Sehlen et al[28]					Sehlen et al[28]					
Salvage surgery	0	0		0	0	0	0		0	0	0	0		0	1 Bozec et al[42]
Surgery approach	0	0		0	0	0	0		0	0	0	0		0	1 Bozec et al[42]
Chemotherapy	5	2	Neilson et al[25]; Qin et al[26]	0	3 Chen et al[12]; Mo et al[24]; Sehlen et al[28]	1	1	Sehlen et al[28]	0	0	3	1	**Fan et al[43]**	0	2 Funk et al[17]; Bozec et al[42];
Radiotherapy	1	0		0	1 Humphris et al[21]	2	1	**Rieke et al[27]**	0	1 Humphris et al[21]	3	1	**Fan et al[43]**	0	2 Funk et al[17]; Bozec et al[42]
Treatment	1	1	**Henry et al[44]**	0	0	5	0		0	5 de Leeuw et al[15]; de Leeuw et al[16]; Llewellyn et al[22]; Llewellyn et al[23]; **Wu et al[32]**	1	0		0	1 de Leeuw et al[16]
Treatment toxicity	1	0		0	1 Chen et al[12]	0	0		0	0	0	0		0	0
Performance (Karnofsky)	2	0		0	2 Hammerlid et al[18]; Sehlen et al[28]	3	0		2	de Graeff et al[14]; Hammerlid et al[18] 1 Sehlen et al[28]	0	0		0	0
Group[1]	0	0		0	0	1	1	de Graeff et al[14]	0	0	0	0		0	0
Tumor location	0	0		0	0	4	0		0	4 Hammerlid et al[19]; Llewellyn et al[22]; Llewellyn et al[23]; **Rieke et al[27]**	3	1	**Fan et al[43]**	0	2 Funk et al[17]; Hammerlid et al[19]
Recurrence	2	0		0	0	1	0		0	1 de Leeuw et al[16]	2	0		0	2 de Leeuw et al[16]; Funk et al[17]
Comorbidity	0	0		0	0	1	0		0	1 **Rieke et al[27]**	2	1	**Fan et al[43]**	0	1 Funk et al[17]
Diet	0	0		0	0	0	0		0	0	1	1		0	0

(Continued)

	≤3 mo after the end of treatment				3 to 12 mo after the end of treatment				>12 mo after the end of treatment			
	N	N+	N−	N0	N	N+	N−	N0	N	N+	N−	N0
										Funk et al[17]		
Dental status	0	0	0	0	0	0	0	0	1	0	0	1 Funk et al[17]
Treating hospital/ region	0	0	0	0	2	0	0	2 Llewellyn et al[22]; **Rieke et al**[27]	0	0	0	0
Inpatient or outpatient	1	0	0	1 Sehlen et al[28]	1	0	0	1 Sehlen et al[28]	0	0	0	0
Time since diagnosis	0	0	0	0	1	0	0	1 **Wu et al**[32]	0	0	0	0
Medical insurance	1	0	0	1 Sehlen et al[28]	1	0	0	1 Sehlen et al[28]	0	0	0	0
Need for home care	1	0	0	1 Sehlen et al[28]	1	0	0	1 Sehlen et al[28]	0	0	0	0
Grade	1	0	0	1 Sehlen et al[28]	1	0	0	1 Sehlen et al[28]				
Histology	1	0	0	1 **Henry et al**[44]								
Patient-reported outcome measures												
Symptoms of depression	3	3 Chen et al[12]; Mo et al[24]; Neilson et al[25]	0	0	4	4 de Graeff et al[14]; de Leeuw et al[15]; de Leeuw et al[16]; Llewellyn et al[22]	0	0	3	2 de Leeuw et al[16]; Hassel et al[20]	0	1 Aarstad et al[11]
Symptoms of anxiety	2	0	1 **Henry et al**[44]	1 Mo et al[24]	0	0	0	0	1	0	0	1 Aarstad et al[11]
Anxiety disorder	1	1 **Henry et al**[442]	0	1 **Henry et al**[44c]	0	0	0	0	0	0	0	0
Depression disorder	1	0	0	1 **Henry et al**[44]	0	0	0	0	0	0	0	0
Substance abuse disorder	1	0	0	1 **Henry et al**[44]	0	0	0	0	0	0	0	0
Sense of humor	0	0	0	0	0	0	0	0	1	1 Aarstad et al[11]	0	0
Childhood trauma	1	0	0	1 Archer et al[29]	1	0	0	1 Archer et al[29]	0	0	0	0
Poor parental care in youth	1	0	0	1 **Henry et al**[44]	0	0	0	0	0	0	0	0

(Continued)

	≤3 mo after the end of treatment				3 to 12 mo after the end of treatment				>12 mo after the end of treatment			
	N	N+	N−	N0	N	N+	N−	N0	N	N+	N−	N0
Number of life events	1	1 Archer et al[29] (6 w)	0	1 Archer et al[29] (12 w)	1	1 Archer et al[29]	0	0	0	0	0	0
Received support	0	0	0	0	2	0	1 de Leeuw et al[16]	1 de Leeuw et al[15]	1	0	1 de Leeuw et al[16] (3 y)	1 de Leeuw et al[16] (2 y)
Available support	0	0	0	0	2	0	2 de Leeuw et al[15] (12 mo); de Leeuw et al[16]	1 de Leeuw et al[15] (6 mo)	1	0	1 de Leeuw et al[16] (2y)	1 de Leeuw et al[16] (3 y)
Social network	0	0	0	0	2	0	2 de Leeuw et al[15]; de Leeuw et al[16]	0	1	0	1 de Leeuw et al[16] (3 y)	1 de Leeuw et al[16] (2 y)
Social support	0	0	0	0	0	0	0	0	1	0	0	1 Funk et al[17]
Satisfaction with social support	1	0	0	1 **Henry et al**[44]	0	0	0	0	0	0	0	0
Openness to discuss cancer in the family	0	0	0	0	1	0	1 de Leeuw et al[16] (6 mo)	1 de Leeuw et al[16] (1 y)	1	0	1 de Leeuw et al[16] (2 y)	1 de Leeuw et al[16] (3 y)
Higher self-esteem	1	0	1 Kobayashi et al[31]	0	1	0	1 Kobayashi et al[31]	0	0	0	0	0
Coping	1	0	0	1 **Henry et al**[44]	3	2 de Leeuw et al[15d]; Llewellyn et al[23c]	0	3 de Leeuw et al[15,f] de Leeuw et al[16]; Llewellyn et al[23f]	1	0	1 de Leeuw et al[16] (3y)	1 de Leeuw et al[16] (2y)
Locus of control	0	0	0	0	2	0	1 de Leeuw et al[16] (1 y)	2 de Leeuw et al[15]; de Leeuw et al[16] (6 mo)	1	0	0	1 de Leeuw et al[16]
Neuroticism	1	0	0	1 **Henry et al**[44]								
Cancer-related symptoms	0	0	0	0	2	0	0	2 de Leeuw et al[15]; de Leeuw et al[16]	2	1 de Leeuw et al[16] (3 y)	0	1 de Leeuw et al[16] (2 y)
HNC-related symptoms	0	0	0	0	2	1 de Leeuw et al[16]	0	1 de Leeuw et al[15]	2	1 Hassel et al[20]	0	1 de Leeuw et al[16]
Physical functioning	0	0	0	0	2	0	0	2 de Leeuw et al[15]; de Leeuw et al[16]	1	0	0	1 de Leeuw et al[16]
Illness perception	0	0	0	0	1	1	0	1	0	0	0	0

(Continued)

	≤3 mo after the end of treatment				3 to 12 mo after the end of treatment				>12 mo after the end of treatment			
	N	N+	N−	N0	N	N+	N−	N0	N	N+	N−	N0
						Llewellyn et al[23]g		Llewellyn et al[23g]				
Beliefs about medicine	0	0	0	0	1	0	0	1 Llewellyn et al[23]	0	0	0	0
Satisfaction with cancer information	0	0	0	0	2	0	2 Llewellyn et al[22h]; Llewellyn et al[23h]	1 Llewellyn et al[23i]	0	0	0	0
Optimism	0	0	0	0	1	0	0	1 Llewellyn et al[23]	0	0	0	0
Poor sleep	2	0	0	2 Mo et al[24]; Qin et al[26]	0	0	0	0	0	0	0	0
Pain	0	0			0	0	0	0	1	1 Funk et al[17]	0	0
Life stressors	1	0	0	1 **Henry et al[44]**								
Inflammatory markers												
TNFα	1	0	0	1 Archer et al[29]	1	0	0	1 Archer et al[29]	0	0	0	0
IL6	1	0	0	1 Archer et al[29]	1	0	0	1 Archer et al[29]	0	0	0	0
C-reactive protein	1	0	0	1 Archer et al[29]	1	0	0	1 Archer et al[29]	0	0	0	0
IFNγ	1	0	0	1 Archer et al[29]	1	0	0	1 Archer et al[29]	0	0	0	0

Note. In bold, the results of the studies on factors associated with clinical depression.

Abbreviations: BDI, Becks Depression Inventory (BDI); HADS-D, Hospital Anxiety and Depression Scale; HNC, head and neck cancer; IL6, interleukin 6; IFNγ, interferon gamma; mo, month(s); N, total number of studies; N+, total number of studies that found a positive association, N-, total number of studies that found a negative association; N0, total number of studies that found no association; post, posttreatment; TNFα, tumor necrosis factor alpha; w, week(s); y, year(s).

[a]Based on site, stage, and treatment.

[b]Lifetime.

[c]Baseline.

[d]Avoidance.

[e]Self-blame and acceptance.

[f]All other domains.

[g]Timeline.

[h]Amount and content.

[i]Type, timing.