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

Laura H.A. Korsten | Femke Jansen | Ben J.F. de Haan | Danielle Sent | Pim Cuijpers | C. René Leemans | Irma M. Verdonck-de Leeuw

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 al2 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 al2 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 al2 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 al7 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 depression33-41,45 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 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 treatment11,16,17,19,20,30,32,42,43 (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 to 2018.45 Studies mainly focused on mixed HNC patients; two studies focused on oral cavity24 or laryngeal cancer.36 Except for one study,29 which used a clinical diagnosis of depression, all studies measured symptoms of depression with 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

FIGURE 1 Flow diagram
| Authors          | Study Locale          | Population                                                                 | Used Measurement Instrument          | Measuring Times                                                                 |
|------------------|-----------------------|----------------------------------------------------------------------------|----------------------------------------|---------------------------------------------------------------------------------|
| Aarstad          | 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            | 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             | 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            | 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        | 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         | 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         | 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              | 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             | 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        | 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        | 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           | 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            | Canada                | Newly diagnosed HNC patients (n = 223)                                      | Structured clinical interview for DSM-IV | 2 (before treatment and 3 mo after baseline)                                      |
| Humphris         | UK                    | HNC patients (n = 87).                                                      | HADS-D                                 | 2 (3- and 7-mo follow-up)                                                        |
| Llewellyn        | UK                    | Newly diagnosed HNC (n = 82).                                               | HADS-D                                 | 3 (pretreatment, 1 mo after treatment, and 6-8 mo after treatment)               |

(Continues)
| Authors      | Study Locale | Population                                                                 | Used Measurement Instrument | Measuring Times                                                                 |
|-------------|--------------|----------------------------------------------------------------------------|----------------------------|--------------------------------------------------------------------------------|
| Llewellyn23 | UK           | Newly diagnosed HNC patients (n = 82).                                      | HADS-D                     | 3 (pretreatment, after treatment and 6-8 mo after treatment)                     |
| Mo24        | 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])                       |
| Neilson25   | 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)                                               |
| Qin26       | 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)                                             |
| Rieke27     | 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. |
| Sehlen28    | 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) |
| Archer29    | UK           | Newly diagnosed HNC (n = 56)                                               | HADS-D                     | 4 (presurgery and 6-, 12-, and 24-w post-surgery)                              |
| Humphris30  | UK           | Newly-diagnosed HNC patients (n = 87)                                      | HADS-D                     | 4 (3, 7, 11, and 15 mo following initial treatment)                             |
| Kobayashi31 | Japan        | HNC patients treated with surgery (n = 58)                                 | HADS-D                     | 3 (presurgery, 7-10 d after surgery and at 6-mo follow-up)                      |
| Wu32        | Taiwan       | Newly diagnosed and untreated HNC patients (n = 106)                       | Structured clinical interview for DSM-IV | 3 (pretreatment, 3- and 6-mo follow-up)                                         |
| Astrup33    | Norway       | HNC patients treated with radiotherapy (n = 133)                           | CES-D                      | 5 (pre-RT, 1, 2, 3, 6 mo after start of RT)                                     |
| Chen34      | 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 Graeff35 | 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)                      |
| Finizia36   | Sweden       | Laryngeal cancer patients (n = 26)                                         | HADS-D                     | 6 (baseline and 1-, 2-, 3-, 6-, and 12-mo follow-up)                           |
| Karnell37   | 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)                              |
| Manuel38    | USA          | Newly diagnosed HNC patients (n = 35)                                       | SCL-90 depression          | 3 (pretreatment, 4- to 6-w and 2- to 3-mo follow-up)                           |

(Continues)
depression using the HADS-D, CES-D, BDI, or SCL-90.

3.4 | Quality assessment

Eleven of the 35 studies were of high methodological quality (Appendix B). The majority of studies (23/35) did not have a baseline participation rate (the percentage of all eligible patients who want to participate) of at least 80% or showed selective nonresponse (characteristics of participants differed from those patients who were not willing to participate). Twenty-one studies included less than 100 patients and about half (17/35) performed multivariate analyses.

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, 1 month after the end of treatment, or at least 1 month after the end of treatment were significantly associated with a higher level of depression at a later time point. The only study that did not find a significant association was Aarstad et al 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, 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, 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, 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 or at least two low-quality studies showed no significant association.

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, while other
### TABLE 2  Overview factors associated with depression at a single time point (all)

| Factors Associated with Depression (all) | N | N+ | N- | N0 | LoE |
|-----------------------------------------|---|----|----|----|-----|
| **Sociodemographic**                   |   |    |    |    |     |
| Female gender                          | 18| 6  | 0  | 15 | ?   |
| de Graeff et al14 (6 mo);              |   |    |    |    |     |
| de Leeuw et al15 (6 mo);              |   |    |    |    |     |
| de Leeuw et al16 (2 and 3 y);         |   |    |    |    |     |
| Mo et al24; Rieke et al27; Fan et al23 |   |    |    |    |     |
| de Leeuw15 (12 mo); de Leeuw16 (6 mo, 1 y); Hammerlid et al18; Hammerlid et al19; Humphris et al21; Llewellyn et al22; Mo et al24; Neilson et al25; Qin et al26; Sehlen et al28; Wu et al32; Bozec et al42; Henry et al44 |   |    |    |    |     |
| Younger age                            | 19| 3  | 1  | 16 | ?   |
| Chen et al12 (HADS); Mo et al24; Fan et al43 |   |    |    |    |     |
| Rieke et al27                          |   |    |    |    |     |
| Chen et al17 (BDI); Derks et al13; de Graeff14; de Leeuw et al15; de Leeuw et al16; Funk et al17; Hammerlid et al19; Hammerlid et al19; Humphris et al21; Llewellyn et al22; Neilson et al25; Qin et al26; Sehlen et al28; Wu et al32; Bozec et al42; Henry et al44 |   |    |    |    |     |
| Being married                          | 6 | 0  | 1  | 5  | ?   |
| Chen et al12                           |   |    |    |    |     |
| Rieke et al27; Sehlen et al28; Wu et al32 |   |    |    |    |     |
| Living alone                           | 2 | 1  | 0  | 1  | ?   |
| Chen et al12                           |   |    |    |    |     |
| Neilson et al25                         |   |    |    |    |     |
| Having children                        | 1 | 0  | 0  | 1  | ?   |
| Chen et al12                           |   |    |    |    |     |
| Sehlen et al28                         |   |    |    |    |     |
| Being employed                         | 5 | 1  | 1  | 3  | ?   |
| Chen et al12                           |   |    |    |    |     |
| Fan et al23                            |   |    |    |    |     |
| Sehlen et al28; Wu et al32; Bozec et al42 |   |    |    |    |     |
| Higher income                          | 3 | 0  | 1  | 2  | ?   |
| Chen et al12; Rieke et al27            |   |    |    |    |     |
| Higher education                       | 9 | 0  | 1  | 9  | ?   |
| Sehlen et al28 (post, 6 w)             |   |    |    |    |     |
| Chen et al12; Llewellyn et al22;       |   |    |    |    |     |
| Llewellyn et al28; Mo et al24; Qin et al26; Rieke et al27; Sehlen et al28 (6 mo); Wu et al32; Bozec et al42 |   |    |    |    |     |
| Urbanization                           | 1 | 0  | 0  | 0  | ?   |
| Fan et al23                            |   |    |    |    |     |
| Ethnicity                              | 3 | 0  | 0  | 3  | ?   |
| Llewellyn et al22; Llewellyn et al23;  |   |    |    |    |     |
| Rieke et al27                          |   |    |    |    |     |
| **Lifestyle**                          |   |    |    |    |     |
| Current smoker                         | 2 | 1  | 0  | 1  | ?   |
| Humphris & Rogers30                    |   |    |    |    |     |
| Bozec et al42                          |   |    |    |    |     |
| Smoking (history)                      | 3 | 0  | 0  | 3  | ?   |
| Chen et al17; Funk et al17; Wu et al32 |   |    |    |    |     |
| History of addiction                   | 1 | 0  | 0  | 1  | ?   |
| Sehlen et al28                         |   |    |    |    |     |
| Alcohol use                            | 4 | 1  | 0  | 3  | ?   |
| Funk et al27; Neilson et al25; Wu et al32 |   |    |    |    |     |
| Clinical                               |   |    |    |    |     |

(Continues)
| Factors Associated with Depression (all) | N     | N+   | N-     | N0    | LoEa  |
|----------------------------------------|-------|------|--------|-------|-------|
| Higher disease stage                   | 15    | 6    | 0      | 11    |       |
| (previous) surgery                     | 5     | 0    | 0      | 5     |       |
| Salvage surgery                        | 1     | 0    | 0      | 1     |       |
| Surgery approach                       | 1     | 0    | 0      | 1     |       |
| Chemotherapy                           | 8     | 4    | 0      | 5     |       |
| Radiotherapy                           | 5     | 2    | 0      | 3     |       |
| Treatment                              | 6     | 1    | 0      | 5     |       |
| Treatment toxicity                     | 1     | 0    | 0      | 1     |       |
| Performance (Karnofsky)                | 3     | 0    | 2      | 2     |       |
| Groupc                                 | 1     | 1    | 0      | 0     |       |
| Tumor location                         | 6     | 1    | 0      | 5     |       |
| Recurrence                             | 2     | 0    | 0      | 2     |       |
| Comorbidity                            | 3     | 1    | 0      | 2     |       |
| Diet                                   | 1     | 1    | 0      | 0     |       |
| Dental status                          | 1     | 0    | 0      | 1     |       |
| Treating hospital/region               | 2     | 0    | 0      | 2     |       |
| Inpatient or outpatient                | 1     | 0    | 0      | 1     |       |
| Time since diagnosis                   | 1     | 0    | 0      | 1     |       |
| Medical insurance                      | 1     | 0    | 0      | 1     |       |
| Need for home care                     | 1     | 0    | 0      | 1     |       |
| Grade                                  | 1     | 0    | 0      | 1     |       |
| Histology                              | 1     | 0    | 0      | 1     |       |

(Continues)
| Factors Associated with Depression (all) | N | N+ | N- | N0 | LoE* |
|-----------------------------------------|---|----|----|----|-----|
| **Patient-reported outcome measures or psychiatric diagnosis** |   |    |    |    |     |
| Symptoms of depression                  | 8 | 7  | 0  | 1  | Aarstad et al11 ++ |
|                                          |   |    |    |    |     |
|                                          |   |    |    |    |     |
| Symptoms of anxiety                     | 3 | 0  | 1  | 2  | Henry et al44 |
| Anxiety disorder                        | 1 | 1  |    |    | Henry et al44 |
| Depression disorder                     | 1 | 0  |    |    | Henry et al44 |
| Substance use disorder                  | 1 | 0  |    |    | Henry et al44 |
| Sense of humor                          | 1 | 1  |    |    | Aarstad et al11 |
| Childhood trauma                        | 1 | 0  |    |    | Archer et al29 |
| Poor parental care in youth             | 1 | 0  |    |    | Henry et al44 |
| Number of life events                   | 1 | 1  |    |    | Archer et al44 |
| Received support                        | 2 | 0  | 1  | 2  | de Leeuw et al15 |
| Available support                       | 2 | 0  | 2  |    | de Leeuw et al15 |
| Social network                          | 2 | 0  | 2  |    | de Leeuw et al15 |
| Social support                          | 1 | 0  |    |    | Funk et al17 |
| Satisfaction with social support        | 1 | 0  |    |    | Henry et al44 |
| Openness to discuss cancer in the family| 1 | 0  | 1  |    | de Leeuw et al15 |
| Higher self-esteem                      | 1 | 0  |    |    | Kobayashi et al21 |
| Coping                                  | 4 | 2  | 1  | 4  | de Leeuw et al16 |
| Locus of control                        | 2 | 0  | 1  |    | de Leeuw et al16 |
| Neuroticism                             | 1 | 0  |    |    | Henry et al44 |
| Cancer-related symptoms                 | 2 | 1  | 0  | 2  | de Leeuw et al16 |

*(Continued)*
### TABLE 2  (Continued)

| Factors Associated with Depression (all) | N+ | N- | N0 | LoE* |
|-----------------------------------------|----|----|----|------|
| **HNC-related symptoms**                | 3  | 0  | 2  | ?    |
| de Leeuw et al15; de Leeuw et al16     |    |    |    | ?    |
| Hassel et al20                         |    |    |    | ?    |
| **Physical functioning**                | 2  | 0  | 2  | ?    |
| de Leeuw et al16; de Leeuw et al15     |    |    |    | ?    |
| **Illness perception**                  | 1  | 1  | 0  | ?    |
| Llewellyn et al23                      |    |    |    | ?    |
| **Beliefs about medicine**              | 1  | 0  | 0  | ?    |
| Llewellyn et al23                      |    |    |    | ?    |
| **Satisfaction with cancer information**| 2  | 0  | 2  | ?    |
| Llewellyn et al23                      |    |    |    | ?    |
| **Optimism**                            | 1  | 0  | 0  | ?    |
| Llewellyn et al23                      |    |    |    | ?    |
| **Poor sleep**                          | 2  | 0  | 0  | ?    |
| Mo et al14                              |    |    |    | ?    |
| Qin et al26                             |    |    |    | ?    |
| **Pain**                                | 1  | 1  | 0  | ?    |
| Funk et al17                            |    |    |    | ?    |
| **Life stressors**                      | 1  | 0  | 0  | ?    |
| Henry et al44                           |    |    |    | ?    |
| **Inflammatory markers**                |    |    |    | ?    |
| TNFα                                    | 1  | 0  | 0  | ?    |
| Archer et al29                          |    |    |    | ?    |
| IL6                                     | 1  | 0  | 0  | ?    |
| Archer et al29                          |    |    |    | ?    |
| C-reactive protein                      | 1  | 0  | 0  | ?    |
| Archer et al29                          |    |    |    | ?    |
| IFNγ                                    | 1  | 0  | 0  | ?    |
| Archer et al29                          |    |    |    | ?    |

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).

*aLevel of evidence was defined as strong, moderate in conclusive.

*bPatients who were treated with surgery only compared to all other treatments or treatment combinations.

*cBased on site, stage and treatment.

*dReference category was larynx.

*eLifetime.

*fBaseline.

*gAvoidance.

*hSelf-blame and acceptance.

*iPalliative coping, direction unknown.

+jAll other domains

*kTimeline.

+lAmount and content.

+mType, timing.
### TABLE 3  
Factors associated with the course of depression

| Factor Associated with the Course of Depression | N | N+ | N- | N0 |
|------------------------------------------------|---|----|----|----|
| **Sociodemographic**                            |   |    |    |    |
| Female gender                                   | 4 | 1  | 0  | 3  | Astrup et al33, Karnell et al37, Neilson et al39 |
| Younger age                                     | 4 | 0  | 0  | 4  | Astrup et al33, de Graeff et al35, Neilson et al39 |
| Being married                                   | 1 | 0  | 0  | 1  | Astrup et al33 |
| Living alone                                    | 1 | 0  | 0  | 1  | Neilson et al39 |
| Children living at home                         | 1 | 0  | 0  | 1  | Astrup et al33 |
| Being employed                                   | 1 | 0  | 0  | 1  | Astrup et al33 |
| Higher education                                | 1 | 0  | 0  | 1  | Astrup et al33 |
| **Lifestyle**                                   |   |    |    |    |
| Smoking                                         | 2 | 1  | 0  | 1  | Karnell et al37 |
| Alcohol use                                      | 1 | 0  | 0  | 1  | Karnell et al37 |
| **Clinical**                                    |   |    |    |    |
| Higher disease stage                            | 3 | 0  | 0  | 3  | Astrup et al33, de Graeff et al35, Karnell et al37 |
| Treatment intent (curative/palliative)          | 1 | 0  | 0  | 1  | Astrup et al33 |
| Treatment                                       | 2 | 0  | 0  | 2  | de Graeff et al35, Karnell et al37 |
| Surgery (previous)                              | 1 | 0  | 0  | 1  | Astrup et al33 |
| Chemotherapy                                    | 3 | 0  | 0  | 3  | Astrup et al33, Chen et al34, Neilson et al39 |
| Performance (Karnofsky)                         | 1 | 0  | 0  | 1  | Astrup et al33 |
| Group*                                          | 1 | 0  | 0  | 1  | de Graeff et al35 |
| Tumor location                                  | 2 | 0  | 0  | 2  | Astrup et al33, Karnell et al37 |
| Recurrence                                      | 1 | 0  | 0  | 1  | Karnell et al37 |
| Comorbidity                                     | 1 | 0  | 0  | 1  | Astrup et al33 |
| Time since diagnosis                            | 1 | 0  | 0  | 1  | Astrup et al33 |
| Weight loss                                     | 1 | 1  | 0  | 0  | Van Liew et al41 |
| **Patient-reported outcome measures**           |   |    |    |    |
| Symptoms of depression                          | 2 | 1  | 0  | 1  | Astrup et al33 |
| Childhood trauma                                | 1 | 1  | 0  | 0  | Archer et al29 |
| Number of life events                           | 1 | 1  | 0  | 0  | Archer et al29 |
| Social support                                  | 1 | 0  | 0  | 1  | Astrup et al33 |
| Higher self-esteem                              | 1 | 0  | 1  | 0  | Kobayashi et al31 |
| Coping (low approach, low avoidance)            | 1 | 1  | 0  | 0  | Manuel et al36 |
| Communication dysfunction                       | 1 | 1  | 0  | 0  | Finizia et al36 |
| Nutrition                                       | 1 | 0  | 0  | 1  | Astrup et al33 |
| HNC-related symptoms                            | 3 | 3  | 0  | 2  | |

(Continues)
studies found no such significant association.\textsuperscript{12,14-16,18,19,21,23-28,32,42,44} Regarding employment one study found a positive association,\textsuperscript{12} one study a negative association,\textsuperscript{43} and three studies found no such association.\textsuperscript{28,32,42} Of the lifestyle factor current smoking, one study found higher depression among those who currently smoked,\textsuperscript{30} while another study found no such association.\textsuperscript{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,\textsuperscript{15,16,19,22,27,44} those treated with chemotherapy (versus no chemotherapy),\textsuperscript{25,26,28,43} those treated with radiotherapy (versus no radiotherapy),\textsuperscript{27,43} patients with a lower performance status,\textsuperscript{14,18} or people with comorbidities.\textsuperscript{43} However, other studies found no significant association.\textsuperscript{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,\textsuperscript{44} with less received support,\textsuperscript{16} less available support,\textsuperscript{15,16} smaller social network,\textsuperscript{15,16} with certain coping styles,\textsuperscript{15,16,23} worse locus of control,\textsuperscript{16} higher level of cancer-related\textsuperscript{16} HNC-related symptoms,\textsuperscript{16,20} and lower satisfaction with cancer information,\textsuperscript{22,23} while others found no significant association.\textsuperscript{11,15,16,22,24,44} Finally, physical functioning was not significantly associated with depression, as these two studies were performed in the same study population.\textsuperscript{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.\textsuperscript{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\textsuperscript{33} or two low-quality studies\textsuperscript{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,\textsuperscript{30} had higher depression at baseline,\textsuperscript{37} experienced (a higher level of) HNC-related symptoms,\textsuperscript{32,37,39} and those who were less satisfied with their body image/looks,\textsuperscript{40} while other studies did not.\textsuperscript{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,\textsuperscript{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,\textsuperscript{15} while other studies showed that palliative coping\textsuperscript{16} and acceptance behavior and self-blame\textsuperscript{23} were significantly associated with depression. In addition, the longitudinal study of Manuel et al\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{49}

More research is also needed on the predictive factor of biomarkers, as so far only one study investigated biomarkers in relation to depression.\textsuperscript{29} Although this study of Archer et al\textsuperscript{29} did not found a significant association between TNF\textalpha, IL6, C-reactive protein, and IFN\gamma and depression over time among HNC patients, they did show a significant association between TNF\textalpha and C-reactive protein, and depression among colorectal cancer patients. Also, other studies have hypothesized that these biomarkers may be associated with depression.\textsuperscript{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.

ACKNOWLEDGEMENT

Funding was obtained from the Dutch Cancer Society/Alpe d’HuZes Foundation (VU 2013-5930).

CONFLICT OF INTEREST

None.

ORCID

Femke Jansen https://orcid.org/0000-0002-0111-0557
Irma M. Verdonck-de Leeuw https://orcid.org/0000-0002-4507-4607

REFERENCES

1. Krebber AM, Buffart LM, Kleijn G, et al. Prevalence of depression in cancer patients: a meta-analysis of diagnostic interviews and self-report instruments. Psychooncology. 2014;23(2):121-130.

2. Haisfield-Wolfe ME, McGuire DB, Soeken K, Geiger-Brown J, De Forge BR. Prevalence and correlates of depression among patients with head and neck cancer: a systematic review of implications for research. Oncol Nurs Forum. 2009;36(3):E107-E125.

3. Lin BM, Starmer HM, Gourin CG. The relationship between depressive symptoms, quality of life, and swallowing function in head and neck cancer patients 1 year after definitive therapy. Laryngoscope. 2012;122(7):1518-1525.

4. Verdonck-de Leeuw IM, Eerenstein SE, Van der Linden MH, Kuik DJ, de Bree R, Leemans CR. Distress in spouses and patients after treatment for head and neck cancer. Laryngoscope. 2007;117(2):238-241.

5. Jacobi I, van der Molen L, Huiskens H, van Rossum MA, Hilgers FJ. Voice and speech outcomes of chemoradiation for advanced head and neck cancer: a systematic review. Eur Arch Otorhinolaryngol. 2010;267:1495-1505.

6. van der Molen L, van Rossum MA, Burkhedt LM, Smeele LE, Hilgers FJ. Functional outcomes and rehabilitation strategies in patients treated with chemoradiotherapy for advanced head and neck cancer: a systematic review. Eur Arch Otorhinolaryngol. 2009;266(6):889-900.

7. Hayden JA, Cote P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. Ann Intern Med. 2006;144(6):427-437.

8. Chinapaw MJ, Proper KL, Brug J, van Mechelen W, Singh AS. Relationship between young peoples’ sedentary behaviour and biomedical health indicators: a systematic review of prospective studies. Obes Rev. 2011;12(7):e621-e632.

9. Kampffhoff CS, Jansen F, van Mechelen W, et al. Determinants of exercise adherence and maintenance among cancer survivors: a systematic review. Int J Behav Nutr Phys Act. 2014;11(1):80.

10. Uijtdewilligen L, Nauta J, Singh AS, et al. Determinants of physical activity and sedentary behaviour in young people: a review and quality synthesis of prospective studies. Br J Sports Med. 2011;45(11):896-905.

11. Aarstad HJ, Aarstad AK, Heimdal JH, Olofsson J. Mood, anxiety and sense of humor in head and neck cancer patients in relation to disease stage, prognosis and quality of life. Acta Otolaryngol. 2005;125(5):557-565.

12. Chen AM, Jennelle RL, Grady V, et al. Prospective study of psychosocial distress among patients undergoing radiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys. 2009;73(1):187-193.

13. Derks J, De Leeuw R, Winnubst J, Hordijk GJ. Elderly patients with head and neck cancer: physical, social and psychological aspects after 1 year. Acta Otolaryngol. 2004;124(4):509-514.

14. de Graeff A, De Leeuw JR, Ros WJ, Hordijk GJ, Blijham GH, Winnubst JA. Pretreatment factors predicting quality of life after treatment for head and neck cancer. Head Neck. 2000;22(4):398-407.

15. de Leeuw JR, de Graeff A, Ros WJ, Blijham GH, Hordijk GJ, Winnubst JA. Prediction of depressive symptomatology after treatment of head and neck cancer: the influence of pre-treatment physical and depressive symptoms, coping, and social support. Head Neck. 2000;22(8):799-807.

16. de Leeuw JR, de Graeff A, Ros WJ, Blijham GH, Hordijk GJ, Winnubst JA. Prediction of depression 6 months to 3 years after treatment of head and neck cancer. Head Neck. 2001;23(10):892-898.

17. Funk GF, Karmell LH, Christensen AJ. Long-term health-related quality of life in survivors of head and neck cancer. Arch Otolaryngol Head Neck Surg. 2012;138(2):123-133.

18. Hammerlid E, Ahlner-Elmqvist M, Bjordal K, et al. A prospective multicentre study in Sweden and Norway of mental distress and psychiatric morbidity in head and neck cancer patients. Br J Cancer. 1999;80(5-6):766-774.

19. Hammerlid E, Silander E, Hornestam L, Sullivan M. Health-related quality of life three years after diagnosis of head and neck cancer—a longitudinal study. Head Neck. 2001;23(2):113-125.

20. Hassel AJ, Danner D, Freier K, Hofele C, Becker-Bikowski K, Engel M. Oral health-related quality of life and depression/anxiety in long-term recurrence-free patients after treatment for advanced oral squamous cell cancer. J Cranio maxillofac Surg. 2012;40(4):e99-e102.

21. Humphris GM, Rogers S, McNally D, Lee-Cones J, Brown J, Vaughan D. Fear of recurrence and possible cases of anxiety and depression in orofacial cancer patients. Int J Oral Maxillofac Surg. 2003;32(5):486-491.
32. Wu YS, Lin PY, Chien CY, et al. Anxiety and depression in patients with head and neck cancer: is Lewtham’s common sense model a useful framework for determining changes in outcomes over time? J Psychosom Res. 2007;63(1):17-26.

24. Mo Y-L, Li L, Qin L, et al. Cognitive function, mood, and sleep quality in patients treated with intensity-modulated radiation therapy for nasopharyngeal cancer: a prospective study. Psychooncology. 2014;23(10):1185-1191.

30. Humphris GM, Rogers SN. The association of cigarette smoking and anxiety, depression and fears of recurrence in patients following treatment with head and neck cancer. Med J Aust. 2010;193(5 Suppl):S48-S51.

26. Neilson KA, Pollard AC, Boonzaier AM, et al. Psychological distress (depression and anxiety) in people with head and neck cancers. Med J Aust. 2010;193(5 Suppl):S48-S51.

34. Chen SC, Lai YH, Liao CT, Lin CC, Chang JT. Changes of symptoms and quality of life of patients with head and neck cancer. Laryngoscope. 2000;110(1):98-106.

13. Finizia C, Palme C, Bergman B. A longitudinal study of the Swedish self-evaluation of communication experiences after Laryngeal Cancer questionnaire in patients treated for laryngeal cancer. Acta Oncol. 2002;41(3):262-268.

37. Karnell LH, Funk GF, Christensen AJ, Rosenthal EL, Magnuson JS. Persistent posttreatment depressive symptoms in patients with head and neck cancer. Head Neck. 2006;28(5):453-461.

38. Manuel GM, Roth S, Keefe FJ, Brantley BA. Coping with cancer. J Human Stress. 1987;13(4):149-158.

39. Neilson K, Pollard A, Boonzaier A, et al. A longitudinal study of distress (depression and anxiety) up to 18 months after radiotherapy for head and neck cancer. Psychooncology. 2013;22(8):1843-1848.

40. Rhoten BA, Deng J, Dietrich MS, Murphy B, Ridner SH. Body image and depressive symptoms in patients with head and neck cancer: an important relationship. Support Care Cancer. 2014;22(11):3053-3060.

41. Van Liew JR, Brock RL, Christensen AJ, Karnell LH, Pageda NA, Funk GF. Weight loss after head and neck cancer: a dynamic relationship with depressive symptoms. Head Neck. 2017;39(2):370-379.

42. Bozec A, Demez P, Gal J, et al. Long-term quality of life and psychosocial outcomes after oropharyngeal cancer surgery and frontal forearm free-flap reconstruction: a GETTEC prospective multicentric study. Surg Oncol. 2018;27(1):23-30.

43. Fan CY, Chao HL, Lin CS, et al. Risk of depressive disorder among patients with head and neck cancer: a nationwide population-based study. Head Neck. 2018;40(2):312-323.

44. Henry M, Rosberger Z, Ianovski LE, et al. A screening algorithm for early detection of major depressive disorder in head and neck cancer patients post-treatment: longitudinal study. Psychooncology. 2018;27(6):1622-1628.

45. Rhoten BA, Murphy BA, Dietrich MS, Ridner SH. Depressive symptoms, social anxiety, and perceived neck function in patients with head and neck cancer. Head Neck. 2018;40(7):1443-1452.

46. Cook SA, Salmon P, Hayes G, Byrne A, Fisher PL. Predictors of emotional distress a year or more after diagnosis of cancer: a systematic review of the literature. Psychooncology. 2018;27(3):791-801.

47. Morris N, Moughaddam N, Tickle A, Biswas S. The relationship between coping style and psychological distress in people with head and neck cancer: a systematic review. Psychooncology. 2018;27(3):734-747.

48. Musliner KL, Munk-Olsen T, Eaton WW, Zandi PP. Heterogeneity in long-term trajectories of depressive symptoms: patterns, predictors and outcomes. J Affect Disord. 2016;192:199-211.

49. Dunne S, Mooney O, Coffey L, et al. Psychological variables associated with quality of life following primary treatment for head and neck cancer: a systematic review of the literature from 2004 to 2015. Psychooncology. 2017;26(2):149-160.

50. Reyes-Gibby CC, Wu X, Spitz M, et al. Molecular epidemiology, cancer-related symptoms, and cytokines pathway. Lancet Oncol. 2008;9(8):777-785.

51. Kim HJ, Barsevick AM, Fang CY, Miaskowski C. Common biological pathways underlying the psychoneurological symptom cluster in cancer patients. Cancer Nurs. 2012;35(6):E1-e20.

52. Sotelo JL, Musselman D, Nemermof C. The biology of depression in cancer and the relationship between depression and cancer progression. Int Rev Psychiatry. 2014;26:16-30.

How to cite this article: Korsten LHA, Jansen F, de Haan BJF, et al. Factors associated with depression over time in head and neck cancer patients: A systematic review. Psycho-Oncology. 2019;28:1159-1183. https://doi.org/10.1002/pon.5058
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

(predict* OR associat* OR correlat* OR preval* OR inciden* OR facilitat* OR prognos* OR determinan* OR mediator*)
## APPENDIX B.
### QUALITY ASSESSMENT OF THE INCLUDED STUDIES

|                                | Aarstad\(^1\) | Bozec\(^2\) | Chen\(^3\) | Derks\(^4\) | de Graeff\(^5\) | de Leeuw\(^6\) | de Leeuw\(^7\) | Fan\(^8\) | Funk\(^9\) | Hammerlid\(^10\) | Hammerlid\(^11\) |
|--------------------------------|---------------|--------------|------------|-------------|-----------------|----------------|----------------|----------|-----------|------------------|---------------|
| **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             |
| Study population and participation | Studies that Investigated both Factors Associated with Depression and the Course of Depression | Studies on Factors Associated with the Course of Depression |
|-----------------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------|
| The sampling frame and recruitment are adequately described (setting and geographical location) | Archer29  Humphris30  Kobayashi31  Wu32  Astrup33  de Graeff26  Finizia36  Karnell27  Manuel28  Nelson25  Rhoten40  Rhoten45  Van Liew41 | +  +  +  +  –  –  –  +  –  +  +  –  – |
| 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 | Henry | Humphris | Llewellyn | Llewellyn | Mo | Neilson | Qin | Rieke | Sehlen |
|--------------------------------|--------|-------|----------|-----------|-----------|----|---------|-----|-------|--------|
| **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      |
| Time Period          | N  | N+ | N  | N+ | N  | N+ | N  | N+ | N  | N+ | N  | N+ |
|---------------------|----|----|----|----|----|----|----|----|----|----|----|----|
| < 3 mo after the end of treatment | 8  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  |
| 3 to 12 mo after the end of treatment | 8  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  |
| > 12 mo after the end of treatment | 0  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  |

**Sociodemographic**

- **Female gender**: 8/0/0/0 (Chen et al., 2012; Neilson et al., 2025; Qin et al., 2026; Sehle et al., 2028; Henry et al., 2044)
- **Younger age**: 8/0/1/1 (Chen et al., 2012; Neilson et al., 2025; Qin et al., 2026; Sehle et al., 2028; Henry et al., 2044)
- **Being married**: 2/0/1/1 (Chen et al., 2012; Neilson et al., 2025; Sehle et al., 2028; Bozec et al., 2042)
- **Living alone**: 0/0/0/0 (Rieke et al., 2027; de Graeff et al., 2014; de Leeuw et al., 2015; Llewellyn et al., 2023; Wu et al., 2032)
|                              | ≤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  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  | N+ | N  | -  | NO | N  |
| Being employed              | 1 1 | 0  | 1  | Sehlen et al28 | 1 0 | 0  | 1  | Sehlen et al28 | 2 0 | 0  | 2  | Sehlen et al28, Wu et al32 |
| Higher income               | 1 0 | 0  | 1  | Chen et al12 | 1 0 | 0  | 1  | Rieke et al27 |
| Higher education            | 4 0 | 1  | 3  | Chen et al12, Mo et al24, Qin et al26 | 5 0 | 0  | 5  | Llewellyn et al22, Llewellyn et al22, Rieke et al7, Sehlen et al28, Wu et al32 |
| Urbanization                | 0 0 | 0  | 0  | 0  | 1  | 0  | 0  | 1  | 0  | 0  | 1  | Fan et al43 |
| Ethnicity                   | 0 0 | 0  | 0  | 3  | 0  | 3  | Llewellyn et al22, Llewellyn et al22, Rieke et al7 |
| Lifestyle                   |                              |                              |                              |                              |                              |                              |                              |                              |                              |                              |                              |                              |
| Current smoker              | 0 0 | 0  | 0  | 1 1 | 0  | 0  | 2 1 | Humphris & Rogers30, 1 Bozec et al12 |
| Smoking history             | 1 0 | 0  | 1  | Chen et al12 | 1 0 | 0  | 1  | Wu et al32, 1 Funk et al17 |
| History of addiction        | 1 0 | 0  | 1  | Sehlen et al28, 1 Sehlen et al28 | 1 0 | 0  | 1  | Sehlen et al28, 0 0 |
| Alcohol use                 | 1 0 | 0  | 1  | Neilson et al25 | 1 0 | 0  | 1  | Wu et al32, 2 1 Bozec et al42, 1 Funk et al17 |
| Clinical                    |                              |                              |                              |                              |                              |                              |                              |                              |                              |                              |                              |
| Higher disease stage        | 7 1 | 0  | 6  | Chen et al12, Hammerlid et al18, Humphris et al21, Mo et al24, Qin et al26, Sehlen et al28 | 10 4 | 4  | de Leeuw et al15, de Leeuw et al16, (6 mo); Llewellyn et al22, Rieke et al27 |
| previous surgery            | 3 0 | 0  | 3  | 1 0 | 0  | 1  | 1 0 | 0 0 |

KORSTEN ET AL. 1179
|                                       | ≤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  | N  | N+ | N  | N  | N  | N+ | N  | N  | N  |
| Salvaage surgery                     | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 1  |
| Surgery approach                     | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 1  |
| Chemotherapy                         | 5  | 2  | 0  | 3  | 1  | 1  | 0  | 3  | 1  | 0  | 2  | 1  |
| Radiotherapy                         | 1  | 0  | 1  | 1  | 2  | 1  | 0  | 1  | 3  | 1  | 0  | 2  |
| Treatment                            | 1  | 1  | 0  | 0  | 5  | 0  | 0  | 5  | 1  | 0  | 1  | 6  |
| Treatment toxicity                   | 1  | 0  | 1  | 0  | 1  | 1  | 0  | 1  | 0  | 0  | 0  | 0  |
| Performance                          | 2  | 0  | 2  | 3  | 0  | 2  | 1  | 0  | 0  | 0  | 0  | 0  |
| Tumor location                       | 0  | 0  | 0  | 4  | 0  | 0  | 4  | 3  | 1  | 0  | 2  | 3  |
| Recurrence                           | 2  | 0  | 1  | 0  | 0  | 1  | 0  | 0  | 2  | 0  | 0  | 2  |
| Comorbidity                          | 0  | 0  | 1  | 1  | 0  | 1  | 1  | 1  | 0  | 0  | 0  | 0  |
| Diet                                 | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 1  | 1  | 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−  NO                   | N  N+  N−  NO                  | N  N+  N−  NO                  |
| Dental status                      | 0  0  0  0                     | 0  0  0  0                     | 1  0  0  1                     |
|                                    | Funk et al17                   |                                      | Funk et al17                   |
| Treating hospital/region           | 0  0  0  0                     | 2  0  0  2                     | Llewellyn et al22; Rieke et al |
|                                    |                                 |                                      |                                 |
| Inpatient or outpatient            | 1  0  0  1                     | 1  0  0  1                     | 0  0  0  0                     |
|                                    | Sehlen et al28                 |                                      |                                 |
| Time since diagnosis               | 0  0  0  0                     | 1  0  0  1                     | Wu et al12                     |
| Medical insurance                  | 1  0  0  1                     | 1  0  0  1                     | 0  0  0  0                     |
|                                    | Sehlen et al28                 |                                      |                                 |
| Need for home care                 | 1  0  0  1                     | 1  0  0  1                     | 0  0  0  0                     |
|                                    | Sehlen et al28                 |                                      |                                 |
| Grade                              | 1  0  0  1                     | 1  0  0  1                     | 0  0  0  0                     |
|                                    | Sehlen et al28                 |                                      |                                 |
| Histology                          | 1  0  0  1                     | 1  0  0  1                     | 0  0  0  0                     |
|                                    | Henry et al44                  |                                      |                                 |
| Patient-reported outcome measures  |                                 |                                      |                                 |
| Symptoms of depression             | 3  0  0  0                     | 4  4  0  0                     | 3  2  0  0                     |
|                                    | Chen et al12; Mo et al34;      | de Graeff et al14; de Leeuw et al15; | de Leeuw et al16; Llewellyn et al |
|                                    | Neilson et al25               |                                    |                                 |
|                                    |                                 |                                      |                                 |
| Symptoms of anxiety                | 2  0  0  0                     | 1  0  0  1                     | 0  0  1  1                     |
|                                    | Henry et al44; Mo et al44      |                                      |                                 |
| Anxiety disorder                   | 1  1  0  0                     | 1  0  0  0                     | 0  0  0  0                     |
|                                    | Henry et al44                  |                                      |                                 |
| Depression disorder                | 1  0  0  1                     | 1  0  0  1                     | 0  0  0  0                     |
|                                    | Henry et al44                  |                                      |                                 |
| Substance abuse disorder           | 1  0  0  1                     | 1  0  0  1                     | 0  0  0  0                     |
|                                    | Henry et al44                  |                                      |                                 |
| Sense of humor                     | 0  0  0  0                     | 0  0  0  0                     | 1  1  0  0                     |
|                                    |                                 |                                      |                                 |
| Childhood trauma                   | 1  0  0  1                     | 1  0  0  1                     | 0  0  0  0                     |
|                                    | Archer et al29                 |                                      |                                 |
| Poor parental care in youth        | 1  0  0  1                     | 1  0  0  1                     | 0  0  0  0                     |
|                                    | Henry et al44                  |                                      |                                 |
|                           | ≤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  | N       | N+   | N   | N0  |
| Number of life events     | 1       | 1    | 0   | 1   | 1       | 1    | 0   | 0   | 0       | 0    | 0   | 0   | 0       | 0    | 0   | 0   |
| Received support          | 0       | 0    | 0   | 0   | 2       | 0    | 1   | 0   | 1       | 0    | 1   | 0   | 1       | 0    | 0   | 0   |
| Available support         | 0       | 0    | 0   | 0   | 2       | 0    | 2   | 0   | 2       | 0    | 1   | 0   | 2       | 0    | 1   | 0   |
| Social network            | 0       | 0    | 0   | 0   | 2       | 0    | 0   | 0   | 0       | 0    | 0   | 0   | 1       | 0    | 0   | 0   |
| Social support            | 0       | 0    | 0   | 0   | 0       | 0    | 0   | 0   | 0       | 0    | 0   | 0   | 0       | 0    | 0   | 0   |
| Satisfaction with social support | 1     | 0    | 0   | 1   | Henry et al^44 | 0       | 0    | 0   | 0       | 0    | 0   | 0   | 0       | 0    | 0   | 0   |
| Openness to discuss cancer in the family | 0     | 0    | 0   | 0   | 1       | 0    | 1   | 0   | 1       | 0    | 1   | 0   | 1       | 0    | 1   | 0   |
| Higher self-esteem        | 1       | 0    | 1   | Kobayashi et al^21 | 0       | 1       | 0    | 1   | Kobayashi et al^21 | 0       | 0    | 0   | 0       | 0    | 0   | 0   |
| Coping                    | 1       | 0    | 0   | 0   | 1       | Henry et al^44 | 3       | 2   | de Leeuw et al^15, Llewellyn et al^26 | 0       | 3       | 2   | de Leeuw et al^15, de Leeuw et al^15; Llewellyn et al^26 | 0       | 1       | de Leeuw et al^15, de Leeuw et al^15 | 1       | 1       | de Leeuw et al^15, de Leeuw et al^15 | 1       | de Leeuw et al^15 (2y) |
| Locus of control          | 0       | 0    | 0   | 0   | 2       | 0    | 1   | 0   | de Leeuw et al^15 | 1       | 0   | 0   | 1       | de Leeuw et al^15 (3y) |
| Neuroticism               | 1       | 0    | 0   | 1   | Henry et al^44 | 0       | 0   | 0   | 0       | 0    | 0   | 0   | 0       | 0    | 0   | 0   |
| Cancer-related symptoms   | 0       | 0    | 0   | 0   | 2       | 0    | 0   | 0   | 0       | 0    | 2   | 1   | de Leeuw et al^15; de Leeuw et al^16 | 2       | 1   | de Leeuw et al^15 (3y) |
| HNC-related symptoms      | 0       | 0    | 0   | 0   | 2       | 1   | de Leeuw et al^16 | 0       | 1   | de Leeuw et al^15 | 2       | 1   | Hasel et al^20 | 0       | 1   | de Leeuw et al^16 |
| Physical functioning      | 0       | 0    | 0   | 0   | 2       | 0    | 0   | 0   | 2       | 0    | 1   | 0   | 1       | 0    | 0   | 0   |
| Illness perception        | 0       | 0    | 0   | 0   | 1       | 1    | 0   | 0   | 1       | 0    | 0   | 0   | 0       | 0    | 0   | 0   |
|                      | ≤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                      |
| Beliefs about medicine | 0  0  0  0              | 1  0  0  0                           | 1  Llewellyn et al[23]           |
| Satisfaction          | 0  0  0  0              | 2  2  1  1                           | 1  Llewellyn et al[23]           |
| with cancer information |                   |                                      |                                  |
| Optimism              | 0  0  0  0              | 1  0  0  0                           | 1  Llewellyn et al[23]           |
| Pain                  | 2  2  0  0              | 0  0  0  0                           | 1  Llewellyn et al[23]           |
| Life stressors        | 1  0  0  1              | 0  0  0  0                           | 1  Funk et al[17]                |
| Inflammatory markers  |                      |                                      |                                  |
| TNFα                  | 1  0  0  1              | 1  0  0  0                           | 1  Archer et al[29]             |
| IL6                   | 1  0  0  1              | 1  0  0  0                           | 1  Archer et al[29]             |
| C-reactive protein    | 1  0  0  1              | 1  0  0  0                           | 1  Archer et al[29]             |
| IFNγ                  | 1  0  0  1              | 1  0  0  0                           | 1  Archer et al[29]             |

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).

*Based on site, stage, and treatment.
*Lifetime.
*Baseline.
*Avoidance.
*Self-blame and acceptance.
*All other domains.
*Timeline.
*Amount and content.
*Type, timing.