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REVIEW

# Metabolic and lifestyle risk factors for chemotherapy-induced peripheral neuropathy in taxane and platinum-treated patients: a systematic review

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## Abstract

**Purpose** Chemotherapy-induced peripheral neurotoxicity (CIPN) is a common dose-limiting toxicity of cancer treatment causing functional impairment and impacting quality of life. Effective prevention and treatment of CIPN are lacking, and CIPN risk factors remain ill-defined. Metabolic syndrome and associated conditions have emerged as potential risk factors, due to their high prevalence and independent association with nerve dysfunction. This systematic review aimed to investigate the association between these common metabolic-lifestyle factors and CIPN.

**Methods** Searches were undertaken using Medline, Embase, CINAHL, Scopus, and Web of Science databases, with additional studies identified from bibliographic references cited by original and review articles. Articles that analyzed metabolic-lifestyle risk factors associated with CIPN for patients treated with platinum- or taxane-based chemotherapy were included.

**Results** Searches identified 6897 titles; 44 articles had full text review, with 26 studies included. Overall incidence of neuropathy ranged from 16.9 to 89.4%. Obesity had the most consistent patient-oriented evidence as a risk factor for CIPN, with moderate evidence suggesting diabetes did not increase CIPN incidence or severity. A limited number of studies supported an association with low physical activity and greater CIPN risk.

**Conclusions** Comorbidities and lifestyle factors, particularly obesity and low physical activity, may contribute to the development of CIPN. The implementation of sensitive outcome measures in large-scale clinical trials is required to further elucidate CIPN risk factors and evaluate if changes in lifestyle would improve long-term CIPN outcomes for cancer survivors.

**Implications for Cancer Survivors** Better understanding of CIPN risk profiles may inform personalized medicine strategies and help elucidate pathophysiological mechanisms which could be targeted for neuroprotection.

**Keywords** Chemotherapy · Neuropathy · Risk factors · Obesity · Diabetes · Physical activity

## Introduction

Chemotherapy-induced peripheral neurotoxicity (CIPN) is a frequently encountered dose-limiting toxicity of commonly used cancer treatments [1]. CIPN can be debilitating and irreversible, impacting long-term quality of life [2, 3]. CIPN's effective prevention and treatment are lacking [4], with dose modification being the only strategy to mitigate neuropathy progression. However, dose modification may attenuate treatment efficacy, potentially affecting clinical and survival outcomes [5, 6]. As such, identifying at-risk patients may assist with personalizing cancer treatment and reducing neuropathy burden [7]. Though identified CIPN risk factors remain ill-defined, increasing comorbidities and lifestyle factors have been identified as potentially contributing to an individual's vulnerability to developing CIPN. In particular, the metabolic

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syndrome and associated conditions have emerged as potential risk factors, especially as they can also produce peripheral neuropathy [8].

Type 2 diabetes mellitus is the world's fastest growing chronic condition [9], with diabetic neuropathy being the most frequent complication. As such, diabetic neuropathy is the most common cause of chronic neuropathy worldwide [10]. Similarly, the prevalence of obesity has reached pandemic levels [11], with 39% of adults being overweight or obese globally [12]. Though obesity is an established risk factor for type 2 diabetes [11], animal models have demonstrated obesity-induced microvascular injury and peripheral nerve dysfunction independent of glycemic status [13]. Similarly, a higher prevalence of neuropathy has been reported for obese participants, even in the absence of diabetes or prediabetes [14]. A sedentary lifestyle is linked to increased prevalence of obesity and type 2 diabetes, with regular physical activity encouraged to prevent and mitigate both conditions and their associated complications [12, 15].

Given the high prevalence of metabolic disorders and associated risk factors and the link of these disorders to neuropathy, it is important to clarify the relationship between metabolic factors and both CIPN incidence and severity. Therefore, this systematic review aimed to evaluate the association between these common metabolic-lifestyle factors and chemotherapy-induced neuropathy.

## Methods

### Search strategy and quality grading

In accordance with the PRISMA statement [16], original research articles were identified by searches of Medline, Embase, CINAHL, Scopus, and Web of Science databases in October 2019. Monthly automated searches were reviewed to ensure results were reflective of current literature up to August 2020. The search strategy (Supplementary Table 1) was tailored to find articles focusing on metabolic-lifestyle risk factors associated with the incidence or severity of neuropathy due to neurotoxic chemotherapies. In addition to being conducted in humans, published from 1980, and in English, searches were specified for obesity, diabetes, and physical activity and limited to title, abstract, or keywords fields. Initial screening was restricted to papers focusing on platinum- or taxane-based cancer treatment. The strength of evidence of the summarized research was graded via the Strength of Recommendation Taxonomy (SORT) algorithm by two reviewers (HT and DM), with level A evidence being of good-quality and patient-oriented, level B evidence comprising inconsistent or limited-quality patient-oriented evidence, and level C evidence comprising recommendation based on disease-oriented evidence, case studies, consensus, usual practice, or opinion [17]. Human studies analyzing metabolic-lifestyle risk factors associated with CIPN for patients treated with platinum- or taxane-based cancer treatment, satisfying level A or B evidence strength, were selected for inclusion. Information was extracted from articles meeting these criteria regarding study design, sample type and size, setting, method of CIPN assessment, overall neuropathy rate, method of measuring of obesity, diabetes and physical activity, and the association with CIPN severity or incidence.

## Results

Initially, searches identified 6897 initial articles, which were reduced to 4200 records after duplicates were removed (Fig.1). Additional searches of review articles were undertaken to ensure coverage, with a further 12 records being identified. Screening eliminated 4168 records, resulting in 44 records that were selected for full-text review (Fig.1).

Twenty-six studies met the criteria to be included, with a total of 21,832 participants. Most included studies were conducted in taxane-treated survivors of breast cancer (11 studies; 14,164 patients; 64.9% of total), with eight studies conducted in oxaliplatin-treated colorectal cancer or esophago-gastric cancer (3910 patients; 17.9% of total) patients. Seven studies were conducted in patients with multiple cancer types treated with platinum or taxanes (3758 patients; 17.2% of total).

Effect size comparison was not possible due to the large variation in included patient populations, treatment type, dose and regimen, and other clinical discrepancies. Inconsistency in the measurement and definition of CIPN and risk factors also limited the pooling of the data. Moreover, CIPN was collected as a secondary measure or evaluated as a secondary analysis in many included studies.

### Overall incidence of CIPN

The overall incidence of CIPN was reported in 22 studies and ranged from 16.9 to 89.4%. CIPN was most commonly assessed using clinician-based grading scales (National Cancer Institute Common Terminology Criteria for Adverse Events, NCI-CTCAE, $n = 12$) [4, 7, 18–28] or validated CIPN patient-reported outcomes (PROs, $n = 7$), including the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity questionnaire (FACT-GOG-Ntx) [8, 29–32] and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ CIPN20) [33, 34]. Five studies used combined clinical examination and patient symptom report [5, 35–38], with two of these studies also including objective neurophysiological measures [5, 38]. Secondary, indirect outcomes to quantify CIPN were used in two studies, including prescriptions of

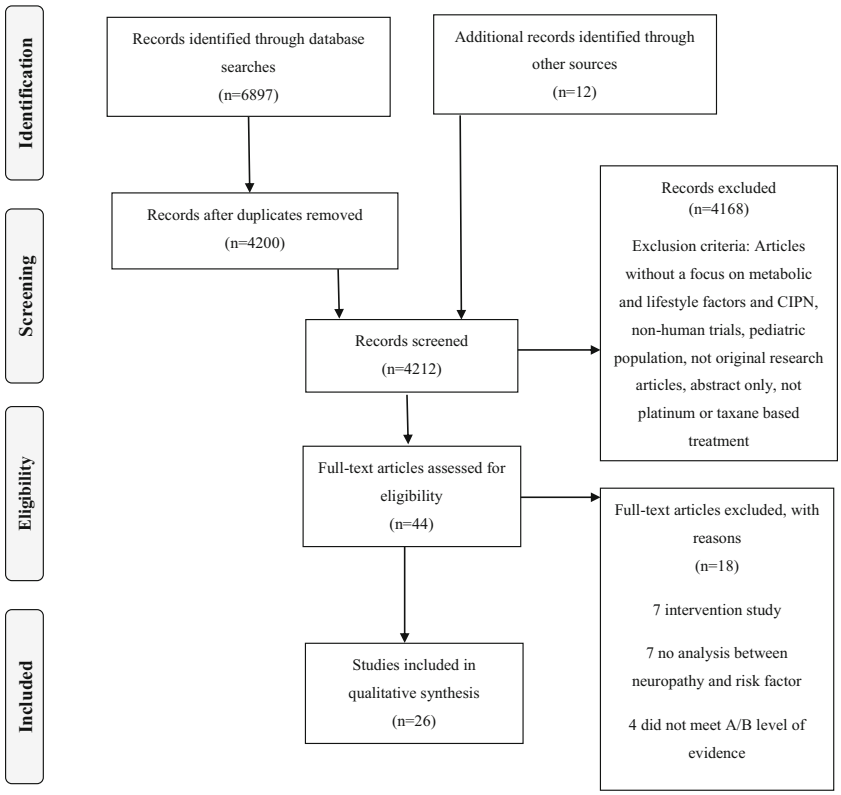


**Fig. 1** Flow diagram

pharmacological treatment [39] and CIPN-related dose reduction as a secondary outcome for identifying CIPN [40].

## Overall level of evidence for metabolic and lifestyle risk factors on CIPN incidence or severity

Moderate to good-quality and patient-oriented evidence (A/B) was most consistently available for an association between obesity and greater CIPN severity or incidence. No association between the severity or incidence of CIPN and the presence of diabetes was supported by moderate-level patient-oriented evidence (B). Similarly, moderate-quality evidence (B) supported an association between physical activity and better CIPN outcomes; however, the number of studies supporting this association was limited (Table 1). It is acknowledged that there is a lack of specific randomized clinical trials focused on metabolic and lifestyle risk factors for CIPN and that the majority of evidence is from observational studies or secondary analyses.

## Effect of obesity on CIPN incidence or severity

In this review, 16 studies were identified relating to CIPN and obesity (Table 2), with 12/16 identifying an association between obesity and greater CIPN severity or incidence and 4/16 finding no association (Table 1). The majority of studies ($n$ = 13) included BMI as a metric of obesity, with this being the sole marker in eight studies. Seven studies supported an association between CIPN and BMI [8, 18, 21, 30, 37–39], with six suggesting no association. However, of the six that found no association with BMI [5, 19, 20, 22, 23, 33], three supported an association with another measure of obesity (body surface area [BSA] = 2, sarcopenic obesity = 1) [5, 22, 23]. BSA was associated with CIPN severity or incidence in an additional 3 studies [35, 36, 38], with one study demonstrating no association with body weight alone [29].

### Taxanes

Nine studies examined the risk of taxane-induced neuropathy in obese breast cancer patients. Of these, five identified a link between CIPN and obesity, with four finding no association in taxane-treated patients.

In two studies using the NCI-CTCAE, obese taxane-treated patients were more likely to experience CIPN of any severity [18, 19]. While there was no significant link between obesity and clinician-graded CIPN in a third analysis of taxane-treated patients, the definition of CIPN was more conservative, with only those experiencing grades 2–4 being classified as having neuropathy [20].

Three studies utilized PROs validated for the assessment of CIPN [8, 29, 33]. Simon et al. found no associations between BMI and CIPN in women evaluated using the EORTC QLQ CIPN20 following taxane treatment [33]. Similarly, pre-treatment body weight was not a significant risk factor for patient-reported CIPN (FACT-GOG-Ntx) [29]. However, in

**Table 1** Number of studies and overall quality of evidence supporting the association between risk factor and CIPN

| | Risk factor | | | | | |
|---|---|---|---|---|---|---|
| | Obesity | | Diabetes | | Low physical activity | |
| | *N* | Ref | *N* | Ref | *N* | Ref |
| Studies supporting an association | 12 | [5, 8, 18, 21–23, 30, 35–39] | 4 | [7, 21, 28, 31] | 4 | [8, 30, 32, 34] |
| Studies showing no association | 4 | [19, 20, 29, 33] | 9 | [5, 23–27, 30, 33, 40] | 1 | [31] |
| Level of evidence | A/B | | B | | B | |

Evidence was graded via the Strength of Recommendation Taxonomy (SORT) algorithm, with only studies meeting level A or B being included. Level A evidence comprised consistent and good-quality patient-oriented evidence; level B comprised inconsistent or limited-quality patient-oriented evidence

another prospective study utilizing the FACT-GOG-Ntx, obese patients demonstrated a 2-fold increased CIPN risk after 24 months compared to patients with a normal-range BMI [8].

Obesity was associated with worse CIPN assessed using objective neurological grading (Total Neuropathy Score reduced version, TNSr©, Johns Hopkins University) in two studies [5, 38]. Worsening symptomatic and objective CIPN (increased TNSr) was significantly associated with higher BSA in breast cancer patients evaluated from the beginning of their paclitaxel treatment [5]. Similarly, Ghoresishi et al. found increased CIPN severity was associated with both higher BSA and BMI in another prospective study utilizing the TNSr [38].

Song et al. defined the presence of CIPN via pharmacological prescription of pain medications [39], with patients receiving treatment for CIPN being more likely to be overweight (BMI > 25 kg/m$^2$) compared to non-treated patients [39].

### Oxaliplatin

Oxaliplatin-induced neuropathy and obesity were assessed in five studies [21–23, 35, 36], with four studies conducted in colorectal cancer patients [21, 23, 35, 36] and one in advanced esophago-gastric cancer patients [22]. All five studies supported a link between increased severity or incidence of oxaliplatin-induced neuropathy and markers of obesity.

Dijksterhuis et al. [22] did not find any association between BMI and NCI-CTCAE ≥ grade 2 CIPN in advanced esophago-gastric cancer patients, evaluated after three cycles of oxaliplatin [22]. However, pre-treatment sarcopenic obesity (sarcopenia + BMI > 25 kg/m$^2$), confirmed by computed tomography (CT) scans, was an independent risk factor for CIPN incidence in this study [22]. Similarly, a retrospective analysis of clinical records revealed no association between BMI and clinician-documented incidence of persistent (≥ 14 days) CIPN, though BSA > 2 was found to be an independent predictor [23]. Conversely, prospectively collected data by Ottaiano et al., revealed a significant association between BMI and the occurrence of NCI-CTCAE ≥ grade 2 CIPN up to 46 months post-oxaliplatin treatment [21]. However, discrepancies between these studies may be related to whether CIPN assessment took place during or post oxaliplatin treatment.

Griffith et al. [35] evaluated oxaliplatin-induced CIPN via PRO and clinical examination. BSA was significantly higher in patients with the most severe signs and symptoms compared to those with the least deficits [35]. Similarly, Hsu et al found that higher BSA was a significant predictor of patient-reported neuropathy severity in another cohort of colorectal cancer patients [36]. However, clinical examination consisting of vibration sensibility and manual muscle testing and balance was not specifically correlated to obesity [36].

### Multiple cancer types treated with platinum or taxanes

Two studies examined the association between obesity and patient-reported CIPN severity and incidence in cohorts with multiple cancer types. Among a cohort comprising mainly breast cancer survivors, patients reporting CIPN symptoms in the lower limbs were significantly more likely to be obese compared to asymptomatic patients [30]. Similarly, Petrovchich et al. found that overweight/obese survivors reported worse pain and balance problems than those classified as normal weight [37]. Additionally, these patients had reduced pain sensation in lower limbs, but no other abnormalities based on quantitative sensory testing [37].

## Effect of diabetes on CIPN incidence or severity

Thirteen studies were identified relating to CIPN risk and diabetes (Table 3). Diabetic status, typically confirmed by medical records, had a reported incidence between 8.5 and 26%. Greater CIPN severity or incidence was associated with diabetic status in 4/13 studies, with no association being identified in 9/13 studies (Table 1).

**Table 2** Studies evaluating obesity and CIPN

| Study | Study type | Timing of measurement | Patients (*n*) | Neurotoxic agent | CIPN measure | Obesity measure | Overall rate of CIPN (*n*) | Rate of obesity (*n*) | Summary of findings | SORT grade |
|---|---|---|---|---|---|---|---|---|---|---|
| Taxane-based chemotherapy treatment | | | | | | | | | | |
| Barginear et al. 2019 [18] | Prospective: baseline – 15 years | Long-term follow-up | Breast cancer (1881) | Paclitaxel | NCI-CTCAE v4 | Pre-treatment BMI Obese: ≥30 kg/m$^2$ | 65% (1226) | 55% (1052) | CIPN was more likely for obese patients ($p$=.006) | B |
| Furlanetto et al. 2016 [19] | Secondary analysis: baseline – end of treatment | Acute post-treatment | Breast cancer (2990) | Paclitaxel | NCI-CTCAE: any grade | BMI, BSA: medical records | 47% (1431) | 44.6% (248) | The proportion of obese patients with CIPN did not differ significantly from non-obese patients (*N.S*) | B |
| Schneider et al. 2012 [20] | Secondary analysis: baseline – 3 weeks post-treatment | Acute post-treatment | Breast cancer (4554) | Taxanes | NCI-CTCAE v2 grades 2–4 | Pre-treatment BMI Obese: ≥ 30 kg/m$^2$ | 16.9% (770) | – | There was a non-significant trend for a higher risk of CIPN for obese patients (*N.S*) | B |
| Greenlee et al. 2017 [8] | Prospective: baseline – 2 years | Long-term follow-up | Breast cancer (1237) | Taxanes | FACT-GOG-Ntx | BMI: medical records Obese: ≥30 kg/m$^2$ | 20.4% (111) | 34.4% (425) | An increased risk of CIPN was more likely to occur in obese ($p$=.003) | A |
| Hershman et al. 2018 [29] | Secondary analysis: baseline – 2 years | Long-term follow-up | Breast cancer (218) | Paclitaxel | FACT/GOG-Nxt | Pre-treatment body weight | 34.4% (69) | – | No association between CIPN and increased body weight (*N.S*) | B |
| Simon et al. 2017 [33] | Cross-sectional | Long-term follow-up | Breast cancer (126) | Taxanes | EORTC QLQ CIPN20 | BMI: medical records | 73% (92) | – | No associations between BMI and CIPN incidence (*N.S*) | B |
| Robertson et al. 2018 [5] | Prospective: baseline – 4 months post-treatment | Mid-term follow-up | Breast cancer (61) | Paclitaxel | TNSr | Pre-treatment BMI and BSA | – | – | CIPN severity was significantly associated with higher BSA ($p$<.05) | A |
| Ghoreishi et al. 2018 [38] | Secondary analysis: baseline – end of treatment | Acute post-treatment | Breast cancer (57) | Paclitaxel | TNSr | BMI: based on median ≤42.95 kg/m$^2$, and > 42.96 kg/m$^2$. BSA | 42% (24) | BMI> 42.96 kg/-m$^2$: 53% (30) | Increased incidence and severity associated with larger BSA ($p$< .05) Greater severity associated with BMI ($p$< .05) | A |
| Song et al. 2017 [39] | Retrospective chart review | Mid-term follow-up | Breast cancer (1516) | Taxanes | Prescription of pharmacological treatment for CIPN | BMI: medical Records | 21.9% (332) | 32.2% (107) | Patients treated for CIPN were more likely to be overweight ($p$=.019) | B |
| Platinum-based chemotherapy treatment | | | | | | | | | | |
| Ottaiano, et al. 2016 [21] | Secondary analysis: baseline – 46 months | Long-term follow-up | Colorectal cancer (102) | Oxaliplatin | NCI-CTCAE v4. CIPN present if ≥grade 2 | Pre-treatment BMI | 17.6% (18) | 27.5% (28) | A significant association was found between BMI and chronic CIPN prevalence ($p$=.01) | B |
| Dijksterhuis et al. 2019 [22] | Prospective: cycles 1–3 | During treatment | Advanced esophago--gastric cancer (88) | Oxaliplatin | NCI-CTCAE v4. Grade 2–4 | Pre-treatment BMI Sarcopenic obesity: sarcopenia (CT scan) and BMI >25 kg/m$^2$ | 20.5% (18) | 19.7% (17) | Sarcopenic obesity patients – greater risk of CIPN ($p$<.05) BMI not an independent risk factor (*N.S*) | B |
| Alejandro et al. 2013 [23] | Retrospective chart review | During treatment | Colorectal cancer (50) | Oxaliplatin | Clinician-documented CIPN persisting >14 days | BSA, BMI, body weight: medical records | 48% (24) | BSA>2: 29% (20) | BSA>2 independently predicted CIPN incidence ($p$<.05)BMI not an independent risk factor (*N.S*) | B |
| Griffith et al. 2017 [35] | Secondary analysis: baseline – end of treatment | Acute post-treatment | Colorectal cancer (148) | Oxaliplatin | TNSc | BSA: medical records | 63% (94) | | Higher BSA in patients with severe CIPN compared to | A/B |

**Table 2** (continued)

| Study | Study type | Timing of measurement | Patients (*n*) | Neurotoxic agent | CIPN measure | Obesity measure | Overall rate of CIPN (*n*) | Rate of obesity (*n*) | Summary of findings | SORT grade |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | those with least deficits ($p<.05$) | |
| Hsu et al. 2019 [36] | Prospective: baseline – end of treatment | Acute post-treatment | Colorectal cancer (77) | Oxaliplatin | Clinician-graded, patient-reported, and clinical examination^ | BSA: medical records | 89.4% (69) | – | Higher BSA was a significant predictor of patient-reported CIPN severity ($p<.0001$)<br>No analysis for clinical examination | B |
| Mixed platinum- and taxane-based chemotherapy treatment | | | | | | | | | | |
| Winters-Stone et al. 2017 [30] | Secondary data analysis: cross-sectional | Long-term follow-up | Mostly breast cancer (512) | Unknown* | FACT-GOG-Ntx (lower limb symptoms) | BMI: patient report | 47% (240) | – | Patients reporting symptoms were more likely to be obese ($p<.05$) | B |
| Petrovchich et al. 2019 [37] | Cross-sectional | Mid-term follow-up | Various cancer types with CIPN (416) | Platinum and taxanes | Patient-reported pain and balance; QST[#] | BMI: patient report | – | 22.1% (92) | Overweight/obese survivors had reduced pain sensation in lower limbs and reported worse pain and balance problems ($p<.05$). | A/B |

*EORTC QLQ CIPN20* European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, *FACT-GOG-Ntx* Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity questionnaire, *OR* odds ratio, *NCI-CTCAE* National Cancer Institute Common Terminology Criteria for Adverse Events, *QST* quantitative sensory testing [#] Light touch, cold sensation, pain sensation, vibration threshold; *TNSc* Total Neuropathy Score clinical version© (Johns Hopkins University) – a validated composite grading measure, comprising clinical examination and patient symptom report, *TNSr* Total Neuropathy Score reduced version© (Johns Hopkins University) – a validated composite grading measure, comprising clinical examination, patient symptom report, and nerve conduction studies, *WHO* (World Health Organization) criterion: physician-rated CIPN item. ^Clinical examination consisting of vibration sensibility and manual muscle testing and balance. Unless otherwise specified, all studies considered the following BMI classifications: normal: $< 25$ kg/m$^2$, overweight: $\geq 25$ kg/m$^2$, obese: $\geq 30$ kg/m$^2$. *Studies with unknown neurotoxic agents were included based on the cancer population likely receiving platinum or taxane treatment. Acute post-treatment: up to 1-month cessation of neurotoxic cancer treatment. Mid-term follow-up: 2 months–12 months post-cessation of neurotoxic cancer treatment. Long-term follow-up: ≥2 years post-cessation of neurotoxic cancer treatment

**Table 3** Studies evaluating diabetes and CIPN

| Study | Study type | Timing of measurement | Patients (*n*) | Neurotoxic agent | CIPN measure | Diabetes measure | Overall rate of CIPN (*n*) | Rate of diabetes (*n*) | Summary of findings | SORT grade |
|---|---|---|---|---|---|---|---|---|---|---|
| Taxane-based chemotherapy treatment | | | | | | | | | | |
| Hershman et al. 2016 [7] | Retrospective chart review | During treatment | Multiple cancer types ≥ 65 years old (1401) | Taxanes | NCI-CTCAE v2 ≥grade 2 | Medical records | 18% (251) | 22–26% (364) | Patients with any diabetes more likely to have CIPN ($p$=.001) With greater risk for those with diabetic complications ($p$<.002) | B |
| Simon et al. 2017 [33] | Cross-sectional | Long-term follow-up | Breast cancer (126) | Taxanes | EORTC QLQ CIPN20 | Medical records | 73% (92) | 19.8% (25) | No associations between presence of diabetes and CIPN incidence (*N.S*) | B |
| Robertson et al. 2018 [5] | Prospective: baseline–4-months post-treatment | Mid-term follow-up | Breast cancer (61) | Paclitaxel | TNSr | Pre-treatment HbA1c analysis | – | 11.5% (7) | Abnormal HgbA1c was not a significant risk factor (*N.S*) | A |
| Bhatnagar et al. 2014 [40] | Retrospective chart review | During neurotoxic treatment | Breast cancer (123) | Taxanes | Dose reductions for CIPN | Medical records | 17% (21) | 16.3% (20) | Diabetes was not a significant risk factor (*N.S*) | B |
| Platinum-based chemotherapy treatment | | | | | | | | | | |
| Ottaiano et al. 2016 [21] | Secondary analysis: baseline – 46 months | Long term follow-up | Colorectal cancer (102) | Oxaliplatin | NCI-CTCAE ≥grade 2 | Medical records Patients with diabetic neuropathy were excluded | 17.6% (18) | 18.7% (19) | A significant association was found between diabetes and the incidence of chronic CIPN ($p$<.001) | B |
| Brown et al. 2019 [24] | Secondary analysis: baseline – 6 years | Long-term follow-up | Colorectal cancer (1796) | Oxaliplatin | NCI-CTCAE ≥grade 2 | Medical records | 36% (653) | 15% (268) | No difference in incidence of ≥grade 2 CIPN for diabetics (*N.S*) | B |
| Uwah et al. 2012 [25] | Retrospective chart review | During treatment | Colorectal cancer (62) | Oxaliplatin | NCI-CTCAE ≥grade 2 | Medical records | 24% (15) | 24% (15) | No difference in the incidence of ≥grade 2 or severity of CIPN for diabetics (*N.S*) | B |
| Ramanathan et al. 2009 [26] | Secondary analysis: baseline – end of treatment | Acute post--treatment | Colorectal cancer (1587) | Oxaliplatin | NCI-CTCAE Oxaliplatin-specific neurotoxicity scale | Medical records | 86.8% (1372) | 8.5% (135) | Incidence of all-grade CIPN did not differ for diabetics (*N.S*) | B |
| Alejandro et al. 2013 [23] | Retrospective chart review | During treatment | Colorectal cancer (50) | Oxaliplatin | Clinician-documented CIPN persisting > 14 days | Medical records | 48% (24) | 12% (6) | Diabetes was not an independent risk factor (*N.S*) | B |
| Mixed platinum- and taxane-based chemotherapy treatment | | | | | | | | | | |
| Molassiotis et al. 2019 [27] | Secondary analysis: cross-sectional | Mid-term follow-up | Multiple cancer types (255) | Platinum and taxanes | NCI-CTCAE | Medical records | 12.9 (33) | 14.5% (37) | Diabetes had a non-significant trend with sensory CIPN ($p$=.09) | B |
| Kus et al. 2016 [28] | Secondary analysis: baseline – end of treatment | Acute post--treatment | Multiple cancer types (374) | Taxanes or taxane and platinum combination | NCI-CTCAE ≥grade 1 | Medical records | Taxane only: 47% (127) Combination:62.5% (65) | 21% (81) | CIPN incidence in combination group was significantly greater for diabetics ($p$=.035) | B |
| Winters-Stone et al. 2017 [30] | Secondary data analysis: cross-sectional | Long-term follow-up | Mostly breast cancer (512) | Unknown | FACT-GOG-Ntx (lower limb symptoms) | Self-report viathe Charlson Comorbidity Index | 47% (240) | 11% (57) | No difference in incidence of diabetes for those reporting symptoms (*N.S*) | B |
| Thomaier et al 2020 [31] | Secondary analysis: baseline – 6 months | Mid-term follow-up | Gynecologic cancer (194) | Unknown | FACT-GOG-Ntx (<11 v≥11points) | Patient report | Greater severity: 34% (66) | 11.6% (22) | Patients with high CIPN severity (≥11points) were more likely have diabetes ($p$=.04) | B |

*EORTC QLQ CIPN20* European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, *FACT-GOG-Ntx* Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity questionnaire, *OR* odds ratio, *NCI-CTCAE* National Cancer Institute Common Terminology Criteria for Adverse Events, *TNSr* Total Neuropathy Score reduced version – a validated composite grading measure, comprising clinical examination, patient symptom report, and nerve conduction studies; *Studies with unknown neurotoxic agents were included based on the cancer population likely receiving platinum or taxane treatment. Acute post-treatment: up to 1-month cessation of neurotoxic cancer treatment. Mid-term follow-up: 2 months–12 months post-cessation of neurotoxic cancer treatment. Long-term follow-up: ≥ 2 years post-cessation of neurotoxic cancer treatment

### Taxanes

Four studies examined the risk of taxane-induced neuropathy and diabetes [5, 7, 33, 40], conducted mostly in breast cancer patients. Of these studies, only one identified a link between diabetes and taxane-induced neuropathy graded via NCI-CTCAE [7].

In a large-scale analysis of clinical trial data utilizing clinician-based grading (NCI-CTCAE), patients with diabetes were more likely to have CIPN following taxane treatment, with those experiencing complications from their diabetes at even greater risk [7]. However, the evaluated cohort consisted of cancer patients ≥ 65 years old [7], with a high incidence of diabetes with or without complications (26%), with a further 8% having confirmed complications. Though this incidence of diabetes may be consistent for this age group, with diabetes estimated to affect up to 26.8% of Americans ≥ 65 years old [41], it may be less representative of some taxane-treated oncological populations. Bhatnagar et al. used recorded dose reduction to identify patients with CIPN. In this study, diabetes was not identified as a significant risk factor for CIPN-associated dose reductions [40]. However, this conservative method of identifying CIPN may not have identified all patients with CIPN. In addition, several other studies have not found any association between diabetic status and CIPN incidence. Simon et al. also found no association between diabetes and the incidence of CIPN based on validated PROs [33]. Similarly, Roberston et al. [5] utilized patient report and objective examination to assess CIPN severity (TNSr) in comparison to baseline HbA1c levels. Abnormal HbA1c status was not associated with increased CIPN severity following taxane treatment, though only seven patients were identified with abnormal HbA1c [5].

### Oxaliplatin

Five studies evaluated diabetes in oxaliplatin-treated colorectal cancer patients [21, 23–26] using clinician-based grading to evaluate CIPN, with only one study demonstrating a significant association between diabetes and CIPN incidence. Ottaiano et al. found a significant association between diabetes and the incidence of NCI-CTCEA ≥ grade 2 CIPN up to 46 months post-oxaliplatin treatment [21], despite exclusion of those with diabetic neuropathy. However, this was not the case in a large trial evaluating CIPN 6 years post-oxaliplatin treatment, with no difference in rates of ≥ grade 2 CIPN being found for diabetics compared to their normoglycemic counterparts [24]. Likewise, Uwah et al. found no difference in CIPN incidence or severity graded throughout oxaliplatin treatment between diabetics and non-diabetics [25]. However, diabetic patients in this study did develop CIPN at a lower cumulative dose [25]. In another large study based on pooled clinical trial data, incidence of all-grade CIPN did not differ for diabetics [26], but contrary to Uwah et al., this study did not find earlier onset of CIPN during oxaliplatin treatment in diabetic patients [26]. Persistent clinician-graded CIPN was also not associated with diabetic status; however, the prevalence of diabetic patients was low in this cohort ($n = 6$) [23].

### Multiple cancer types treated with platinum or taxanes

Four studies evaluated mixed cohorts of patients receiving platinum-, taxane-, or combination-based therapy [27, 28, 30, 31]. The incidence of ≥ grade 1 CIPN was significantly greater for diabetics after completing combination platinum/taxane treatment compared to non-diabetic patients [28]. However, this was not the case for patients receiving taxane-only treatment, with the incidence of CIPN being comparable between diabetic and non-diabetic patients [28]. Similarly, Molassiotis et al found no association between diabetic status and any-grade sensory CIPN in patients receiving platinum or taxane treatment, though they highlighted a trend toward significance ($p = 0.09$) [27]. Thomaier et al. investigated gynecologic cancer survivors treated with neurotoxic chemotherapy. Patients reporting greater CIPN symptom severity at 6 months post-treatment were more likely to have diabetes, compared to those who reported less severe symptoms [31]. However, in another cohort consisting mostly of breast cancer patients, there was no difference in incidence of diabetes for those reporting lower limb CIPN symptoms compared to asymptomatic patients [30].

## Effect of physical activity on CIPN incidence or severity

Five articles were identified investigating the impact of physical activity on CIPN, which mostly included breast, colorectal, ovarian, and mixed cancer types (Table 4). One study investigated physical activity levels during treatment, three post-treatment, and one across both phases. Four studies found an association between higher self-reported physical activity and lower CIPN symptoms, while one study found no association (Table 2). All studies utilized a validated CIPN PRO. A variety of different physical activity measures were used, with three studies using physical activity guidelines to dichotomize participants as active or inactive.

In the Greenlee et al. prospective cohort study, breast cancer survivors who received taxanes participating in > 5 h/week of moderate-to-vigorous-intensity physical activity within 2 months of diagnosis were 44% less likely at 6 months post-treatment and 57% less likely at 24 months post-treatment to have increased CIPN symptoms (FACT-GOG-Ntx) compared to those who participated in < 2.5 h/week [8]. Stevinson et al. found that ovarian cancer survivors during and post treatment (mean 73 months post-diagnosis) who met the 150–300 min/week physical activity guidelines had less CIPN

**Table 4** Studies evaluating physical activity and CIPN

| Study | Study type | Timing of measurement | Patients (*n*) | Neurotoxic agent | CIPN measure | Physical activity measure | Overall rate of CIPN (*n*) | Physical activity levels | Summary of findings | SORT grade |
|---|---|---|---|---|---|---|---|---|---|---|
| Greenlee et al. 2017 [8] | Prospective: baseline – 6 months and 2 years | Long-term follow-up | Breast cancer (1237) | Taxanes | FACT-GOG-Ntx | Arizona Activity Frequency Questionnaire | 20.4% (111) | 70.1% achieved PA guidelines within 2 months post-diagnosis | High MVPA within 2 months post-diagnosis has 44% and 57% less likelihood to have increased CIPN at 6-month ($p$=.03) and 24-month ($p$=.02) follow-up | A |
| Stevinson et al. 2009 [32] | Cross-sectional | On- and off-treatment | Ovarian cancer (359) | Unknown* | FACT-GOG-Ntx | Godin Leisure-Time Exercise Questionnaire | – | 31.1% achieved PA guidelines<br>Mean=99± 161 min/week of MVPA | Meeting PA guidelines^ on average 6.1 years post-diagnosis (9% receiving treatment) was significantly associated with less peripheral neuropathy ($p$<.001) | B |
| Winters-Stone et al. 2017 [30] | Secondary analysis: cross--sectional | Long-term follow-up | Mostly breast cancer (512) | Unknown* | Patients classified as having CIPN based on presence of lower limb symptoms from FACT-GOG-N-tx | Community Healthy Activities Model Program for Seniors Questionnaire | 47% (240) | 171±204 kcal/day of MVPA | Reduced MVPA and total PA energy expenditure (kcal/day) in those with CIPN symptoms ($p$<.01) on average 6 years post-treatment | B |
| Mols et al 2015 [34] | Cross-sectional | Long-term follow-up | Colorectal cancer (1648) | Unknown* | EORTC QLQ-CIPN20 | European Prospective Investigation into Cancer Physical Activity Questionnaire | – | 93% of chemotherapy--treated patients achieved PA guidelines<br>Mean=12.2± 8.8 h/week of MVPA | Not meeting PA guidelines^ on average 5.6 years post-diagnosis associated with more sensory and motor CIPN among patients treated with chemotherapy ($p$<.05) | B |
| Thomaier et al 2020 [31] | Prospective: baseline and 6 months | Mid-term follow-up | Gynecological cancer (194) | Unknown* | FACT-GOG-Ntx (<11 v≥11points) | Patient report: min/week of MVPA | Greater severi-ty: 34% (66) | 60% achieved PA guidelines | No difference in the proportion of participants meeting PA guidelines^ (mostly 1 to 5 years post-diagnosis) between those with low and high CIPN symptoms (*N.S*) | B |

*EORTC-QLQ-CIPN20* European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, *FACT-GOG-Ntx* Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity questionnaire, *OR* odds ratio, *CI* confidence interval, *PA* physical activity, *MVPA* moderate-vigorous physical activity. ^150 min/week MVPA *Studies with unknown neurotoxic agents were included based on the cancer population likely receiving platinum or taxane treatment. Acute post-treatment: up to 1-month cessation of neurotoxic cancer treatment. Mid-term follow-up: 2 months–12 months post-cessation of neurotoxic cancer treatment. Long-term follow-up: ≥2 years post-cessation of neurotoxic cancer treatment

symptoms (FACT-GOG-Ntx) [32]. However, there was no dose-response relationship between physical activity levels in excess of the guidelines and reduced CIPN symptoms [32]. Regarding studies reporting on post-treatment physical activity levels, participants who received neurotoxic chemotherapy 6 years prior (mostly breast cancer) in the Winters-Stone et al. study who experienced CIPN symptoms reported lower total and moderate-to-vigorous physical activity compared with those without any CIPN symptoms, as well as reduced physical function, slower gait, increased disability, and increased fall risk [30]. In the Mols et al. study, colorectal cancer survivors on average 5.6 years post-diagnosis who did not achieve 150 min/week of moderate-to-vigorous-intensity physical activity had more severe CIPN (EORTC-QLQ-CIPN20), as well as worse quality of life across almost all domains [34]. Conversely, in the Thomaier et al. prospective study, there was no difference in the proportion of gynecological cancer survivors, mostly 1–5 years post-diagnosis, who achieved 150 min/week physical activity among patients with low and high CIPN symptom levels (FACT-GOG-Ntx; 60.9% vs 59.1%) [31].

## Discussion

CIPN displays a spectrum of symptom onset and severity, suggesting a role for individual risk factors. Identification of these risk factors may assist with personalizing cancer treatment and meditating CIPN burden [7]. Accordingly, this systematic review evaluated the relationships between common metabolic-lifestyle factors and chemotherapy-induced neuropathy associated with taxane and oxaliplatin treatment. Twenty-six studies evaluating the role of metabolic-lifestyle risk factors associated with CIPN met the criteria to be included. Based on these studies, obesity as a risk factor for CIPN had the most consistent patient-oriented evidence, with moderate evidence suggesting diabetes did not increase CIPN incidence or severity and only a limited number of studies evaluating the role of physical activity and CIPN outcomes.

A broad range of CIPN incidence was identified in this review (16.9–89.4%). This large variation represents heterogeneous patient populations; variability in the duration of follow-up, method, and timing of the CIPN assessment; and inconsistencies in when risk factors were measured [42, 43]. Though the majority of studies included in this review utilized clinician-graded scales to quantify CIPN, the NCI-CTCAE is generally criticized due to a lack of inter-rater relatability and sensitivity to change [44, 45]. Patient-reported outcomes were used in 7 of the reviewed studies and are generally considered to better capture the impact of CIPN and demonstrate greater sensitivity to change compared to clinician-graded scales [46]. However, inconsistencies between the patients' interpretation of questions and severity and the influence of other psychological factors may pose potential limitations [47, 48]. Accordingly, objective techniques in addition to PROs may provide a more thorough insight into CIPN. Only five studies in this review included clinical examination, with only two of these adding an objective neurophysiological measure. Similarly, objective assessment of diabetic status and physical activity was limited, with most patients identified via medical records or patient report. Moreover, information about the duration and persistence of these factors was not always available. Importantly, this means that it is not always possible to examine risk factors in the context of the natural history of CIPN progression and recovery, which may limit the interpretation of findings. As such, evaluating CIPN risk factors and pooling data across studies remains a challenge due to the diversity of CIPN assessment tools.

### Obesity

In this review, good-to-moderate patient-centered evidence was found supporting an association between obesity and increased severity or incidence of CIPN. An identical number of studies supported an association in taxane- and platinum-treated cohorts ($n = 5$). However, four studies conducted in taxane-treated patients demonstrating no association between CIPN and obesity were also identified.

Obesity is a common comorbidity of diabetes; however, in the current review, many of the studies assessing obesity and CIPN excluded patients with diabetes, suggesting a more obesity-specific mechanism contributing to nerve dysfunction [38]. Notably, only one of the reviewed studies objectively measured HbA1c [5] to confirm glycemic status; consequently, individuals with unconfirmed diabetes or prediabetes may have gone unrecognized. However, there is a growing body of evidence, including objective assessment, that supports obesity-related neuropathy among normoglycemic obese individuals without cancer [14, 49, 50]. Specifically, normoglycemic obese participants with neuropathy had larger waist circumference measurements, compared with individuals without neuropathy, despite being comparable in BMI and other anthropometric measures. These findings suggest that the distribution of fat may be important in mediating nerve injury [50] and that central obesity more so than general obesity may be a risk factor for the development of neuropathy [50]. Accordingly, as BMI and to an extent BSA are metrics of generalized obesity, the lack of detailed anthropometric measurements in the studies under review may limit the ability to provide mechanistic insights into CIPN risk.

Being overweight can have deleterious effects on sensation and function in the extremities, resulting from increased mechanical force on the weight-bearing joints, which may affect patient perception of symptoms [37]. However, among the 12 studies finding an association between obesity and CIPN, only 2 relied solely on patient symptom report with the remaining

10 employing other measures to define CIPN. Additionally, no association between CIPN symptoms and obesity was found in a further two studies using only PROs, suggesting that differences in symptom perception between obese and non-obese patients may not be solely driving the differences.

Similarly, the type of metric used to classify obesity may be important in assessing toxicity risk. BMI was the most frequently utilized metric to classify obesity ($n = 13$) mostly in taxane-treated cohorts, with 5 of these studies also including another metric of obesity (BSA = 4, sarcopenic obesity = 1). Consequently, among oxaliplatin-treated cohorts, an association with CIPN and BMI was found in only one study, where BMI was the sole marker of obesity [21]. The remaining four studies focusing on oxaliplatin demonstrated an association with larger BSA [23, 36, 44] or more specific composite body measures such as sarcopenic obesity [22]. BMI is a crude metric of body composition, which may provide an inaccurate estimate muscle mass and adipose tissue [51, 52]. Consequently, despite being correlated with BMI, BSA is employed in the oncology setting as it mitigates the variability of patient size and abnormal adiposity that can affect BMI to a greater extent [53]. However, BSA still does not comprehensively reflect body composition and may result in greater toxicity for individuals with larger BSA and unfavorable body compositions [5, 38]. Specifically, reduced muscle mass and increased body fat can impact the pharmacokinetics of a large number of anti-cancer treatments depending on lipo- or hydrosolubility [52]. Paclitaxel and oxaliplatin are lipophilic agents that subsequently accumulate in adipose tissue and may be rereleased [52, 54]. Consequently, individuals with higher body fat percentage may have longer exposure to neurotoxic agents and possibly greater CIPN risk [22]. Similarly, lower lean body mass (LBM), a more common occurrence in women, may be associated with dose-limiting CIPN, as patients with low LBM relative to their BSA may effectively receive a higher dose of neurotoxic treatment [55]. As such, more accurate evaluation of body composition and subsequent normalization of dosing could assist in reducing toxicity [55].

## Diabetes

Articles included in this review provided moderate patient-oriented evidence suggesting diabetes was not associated with increased CIPN incidence or severity. Diabetic peripheral neuropathy is the primary complication in patients with diabetes and the most common etiology of neuropathy globally [56]. Consequently, many oncology trials including neurotoxic agents typically exclude patients with diabetes [7]. Five of the reviewed studies specifically excluded diabetics [20, 29, 35, 36, 38], with the majority of the remaining studies without specific analyses of diabetic patients providing no details surrounding the inclusion or exclusion of diabetic individuals. Among studies evaluating the relationship between diabetes and CIPN, only one objectively confirmed diabetic status [5]. Subsequently, the prevalence of patients with diabetes or prediabetes in these cohorts may be underestimated. Moreover, there is a lack of characterization of included diabetic patients and their neuropathy status. It may be that only a subset of diabetic patients face additional risk when exposed to neurotoxic agents, with time of diagnosis, extent of diabetic control, or presence of diabetic neuropathy being more informative than status alone. Specifically, of the studies focusing on taxane-treated cohorts, only one identified an increased risk of CIPN for patients with diabetes. This cohort focused on an older survivor population (≥ 65 years) with the highest rate of diabetes of all the evaluated studies, which also included patients with diabetic complications. Though less representative of some clinical populations of taxane-treated patients, results may indicate that diabetes duration and complications contribute to an individual's vulnerability for developing CIPN.

Among platinum-treated patients, one study demonstrated a significant association between diabetes and the incidence of chronic CIPN, despite excluding diabetic neuropathy. Other reviewed studies utilizing the same CIPN assessment (NCI-CTCAE), with similar rates of diabetes, found no association, possibly reflecting differences in sample size and time of assessment. Though most of the reviewed studies did not support an association between diabetes and CIPN incidence or severity, Uwah et al. demonstrated a difference in onset, with diabetics developing CIPN at a significantly lower cumulative dose of oxaliplatin [25]. Though this study did not specifically report the rate of dose modification, this finding may suggest that diabetics receiving oxaliplatin are more vulnerable to develop CIPN earlier in the treatment course, potentially affecting treatment tolerability.

## Physical activity

Only five studies focusing on self-reported physical activity levels as a risk factor for CIPN met the criteria to be included in this review. Four studies supported the association between low physical activity and greater CIPN incidence or severity, with majority of studies displaying moderate levels of evidence. Physical activity outcomes were solely self-reported, and results are likely less accurate than studies using objective measures such as accelerometers [57]. Consequently, only tentative conclusions can be drawn from the current literature, which mostly investigated post-treatment physical activity. The only study investigating physical activity during treatment found higher physical activity during treatment associated with lower CIPN severity 6 and 24 months later [8]. Potential reasons linking higher baseline physical activity levels to reduced CIPN risk include physical activity participation protecting against physical function impairments related to CIPN [58]. Further, the accumulation of CIPN symptoms may reduce the ability to participate in physical activity

over time and even years after treatment, which may explain the relationship we identified in three post-treatment studies [30, 32, 34]. Accordingly, there is a growing body of literature investigating whether exercise interventions are beneficial for patients with CIPN, with results demonstrating improvements in both symptomatic and functional CIPN outcomes with participation [58–61]. Benefits in CIPN symptoms due to increasing physical activity levels have been identified to be more prominent among older patients, with these benefits theorized to be related to exercise dose, while reduced chronic inflammation has been implicated as a contributing factor to the etiology of CIPN across all age groups [8, 60]. Higher physical activity levels before diagnosis and during and after treatment may facilitate improved cardio-metabolic health and reduce the likelihood of developing diabetes and obesity [62], potentially playing a secondary role in mediating known CIPN risk factors [30]. Finally, general health benefits due to physical activity participation including improved balance, cardiorespiratory fitness, and muscle strength may contribute to improved physical function and quality of life [63], both of which may be diminished with severe CIPN.

### Interactions between metabolic and lifestyle risk factors

Though some evidence exists for the independent role of obesity, diabetes, and low physical activity in neuropathy risk, there exists a high degree of comorbidity. Obesity is an established risk factor for type 2 diabetes [11], with physical activity indicated as a mediating factor in both conditions [12, 15]. In addition to potentially contributing to the etiology, shared mechanisms may exist that mediate CIPN development. Diabetes and obesity have both been likened to increased chronic systemic inflammation [64, 65]. Likewise, the benefits of physical activity have been in part attributed to mitigating inflammatory processes [66]. However, the role of inflammation in the etiology of CIPN needs to be further elucidated. Nevertheless, there may be complex interactions between risk factors that contribute to an individual's overall vulnerability for developing CIPN.

## Conclusions

Identifying risk factors for the development and severity of CIPN is valuable for informing treatment decisions and meditating CIPN burden. Comorbidities and lifestyle factors, particularly obesity and low physical activity, may contribute to an individual's vulnerability to developing CIPN. However, the implementation of sensitive outcome measures in large-scale clinical trials is required to further elucidate the patient-specific and treatment-related determinants of CIPN risk and to provide more definitive, high-level evidence [67]. Additionally, given the obesity pandemic and the increasing incidence of diabetes and other associated metabolic comorbidities, specific investigations are required to ascertain whether the implementation of supportive services and changes in lifestyle during or post treatment to improve metabolic health and subsequently impact long-term CIPN outcomes for cancer survivors. Better understanding of individual risk profiles may inform personalized medicine strategies and potentially elucidate pathophysiological mechanisms that could be targeted for neuroprotection.

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### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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