

## **Combined association between dietary antioxidant quality score and leisure-time physical activity on sleep pattern in cancer survivors: a cross-sectional study of NHANES database**

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This peer-reviewed article has been accepted for publication but not yet copyedited or typeset, and so may be subject to change during the production process. The article is considered published and may be cited using its DOI

10.1017/S0007114524001831

The British Journal of Nutrition is published by Cambridge University Press on behalf of The Nutrition Society

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**Short title:** DAQS and leisure-time physical activity on sleep patterns in cancer survivors

**Keywords:** dietary antioxidant quality score, leisure-time physical activity, sleep pattern, combined association, cancer survivor

Abbreviations: vit A: vitamin A, vit E: vitamin E, vit C: vitamin C, Zn: zinc, Se: selenium, Mg: magnesium, DAQS: dietary antioxidant quality score, NHANES: National Health and Nutrition Examination Surveys, BMI: body mass index, WBC: white blood cell, eGFR: estimated glomerular filtration rate, PAQ: Physical Activity Questionnaire, MET: metabolic equivalent, PIR: poverty income ratio, DM: diabetes mellitus, CVD: cardiovascular disease, COPD: chronic obstructive pulmonary disease, ASH: anxiolytics/sedatives/hypnotics, SE: standard error, OR: odds ratio, CI: confidence interval.

**Abstract**

This study aimed to explore the combined association between the dietary antioxidant quality score (DAQS) and leisure-time physical activity on sleep patterns in cancer survivors. Data of cancer survivors were extracted from the National Health and Nutrition Examination Surveys (NHANES) database in 2007-2014 in this cross-sectional study. Weighted multivariable logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association of DAQS and leisure-time physical activity on sleep patterns. The combined association was also assessed in subgroups of participants based on age, and use of painkillers and antidepressants. Among the eligible participants, 1,133 had unhealthy sleep patterns. After adjusting for covariates, compared to low DAQS level combined with leisure-time physical activity level  $<600$  MET·min/week, high DAQS level combined with leisure-time physical activity  $\geq 600$  MET·min/week was associated with lower odds of unhealthy sleep patterns (OR=0.41, 95%CI: 0.23-0.72). Additionally, the association of high DAQS level combined with high leisure-time physical activity with low odds of unhealthy sleep patterns was also significant in  $<65$  years old (OR=0.30, 95%CI: 0.13-0.70), non-painkiller (OR=0.39, 95%CI: 0.22-0.71), non-antidepressant (OR=0.49, 95%CI: 0.26-0.91) and antidepressant (OR=0.11, 95%CI: 0.02-0.50) subgroups. DAQS and leisure-time physical activity had a combined association on sleep patterns in cancer survivors. However, the causal associations of dietary nutrient intake and physical activity with sleep patterns in cancer survivors needs further clarification.

## Introduction

Cancer is a leading cause of human deaths at present and becomes a major public health issue over the world <sup>(1)</sup>. According to the American Cancer Society, 1,958,310 new cancer cases and 609,820 cancer deaths are projected to occur in the United States in 2023 <sup>(2)</sup>. Significant strides in cancer screening, diagnostics and therapeutics have contributed to a growing population of cancer survivors in recent decades <sup>(3; 4)</sup>. However, cancer survivors are at risk of physical and psychological morbidity in the years after treatment completion, including increased sleep disturbance <sup>(5)</sup>.

Sleep pattern is a composite sleep behavior, including sleep duration, sleeping difficulties and sleep disorders, reflecting the sleep conditions of individuals. A prior study showed that between 30% to 80% of cervical cancer survivors demonstrated unhealthy sleeping patterns, such as insomnia, excessive sleep, sleep disorders, and sleep difficulties <sup>(6)</sup>. Sleep plays an important role in the regulation of immunity, metabolism and body repair in humans <sup>(7)</sup>. A poor sleep condition is closely associated with increased pain, decreased life quality, anxiety and depression in patients with cancer, and thus has a greater negative impact on their prognoses <sup>(8)</sup>. Therefore, adequately understanding and addressing sleep problems in cancer survivors is important for improving the disease prognoses and living quality.

It is known that the occurrence of cancer is closely linked to oxidative stress and chronic inflammation, which can activate growth factors and inflammatory factors, leading to abnormal transformation of normal cells and the proliferation and invasion of tumor cells <sup>(9)</sup>. On the other hand, inflammatory process disorder can activate sleep-related inflammatory molecules, affecting the sleep and circadian rhythms, and further result in sleep disorders, sleep deprivation and other sleep problems <sup>(10; 11)</sup>. Hence, oxidative stress and chronic inflammation may be involved in both sleep process and cancer development.

In addition to clinical therapies, diet and physical activity are major regulatable and controllable lifestyle factors associated with the health maintenance in patients with cancer <sup>(12)</sup>. Adequate intake of dietary components with antioxidant and anti-inflammatory properties, such as vitamin A (vit A), vitamin E (vit E), vitamin C (vit C), zinc (Zn), selenium (Se), and magnesium (Mg), can help reduce the oxidative stress and chronic inflammatory response,

thereby improving sleep conditions and prognoses in cancer patients <sup>(13; 14; 15)</sup>. Similarly, keeping a high level of physical activity can enhance the body's antioxidant response, and these individuals are more likely to achieve better sleep quality and disease prognoses <sup>(15; 17; 18)</sup>. In fact, more than one-third of cancer patients are sedentary or not engage in leisure-time physical activity for long periods of time, leading to an increased risk of adverse outcomes <sup>(19)</sup>. Higher levels of leisure-time physical activity can counteract the negative effects of sedentary behavior <sup>(19)</sup>. However, the combined association between antioxidant/anti-inflammatory dietary nutrient intake and leisure-time physical activity on sleep patterns in cancer survivors are still unclear.

Herein, this study aims to explore the combined association between the composite index of multiple antioxidant and anti-inflammatory dietary components (including vit A, vit E, vit C, Zn, Se, and Mg), namely the dietary antioxidant quality score (DAQS), and the leisure-time physical activity on sleep patterns in cancer survivors, in order to provide insight for improving cancer survivors' living quality.

## **Methods**

### **Study design and population**

Data of cancer survivors in this cross-sectional study were extracted from the National Health and Nutrition Examination Surveys (NHANES) database in 2007-2014. The NHANES survey is conducted by the Centers for Disease Control and Prevention and the National Center for Health Statistics jointly, with the aim to assess the nutritional and health status of the noninstitutionalized population in the United States. It includes a complex, multistage stratified probability sample based on selected counties, blocks, households, and persons within households. The National Center for Health Statistics' well-trained professionals conducts interviews in participants' homes, and extensive physical examinations were conducted at mobile exam centers. For more details, please visit the NHANES website: <https://wwwn.cdc.gov/nchs/nhanes/index.htm>.

We initially included 2,173 cancer survivors who have information on sleep patterns (including sleep duration, sleeping difficulties, and sleep disorders) assessment, dietary intake

and physical activity. The exclusion criteria were (1) having an extreme energy intake (<500 kcal or >8000 kcal for male; <500 kcal or >5000 kcal for female), and (2) missing information on the study variables, including sedentary time, body mass index (BMI), white blood cell (WBC), lymphocyte, neutrophil, estimated glomerular filtration rate (eGFR), marital status, and education level. The final sample size was 1,936. The NHANES survey was approved by the institutional review board of the National Center for Health Statistics. Since the study data were de-identified, and all the participants have provided informed consent, no ethical approval from our agency's institutional review board was required.

### **Definition of sleep patterns**

Assessment of sleep pattern was on the basis of three sleep related factors, including sleep duration, sleeping difficulties, and sleep disorders. Sleep duration was self-reported through the question “How much sleep do you usually get at night on weekdays or workdays?” The quantity of time recorded was grouped as short (<7 hours per night), normal (7-9 hours per night) and long (>9 hours per night)<sup>(20)</sup>. The responses to ‘Have you ever told a doctor or other health professional that you have trouble sleeping?’ and ‘Have you ever been told by a doctor or other health professional that you have a sleep disorder?’ were respectively used to assess the sleeping difficulties and sleep disorders. A short/long sleep duration, having sleeping difficulties and having sleep disorders were respectively classified as 0, whereas normal sleep duration, non-sleeping difficulties and non-sleep disorders were respectively classified as 1. Then scores of the above three sleep related factors were used to generate overall sleep scores, ranging from 0 to 3. An overall sleep score of 3 indicated a healthy sleep pattern, while the score of 0, 1, or 2 indicated an unhealthy sleep pattern<sup>(21; 22; 23)</sup>.

### **Assessment of dietary intake and calculation of DAQS**

Dietary total energy intake was calculated through information on “total nutrient intakes” and “total dietary supplements” collected from two 24-hour dietary recalls in the NHANES. The first recall was conducted in person, and later recall was conducted 3-10 days after the first one via a phone call. Also, information on dietary supplements intake was collected at the

NHANES household interview through a dietary supplement questionnaire. The DAQS was assessed by dietary intake as well as supplements. DAQS calculation was according to the aggregate score of the six nutrients, including vit A, vit E, vit C, Zn, Se, and Mg<sup>(24; 25)</sup>. Specifically, the intake of each nutrient was compared with its recommended intake level, and that less than 2/3 of the recommended intake level was classified as 0, otherwise classified as 1. The aggregate score ranged from 0 to 6, and a higher score indicated a higher dietary antioxidant level. We divided the DAQS into three levels according to the tertiles, where DAQS of 0-3 represented a low dietary antioxidant level, DAQS of 4-5 represented a median dietary antioxidant level and DAQS of 6 represented a high dietary antioxidant level. More details on dietary recommendation of vitamins and minerals are shown elsewhere: <https://www.ncbi.nlm.nih.gov/books/NBK56068/table/summarytables.t2/?report=objectonly>; [https://www.ncbi.nlm.nih.gov/books/NBK545442/table/appJ\\_tab3/?report=objectonly](https://www.ncbi.nlm.nih.gov/books/NBK545442/table/appJ_tab3/?report=objectonly).

### **Assessment of leisure-time physical activity**

Information on leisure-time physical activity was collected using the NHANES Physical Activity Questionnaire (PAQ). The questions used to assess leisure-time physical activity included PAQ655 (days vigorous recreational activities), PAD660 (minutes vigorous recreational activities), PAQ640 (number of days walk or bicycle), PAD645 (minutes walk or bicycle for transportation), PAQ670 (days moderate recreational activities), and PAD675 (minutes moderate recreational activities). The physical activity level was transformed into energy consumption using the formula: energy consumption = recommended metabolic equivalent (MET) × daily duration of the activities (min) × weekly frequency of activities. The unit of energy consumption was MET·min/week. Therefore, leisure-time physical activity =  $PAQ655 \times PAD660 \times 8 + PAQ640 \times PAD645 \times 4 + PAQ670 \times PAD675 \times 4$ . In accordance with the previous study, leisure-time physical activity was divided into two categories, including low level (<600 MET·min/week) and high level ( $\geq 600$  MET·min/week)<sup>(26; 27)</sup>.

### **Variables selection**

We also selected potential covariates from the database, including (1) demographic variables (age, gender, race, educational level, poverty income ratio (PIR) and marital status), (2) physical examination variables (height, weight, BMI, WBC, lymphocyte, neutrophil and eGFR), (3) lifestyle information (smoking, drinking, physical work and sedentary time), and (4) diseases and medication that associated with cancer or sleep quality (hypertension, diabetes mellitus (DM), dyslipidemia, cardiovascular disease (CVD), chronic obstructive pulmonary disease (COPD), antineoplastic agents use, painkiller use, anxiolytics/sedatives/hypnotics (ASH) use, antidepressant use, cancer site and cancer duration).

Demographic variables and physical examination variables were collected by well-trained NHANES interviewers at mobile exam centers, and transferred to laboratory for further testing. In our analyses, PIR was divided into low level ( $PIR \leq 1.01$ ) and high level ( $PIR > 1.01$ ). BMI were divided into three levels, including  $< 25 \text{ kg/m}^2$  (underweight/normal), 25 to  $30 \text{ kg/m}^2$  (overweight), and  $\geq 30 \text{ kg/m}^2$  (obese)<sup>(28)</sup>. The eGFR was calculated by the following formula:  $eGFR = 175 \times \text{standardized Scr} - 1.154 \times \text{age} - 0.203 \times 1.212$  (if black)  $\times 0.742$  (if female), where GFR is expressed as mL/min/1.73 m<sup>2</sup> of body surface area<sup>41</sup> and Scr is expressed in mg/dL<sup>(29)</sup>.

Lifestyle information was collected during the NHANES household interview. Participants who claimed to have smoked fewer than 100 cigarettes in their lives were labeled as 'non-smoking'. The answer to another question "Does you now smoke cigarettes?" was used to further divided participants into "current smoking" and "former smoking". Alcohol consumption was also captured by questionnaires, and the drinking patterns were divided into non-drinking, light drinking, moderate drinking and heavy drinking<sup>(30)</sup>. Physical work was assessed according to the formula:  $\text{physical work} = \text{days vigorous work} \times \text{minutes vigorous-intensity work} \times 8 + \text{number of days moderate work} \times \text{minutes moderate-intensity work} \times 4$ <sup>(31)</sup>. Sedentary time was similarly self-reported via questionnaires, which were divided into  $< 480 \text{ min/day}$  (low level sedentary activity) and  $\geq 480 \text{ min/day}$  (high level sedentary activity)<sup>(32)</sup>.

Hypertension was defined by the laboratory inspection (a measured systolic blood pressure  $\geq 130 \text{ mm Hg}$  or diastolic blood pressure  $\geq 80 \text{ mm Hg}$ ), self-reported hypertension or



currently use of hypotensive drugs. DM was defined according to a self-reported diagnosis, the use of oral hypoglycemic agents or insulin, glycosylated hemoglobin  $\geq 6.5\%$ , a plasma glucose level  $\geq 200$  mg/dL at 2 hours after the oral glucose tolerance test, or a fasting glucose level  $\geq 126$  mg/dL. Patients with total cholesterol  $\geq 200$  mg/dL (5.2 mmol/L) or triglycerides  $\geq 150$  mg/dL (1.7 mmol/L) or low-density lipoprotein cholesterol  $\geq 130$  mg/dL (3.4 mmol/L) or high-density lipoprotein cholesterol  $\leq 40$  mg/dL (1.0 mmol/L) or self-report hypercholesteremia or receiving lipid-lowering therapy were identified as dyslipidemia. CVD was diagnosed according to the positive answer to the multiple-choice question: 'Have you ever been told you had (congestive) heart failure, coronary heart disease, angina/angina pectoris, heart attack and stroke' or using of cardiovascular drugs in any one or more diseases or medications. COPD was defined as a positive response to any of the following questions: (1) "Has a doctor or other health professional ever told you that you have chronic bronchitis?" (2) "Has a doctor or other health professional ever told you that you have emphysema?" (3) "Has a doctor or other health professional ever told you that you have COPD?" (4) "Are you over 40 years old and have a history of smoking or chronic bronchitis, and take one of the following medications: mast cell stabilizers, inhaled corticosteroids, leukotriene modifiers, or selective phosphodiesterase-4 inhibitors?" In addition, cancer site, cancer duration and medication use situations were assessed by questionnaires.

### Statistical analysis

Normally distributed data were described using mean  $\pm$  standard error (mean  $\pm$  SE), and t test was utilized for comparison between healthy sleep pattern group and unhealthy sleep pattern group. Enumeration data were expressed as frequency and constituent ratio [N (%)], and chi-square test ( $\chi^2$ ) was used for comparison. According to the NHANES guideline, day 1 dietary sample weights were used to adjust for oversampling, non-response rates, non-coverage and day of week. Weighted univariable logistic regression analysis was utilized to screen covariates that significantly associated with unhealthy sleep patterns in cancer survivors (with two-sided  $P < 0.05$  was considered as statistically significant). Weighted multivariable logistic regression models were used to estimate odds ratios (ORs) and 95%

confidence intervals (CIs) for the association of DAQS, leisure-time physical activity, and the combined effects between them on sleep patterns. Low-DAQS level combined with leisure-time physical activity <600 MET·min/week was recognized as reference (the worst condition in our study), other combined associations between DAQS levels and leisure-time physical activity levels (5 types of combined associations) on unhealthy sleep pattern were analyzed compared to the reference. Model 1 was unadjusted model. Model 2 adjusted for covariates including age, race, PIR, cancer site, painkiller, ASH, antidepressant, and total energy intake. In addition, subgroup analyses of age, painkiller use and antidepressant use were performed to assess the combined associations between DAQS levels and leisure-time physical activity levels on unhealthy sleep pattern. Statistical analyses were performed using R (version 4.2.0, Institute for Statistics and Mathematics, Vienna, Austria) and SAS 9.4 (SAS Institute, Cary, NC, USA).

## Results

### Characteristics of cancer survivors

Figure 1 shows the flowchart of the participants screening. There were 2,444 cancer survivors in the NHANES database in 2007-2014. We initially included individuals aged  $\geq 20$  years old, with information on sleep pattern, dietary intake, and physical activity (n=2173). Then, those who have extreme energy intake (n=24) or missing information on sedentary time (n=7), BMI (n=37), WBC (n=120), lymphocyte (n=6), neutrophil (n=0), eGFR (n=41), marital status (n=1), or education level (n=1) were excluded. Finally, 1,936 were eligible.

Table 1 shows the characteristics of cancer survivors between healthy sleep pattern group and unhealthy sleep pattern group. Among the eligible patients, 1,133 had unhealthy sleep patterns. The average age of cancer survivors was 61.55 years old, and 1,070 (58.74%) were female. Skin cancer accounted for the majority (34.4%), followed by respiratory cancer (12.0%) and reproductive system cancer (11.8%). More than half of the participants (55.0%) had a cancer duration >5 years. The mean DAQS was significantly different between healthy sleep pattern group and unhealthy sleep pattern group (4.25 vs. 4.03), in which the average vit A intake was significant higher in healthy sleep pattern group than that in unhealthy sleep pattern

group (775.29 mg vs. 69.16 mg). In addition, compared to healthy sleep pattern group, the proportion of individuals with leisure-time physical activity levels  $<600$  MET·min/week was higher in unhealthy sleep pattern group ( $P<0.001$ ).

### **Associations of DAQS and leisure-time physical activity with unhealthy sleep patterns in cancer survivors**

We firstly screened the covariates associated with unhealthy sleep patterns in cancer survivors (Table S1). The results showed that age (OR=0.66, 95%CI: 0.49-0.88), race (Non-Hispanic White: OR=0.57, 95%CI: 0.39-0.84), PIR (PIR  $>1.01$ : OR=0.43, 95%CI: 0.29-0.65), cancer site (skin: OR=1.86, 95%CI: 1.20-2.88; digestive system: OR=2.02, 95%CI: 1.06-3.83), painkiller (OR=1.89, 95%CI: 1.21-2.96), ASH (OR=7.04, 95%CI: 3.55-13.96) and antidepressant (OR=2.00, 95%CI: 1.23-3.25) were all significantly associated with unhealthy sleep patterns.

Then, we explored the associations of DAQS and leisure-time physical activity with unhealthy sleep patterns in cancer survivors (Table 2). After adjusting for covariates, the highest tertile of DAQS level (OR=0.60, 95%CI: 0.36-0.99) and leisure-time physical activity  $\geq 600$  MET·min/week (OR=0.76, 95%CI: 0.58-1.00) were both associated with lower odds of unhealthy sleep patterns in cancer survivors. We further assessed the combined associations between different DAQS levels and leisure-time physical activity levels on unhealthy sleep patterns (Table 3). Compared to low DAQS level combined with leisure-time physical activity level  $<600$  MET·min/week, median level of DAQS combined with leisure-time physical activity  $\geq 600$  MET·min/week (OR=0.62, 95%CI: 0.43-0.88) or high level of DAQS combined with leisure-time physical activity  $\geq 600$  MET·min/week (OR=0.41, 95%CI: 0.23-0.72) was linked to lower odds of unhealthy sleep patterns.

### **Combined associations between different DAQS levels and leisure-time physical activity levels on sleep patterns in age, painkiller use and antidepressant use subgroups**

We also investigated the combined associations between different DAQS levels and leisure-time physical activity levels on sleep patterns in cancer survivors with different age and medication situations (Figure 2). The combined association between high DAQS level and high leisure-time physical activity level had a negative association with unhealthy sleep patterns in age <65 years old (OR=0.30, 95%CI: 0.13-0.70), non-painkiller (OR=0.39, 95%CI: 0.22-0.71), non-antidepressant (OR=0.49, 95%CI: 0.26-0.91) and antidepressant (OR=0.11, 95%CI: 0.02-0.50) use subgroups. No interaction effect was observed between age or medication situations and DAQS combined with leisure-time physical activity on sleep patterns in cancer survivors (all  $P>0.05$ ), indicating these two factors may not impact the associations.

## Discussion

This cross-sectional study explored the combined association between different DAQS levels and leisure-time physical activity levels on sleep patterns in cancer survivors. The study results indicated that higher DAQS combined with higher leisure-time physical activity levels was associated with lower odds of unhealthy sleep patterns in cancer survivors. Moreover, this joint association was also found in aged <65 years old, non-painkiller, non-antidepressant and antidepressant use subgroups.

Dietary habits and physical activity are common factors influencing human health. Growing scientific evidence has suggested that a healthy sleep pattern is strongly associated with improved adverse outcomes for cancer survivors, and therefore it is necessary to investigate the beneficial factors that can improve sleep in this population<sup>(33; 34)</sup>. However, to the best of our knowledge, no study has discussed the combined association between DAQS and leisure-time physical activity on sleep patterns in cancer survivors. In the current study, we included the representative population in the United States from the NHANES database, and explored the combined association between DAQS and leisure-time physical activity on sleep patterns. We found that compared to cancer survivors with low levels of both DAQS and leisure-time physical activity, those who had both higher DAQS and higher leisure-time physical activity levels seemed to have lower odds of unhealthy sleep patterns.

The DAQS and leisure-time physical activity were respectively negatively associated with the odds of unhealthy sleep pattern, which was in accordance with previous studies. A cross-sectional study among women with DM conducted by Daneshzad et al. <sup>(35)</sup> showed that subjects in the highest tertile of the ferric reducing ability of plasma and the oxygen radical absorbance capacity score compared to those in the lowest tertile of these scores had respectively 94% and 87% lower risk of poor sleep. Differently, we used the DAQS to reflect the dietary antioxidant capacity, which not only included dietary vitamins indexes but also dietary minerals. In addition, interventions to promote leisure-time physical activity and/or exercise-based rehabilitation may improve quality of life among cancer survivors <sup>(36)</sup>. It has been reported that adequate adherence to the 2018 diet and exercise recommendations of the World Cancer Research Fund/American Institute for Cancer Research can possibly result in less oxidative stress, lower risk to chemo- and radiotoxicity, lower risk of relapse, and increased quality of life in breast cancer survivors <sup>(37)</sup>. Basing on these evidences, we speculated that DAQS and leisure-time physical activity may be at the same time involved in sleep conditions improvement in cancer survivors. Although DAQS and leisure-time physical activity were both beneficial factors for quality of life in cancer survivors, causal associations of these two indexes with sleep patterns are still needed to be clarified.

The DAQS included many ingredients that have been proven to have antioxidant effects in previous studies, which may be involved in pathways associated with physical activity and/or sleep quality. Vit C supplementation helped to reduce oxygen free radicals produced by radiation and chemotherapy, and relieved patients of symptoms related to cancer treatment, such as fatigue, insomnia, and sleep disturbances <sup>(38; 39)</sup>. Vit E acts through antioxidant mechanisms to initiate T-cell activation signals, enhance inflammatory cytokine secretion and natural killer cell responses, and reduce the risk of infection <sup>(40)</sup>. Zn and Se, essential trace elements, play crucial roles in the development and maintenance of immune cells and mammalian redox biology. Insufficient Zn and Se levels may lead to impaired humoral function and cell-mediated immunity <sup>(41)</sup>. A cross-sectional analysis basing on the NHANES database showed that serum Zn, Zn/Cu ratio, and Zn/Se ratio were all associated with a

reduced likelihood of self-reported sleep disturbance in adults <sup>(42)</sup>. Another study found that Mg ions might influence sleep duration by regulating circadian rhythms, with people who slept longer having significantly higher levels of Mg <sup>(38)</sup>. Mg has a crucial role in numerous biological processes, including oxidative phosphorylation, energy production, glycolysis, protein and nucleic acid synthesis <sup>(43)</sup>. Mg deficiency may produce overexcitation of the central nervous system, while severe Mg deficiency is thought to cause weakness, muscle pain, and nighttime cramps <sup>(44)</sup>. Besides, among the DAQS components, we only found the average vit A concentration was significantly different between healthy sleep pattern group and unhealthy sleep pattern group (775.29 mcg vs. 619.16 mcg). Previous human studies reported that lower vit A intake levels were associated with disturbed wake-sleep cycles <sup>(45)</sup>. Vit A may influence biological rhythms, and various diseases, including but not limited to metabolic syndromes, cardiovascular diseases, cancers, and inflammations through retinoid-related orphan receptors, constituting an important part of the molecular mechanism of biorhythm regulation <sup>(46; 47)</sup>. Nevertheless, the potential mechanisms that combined association between DAQS and leisure-time physical activity on sleep pattern in cancer survivors are still unclear.

Hypothesized biologic mechanisms that physical activity influencing sleep quality in cancer survivors could through the main pathways including metabolic and sex hormones, inflammation, and immunity <sup>(48)</sup>. The growing evidence from experimental studies indicated that prolonged and uninterrupted sitting are associated with impaired glucose metabolism and increased systemic inflammation <sup>(49)</sup>. Low leisure-time physical activity and prolonged sitting may also contribute to increased risk of cachexia, thromboembolic events, and fatigue, which all influence survival after cancer <sup>(50)</sup>. Traditional exercise training focuses on moderate-to-vigorous intensity physical activity and exercise, which can be challenging for patients who are older and have substantial physical and psychosocial barriers, high frailty, comorbidity burden, more advanced disease, and cancer survivors <sup>(51; 52; 53)</sup>. Therefore, increasing light-intensity physical activity and exercise and reducing sedentary behavior are also recognized as important <sup>(31)</sup>. Although the limited evidence available, the World Health Organization in its 2020 guidelines on physical activity and sedentary behavior strongly

recommends limiting the amount of sedentary time and substituting it with any physical activity to improve health, particularly for individuals with long-term diseases<sup>(54)</sup>.

Additionally, the combined association between DAQS and leisure-time physical activity on sleep pattern was also found in <65 years old, non-painkiller, non-antidepressant and antidepressant use subgroups. Previous studies have reported that higher dietary antioxidant levels were associated with better nutritional status and better sleep quality in the elderly population<sup>(18; 55)</sup>. DNA damage, telomere dysfunction, epigenetic disruption, mitogenic signaling and oxidative stress increase with aging<sup>(56; 57; 58; 59)</sup>. However, we did not observe the combined association between higher levels of DAQS and leisure-time physical activity on lower odds of unhealthy sleep pattern in cancer survivors aged  $\geq 65$  years old, which we speculated that may be because of the influence from a more healthier body condition and higher adherence to medical advice in younger persons. Furthermore, this combined association was found in non-painkiller, non-antidepressant and antidepressant subgroups. Although painkillers and antidepressants act on the nervous system, their usage was generally in accordance with medical advice, and clinicians may also recommend periodic inspection on relative indexes of drug metabolism. Therefore, whether the use of such drugs can affect the combined association between DAQS and leisure-time physical activity on sleep patterns is still unclear.

This study was the first to explore the combined association between DAQS and leisure-time physical activity on sleep patterns in cancer survivors, which may provide some references for the improvement of living quality in these populations with unhealthy sleep patterns. Based on the NHANES database, the study subjects were the representative population in the United States so that our findings were relatively credible. However, there are still some limitations in our research. We could not conclude causal associations of DAQS and leisure-time physical activity with sleep patterns in cancer survivors due to the study design being cross-sectional. The information on dietary intake, sleeping and leisure-time physical activity were self-reported, which may cause recalling biases. Information on dietary intake was collected through 24-hour dietary recalls in the NHANES, which could only reflect the short-term dietary intake status instead of the long-term influence. The database only

collected data of sleeping in 2005-2014, and data of dietary supplement were collected starting from 2007, and therefore, the data we used for analyses were 2007-2014 considering both sleep and dietary information. The exclusion of persons missing information on study variables may result in selection bias. Additionally, detailed information on painkiller type, which may affect sleep patterns, was not available in the database.

### **Conclusion**

Higher level of DAQS combined with higher level of leisure-time physical activity was associated with lower odds of unhealthy sleep patterns in cancer survivors. These findings indicated that, in addition to dietary, focusing on combined effect among multi-angle lifestyle factors has significance in management of cancer survivors and improving their living quality.

### **Acknowledgements**

None.

### **Financial support**

This study was supported by the National Natural Science Foundation of China (No.82172804), the Jiangsu Commission of Health Foundation of China (No.M2021114), and Research Project of Jiangsu Cancer Hospital (No. ZH202105).

### **Conflict of Interest**

None.

### **Author contributions**

RY, XL, LZ and XH designed the study. RY and XL wrote the manuscript. FP, CL, YN, SW, and SS collected, analyzed, and interpreted the data. LZ and XH critically reviewed, edited, and approved the manuscript. All authors read and approved the final manuscript.



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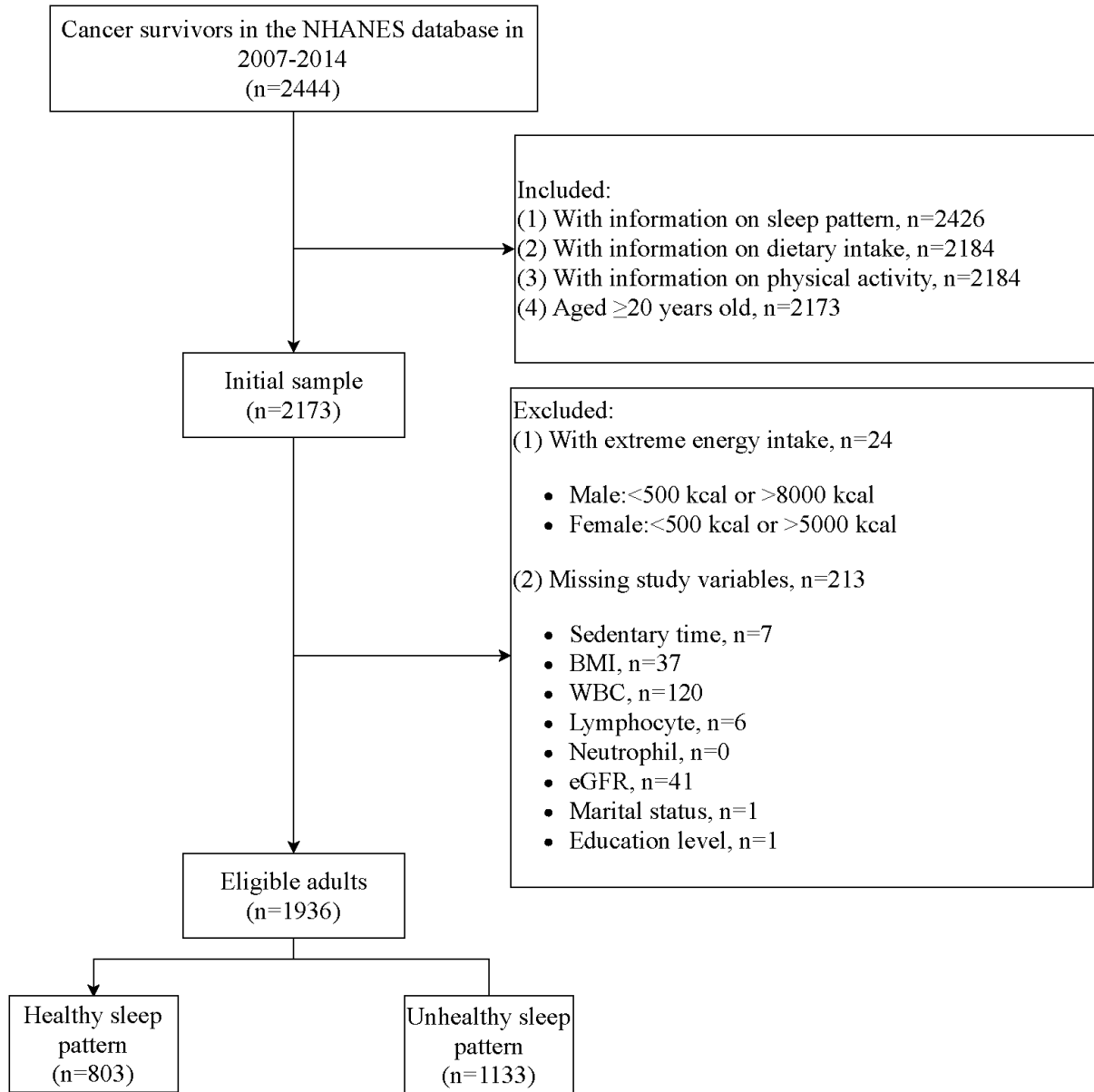
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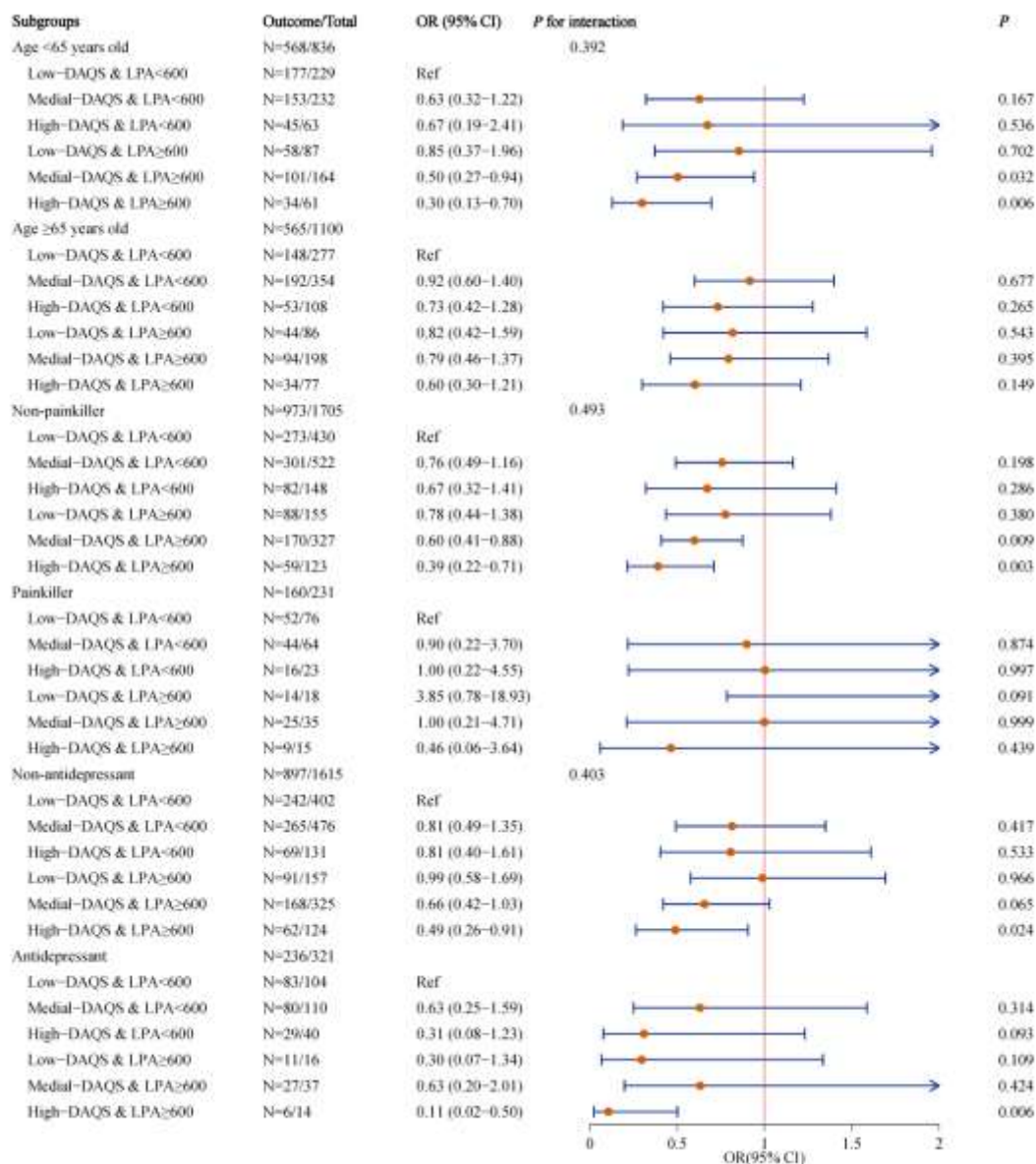
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**Figure 1.** Flowchart of cancer survivors screening.



**Figure 2.** Subgroup analyses of combined association between different DAQS levels and leisure-time physical activity levels on unhealthy sleep patterns in cancer survivors.

**Table 1 Characteristics of cancer survivors with different sleep patterns**

Variables	Total (n=1936)	Healthy sleep pattern (n=803)	Unhealthy sleep pattern (n=1133)	<i>P</i>
Age, years, Mean $\pm$ SE	61.55 $\pm$ 0.47	63.91 $\pm$ 0.60	59.89 $\pm$ 0.56	<0.001
Age, years, n (%)				<0.001
<65	836 (53.5)	268 (45.6)	568 (59.0)	
$\geq$ 65	1100 (46.5)	535 (54.4)	565 (41.0)	
Gender, n (%)				0.150
Male	866 (41.3)	387 (44.1)	479 (39.3)	
Female	1070 (58.7)	416 (55.9)	654 (60.8)	
Race, n (%)				0.022
Non-Hispanic Black	257 (5.3)	88 (4.1)	169 (6.1)	
Non-Hispanic White	1365 (86.9)	597 (89.3)	768 (85.2)	
Mexican American	126 (2.4)	45 (2.3)	81 (2.5)	
Other	188 (5.4)	73 (4.2)	115 (6.3)	
PIR, n (%)				<0.001
$\leq$ 1.01	265 (8.5)	69 (4.6)	196 (11.3)	
>1.01	1539 (84.8)	672 (89.1)	867 (81.8)	
Unknown	132 (6.7)	62 (6.3)	70 (6.9)	
Marital status, n (%)				0.106
Married/living with partner	1199 (67.1)	528 (70.7)	671 (64.6)	



Variables	Total (n=1936)	Healthy sleep pattern (n=803)	Unhealthy sleep pattern (n=1133)	<i>P</i>
Spinsterhood/divorced/widowed/separated	737 (32.9)	275 (29.3)	462 (35.4)	
Height, cm, Mean $\pm$ SE	167.52 $\pm$ 0.34	167.60 $\pm$ 0.52	167.47 $\pm$ 0.47	0.855
Weight, kg, Mean $\pm$ SE	80.90 $\pm$ 0.62	78.85 $\pm$ 0.71	82.34 $\pm$ 0.91	0.003
BMI, kg/m <sup>2</sup> , n (%)				0.027
<25	560 (30.8)	240 (31.0)	320 (30.8)	
[25, 30)	664 (34.5)	302 (38.6)	362 (31.6)	
$\geq$ 30	712 (34.7)	261 (30.5)	451 (37.7)	
Physical work, MET·min/week, n (%)				0.717
<600	1383 (70.0)	573 (69.5)	810 (70.4)	
$\geq$ 600	553 (30.0)	230 (30.6)	323 (29.6)	
Sedentary time, min/d, n (%)				0.529
<480	1233 (58.3)	512 (59.5)	721 (57.5)	
$\geq$ 480	703 (41.7)	291 (40.6)	412 (42.5)	
Smoking, n (%)				0.089
No	891 (46.8)	399 (49.5)	492 (44.9)	
Former	747 (37.9)	319 (38.3)	428 (37.7)	
Now	298 (15.3)	85 (12.2)	213 (17.4)	
Drinking, n (%)				0.288
No	545 (22.7)	225 (23.2)	320 (22.4)	
Light	400 (21.5)	150 (19.8)	250 (22.8)	

Variables	Total (n=1936)	Healthy sleep pattern (n=803)	Unhealthy sleep pattern (n=1133)	<i>P</i>
Moderate	430 (28.0)	200 (30.0)	230 (26.5)	
Heavy	185 (11.3)	89 (12.6)	96 (10.4)	
Unknown	376 (16.5)	139 (14.5)	237 (17.9)	
Hypertension, n (%)				0.892
No	488 (30.3)	208 (30.1)	280 (30.5)	
Yes	1448 (69.7)	595 (69.9)	853 (69.6)	
DM, n (%)				0.968
No	1471 (80.4)	619 (80.4)	852 (80.5)	
Yes	465 (19.6)	184 (19.6)	281 (19.5)	
Dyslipidemia, n (%)				0.636
No	334 (17.5)	136 (16.8)	198 (18.0)	
Yes	1602 (82.5)	667 (83.2)	935 (82.0)	
CVD, n (%)				0.896
No	1233 (70.3)	520 (70.1)	713 (70.5)	
Yes	703 (29.7)	283 (29.9)	420 (29.5)	
COPD, n (%)				0.038
No	1650 (85.3)	713 (87.8)	937 (83.6)	
Yes	286 (14.7)	90 (12.2)	196 (16.4)	
Cancer site, n (%)				0.118
Urinary	291 (9.2)	141 (12.1)	150 (7.2)	

Variables	Total (n=1936)	Healthy sleep pattern (n=803)	Unhealthy sleep pattern (n=1133)	<i>P</i>
Digestive	111 (4.4)	40 (3.8)	71 (4.9)	
Reproductive	240 (11.8)	79 (10.3)	161 (12.9)	
Respiratory	261 (12.0)	114 (13.5)	147 (11.0)	
Skin	507 (34.4)	217 (32.8)	290 (35.6)	
Hematopoietic	49 (2.7)	27 (3.8)	22 (1.9)	
Thyroid	37 (2.1)	13 (1.3)	24 (2.6)	
Neural/cerebric	8 (0.4)	0 (0.0)	8 (0.6)	
Others	95 (5.5)	39 (5.8)	56 (5.3)	
2 sites	158 (8.0)	69 (7.8)	89 (8.3)	
3 sites	13 (0.8)	6 (0.8)	7 (0.8)	
≥3 sites	2 (0.1)	1 (0.1)	1 (0.1)	
Unknown	164 (8.6)	57 (8.2)	107 (9.0)	
Cancer duration, years, n (%)				0.424
≤1	249 (14.1)	106 (14.9)	143 (13.5)	
(1, 3]	239 (11.7)	89 (10.8)	150 (12.3)	
(3, 5]	200 (10.7)	96 (12.8)	104 (9.2)	
>5	1089 (55.0)	456 (53.4)	633 (56.2)	
Unknown	159 (8.6)	56 (8.1)	103 (8.9)	
Antineoplastic agents, n (%)				0.825
No	1683 (87.1)	709 (87.6)	974 (86.6)	

Variables	Total (n=1936)	Healthy sleep pattern (n=803)	Unhealthy sleep pattern (n=1133)	<i>P</i>
Antimetabolite	71 (3.7)	22 (3.3)	49 (3.9)	
Other antineoplastic agents	182 (9.3)	72 (9.1)	110 (9.5)	
Painkiller, n (%)				0.001
No	1705 (89.3)	732 (93.0)	973 (86.7)	
Yes	231 (10.7)	71 (7.0)	160 (13.3)	
ASH, n (%)				<0.001
No	1794 (92.7)	784 (98.4)	1010 (88.7)	
Yes	142 (7.3)	19 (1.6)	123 (11.3)	
Antidepressant, n (%)				0.001
No	1615 (81.0)	718 (88.2)	897 (75.9)	
Yes	321 (19.0)	85 (11.8)	236 (24.1)	
Total energy intake, kcal, Mean ± SE	1935.69 ± 28.01	1917.29 ± 33.11	1948.68 ± 39.64	0.525
WBC, 1000/μL, Mean ± SE	7.16 ± 0.08	6.95 ± 0.10	7.31 ± 0.11	0.020
Lymphocyte, 1000/μL, Mean ± SE	2.02 ± 0.03	1.94 ± 0.04	2.08 ± 0.05	0.080
Neutrophil, 1000/μL, Mean ± SE	4.33 ± 0.06	4.21 ± 0.08	4.41 ± 0.08	0.063
eGFR, mL/min/1.73m <sup>2</sup> , n (%)				0.735
<60	276 (10.9)	116 (11.3)	160 (10.7)	
≥60	1660 (89.1)	687 (88.7)	973 (89.3)	
DAQS, Mean ± SE	4.12 ± 0.05	4.25 ± 0.07	4.03 ± 0.08	0.041
DAQS levels, n (%)				0.070

Variables	Total (n=1936)	Healthy sleep pattern (n=803)	Unhealthy sleep pattern (n=1133)	<i>P</i>
Low	679 (30.1)	252 (25.9)	427 (33.0)	
Median	948 (51.2)	408 (53.2)	540 (49.7)	
High	309 (18.8)	143 (20.9)	166 (17.3)	
Vit A, mcg, Mean ± SE	683.76 ± 29.50	775.29 ± 59.64	619.16 ± 23.81	0.016
Vit E, mg, Mean ± SE	9.25 ± 0.27	9.68 ± 0.48	8.94 ± 0.35	0.237
Vit C, mg, Mean ± SE	213.61 ± 13.99	211.26 ± 16.64	215.27 ± 20.42	0.878
Zn, mg, Mean ± SE	17.77 ± 0.44	19.01 ± 0.90	16.90 ± 0.60	0.086
Se, mcg, Mean ± SE	125.26 ± 2.34	125.06 ± 3.02	125.40 ± 3.66	0.946
Mg, mg, Mean ± SE	337.75 ± 8.84	353.44 ± 14.98	326.68 ± 9.46	0.112
Leisure-time physical activity, MET·min/week, n (%)				0.001
<600	1263 (61.3)	495 (55.7)	768 (65.3)	
≥600	673 (38.7)	308 (44.3)	365 (34.8)	
Sleep duration, hours/day, Mean ± SE	7.00 ± 0.04	7.69 ± 0.03	6.51 ± 0.06	<0.001
Sleep duration levels, hours/day, n (%)				<0.001
7-9	1167 (65.0)	803 (100.0)	364 (40.3)	
<7	704 (32.6)	0 (0.0)	704 (55.6)	
>9	65 (2.4)	0 (0.0)	65 (4.1)	
Sleeping difficulties, n (%)				<0.001
No	1249 (61.3)	803 (100.0)	446 (34.0)	
Yes	687 (38.7)	0 (0.0)	687 (66.0)	

Variables	Total (n=1936)	Healthy sleep pattern (n=803)	Unhealthy sleep pattern (n=1133)	<i>P</i>
Sleep disorders, n (%)				<0.001
No	1697 (86.6)	803 (100.0)	894 (77.2)	
Yes	239 (13.4)	0 (0.0)	239 (22.8)	

SE: standard error, PIR: poverty income ratio, BMI: body mass index, MET: metabolic equivalent, DM: diabetes mellitus, CVD: cardiovascular disease, COPD: chronic obstructive pulmonary disease, ASH: anxiolytics, sedatives and hypnotics, WBC: white blood cell, eGFR: estimated glomerular filtration rate, DAQS: dietary antioxidant quality score, vit A: vitamin A, vit E: vitamin E, vit C: vitamin C, Zn: zinc, Se: selenium, Mg: magnesium.

Comparations used t test and chi-square test.

**Table 2. Associations of DAQS and leisure-time physical activity with unhealthy sleep patterns in cancer survivors**

Variables	Model 1		Model 2		Model 3	
	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>
DAQS	0.85 (0.73-0.99)	0.039	0.84 (0.70-1.00)	0.050	0.85 (0.71-1.03)	0.090
DAQS levels						
Low	Ref		Ref		Ref	
Median	0.73 (0.54-1.00)	0.050	0.75 (0.53-1.05)	0.092	0.76 (0.54-1.08)	0.124
High	0.65 (0.43-0.98)	0.039	0.57 (0.34-0.93)	0.026	0.60 (0.36-0.99)	0.046
Leisure-time physical activity						
<600	Ref		Ref		Ref	
≥600	0.67 (0.53-0.84)	0.001	0.73 (0.56-0.95)	0.019	0.76 (0.58-1.00)	0.048

DAQS: dietary antioxidant quality score, OR: odds ratio, CI: confidence interval, Ref: reference.

Model 1: unadjusted model;

Model 2: adjusted for age, race, PIR, cancer site, painkiller, ASH, antidepressant, and total energy intake;

Model 3: adjusted for covariables in the adjustment of Model 2 and DAQS or leisure-time physical activity adjusted for each other.

**Table 3. Combined association between DAQS and leisure-time physical activity on unhealthy sleep patterns in cancer survivors**

Variables	Model 1		Model 2	
	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>
Low DAQS & leisure-time physical activity <600	Ref		Ref	
Median DAQS & leisure-time physical activity <600	0.73 (0.50-1.07)	0.105	0.77 (0.50-1.17)	0.211
High DAQS & leisure-time physical activity <600	0.77 (0.44-1.34)	0.346	0.70 (0.35-1.41)	0.308
Low DAQS & leisure-time physical activity ≥600	0.69 (0.41-1.16)	0.158	0.83 (0.48-1.44)	0.495
Median DAQS & leisure-time physical activity ≥600	0.55 (0.39-0.78)	0.001	0.62 (0.43-0.88)	0.010
High DAQS & leisure-time physical activity ≥600	0.43 (0.23-0.78)	0.007	0.41 (0.23-0.72)	0.003

DAQS: dietary antioxidant quality score, OR: odds ratio, CI: confidence interval, Ref: reference.

Model 1: unadjusted model;

Model 2: adjusted for age, race, PIR, cancer site, painkiller, ASH, antidepressant, and total energy intake.