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ORIGINAL ARTICLE

Alcohol intake and the risk of osteonecrosis of the femoral head in Japanese populations: a dose-response meta-analysis of case-control studies

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Abstract Studies examining the association between alcohol intake and the risk of osteonecrosis of the femoral head (ONFH) have inconsistent results. The purpose of this study was to examine and summarize the evidence regarding the association between alcohol intake and ONFH based on results from case-control studies. This analysis included five case-control studies reporting data from 1251 individuals. Alcohol intake habits (never, former, or current), average drinking consumption (g/week), and cumulative drinking consumption (drink-years) were extracted. The risk of ONFH was evaluated, and a two-stage dose-response meta-analysis was performed using restricted cubic splines with four knots at fixed percentiles of 5, 35, 65, and 95% of the distribution. Former alcohol intake increased the risk of ONFH with a marginal significance (odds ratio [OR], 2.62; $p = 0.055$). Current alcohol intake was associated with an increased risk of ONFH (OR, 3.63; $p < 0.001$ in occasional drinkers, OR, 5.90; $p < 0.001$ in daily drinkers). The dose-response meta-analysis revealed that the risk of ONFH increased by 35.3% for every 100 g/week (95% confidence interval [CI], 1.24–1.47; $p < 0.001$) and by 44.1% for every 500 g drink-years (95% CI, 1.295–1.601; $p < 0.001$). Current intake and the dose of alcohol were positively associated with an increased risk of ONFH in a non-linear pattern.

Keywords Alcohol · Avascular necrosis · Dose-response · Hip · Meta-analysis · Osteonecrosis

Byung-Ho Yoon and Tae-young Kim equally contributed to this work and are co-first authors.

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Introduction

Osteonecrosis of the femoral head (ONFH) frequently leads to hip joint destruction and damages patient's quality of life [1]. This debilitating disease represents a significant socioeconomic burden on both individuals and healthcare systems because it commonly occurs in young and active adults and the incidence has increased annually [2, 3]. In nationwide surveys from Korea and Japan, the annual prevalence of the disease was more than 10,000 [4]. In the USA, approximately 20,000 patients are affected with the disease each year [5]. Osteonecrosis has a multifactorial etiology [3]. Underlying genetic predisposition and exposure to risk factors including alcohol and steroids have synergistic role in the pathogenesis of the disease [6].

Although individual sensitivity to alcohol also appears to be an important factor for ONFH development, alcohol has been known as an independent risk factor, when taken in excess [7, 8]. However, detailed pathogenesis for alcohol-

induced ONFH has not been well established. Suggested mechanism includes fat cell proliferation and hypertrophy, diminished hematopoiesis, and decreased osteogenesis, which interact together, forming a vicious cycle of ischemia in the femoral head [9, 10].

The relationship between alcohol intake and the risk of ONFH was first reported in a multicenter case-control study [8]. Although a dose-dependent association was observed, the odds ratios (ORs) were not consistent among the studies [11, 12], and the exact dose-response relationship has not been determined yet.

Thus, a dose-response meta-analysis was conducted to assess the relationship between the quantity of alcohol intake and the risk of ONFH [13]. For the measurement of cumulative exposure, we used drink-years of alcohol.

Materials and methods

Literature search and study selection criteria

This review was performed according to the criteria for conducting and reporting meta-analysis of observational studies in epidemiology (Online Resource 1) [14]. PubMed-Medline, Embase, Cochrane Library, and Web of Science were searched in January 2016 by combining synonymous or related key terms (osteonecrosis OR avascular necrosis OR aseptic necrosis) AND (alcohol OR ethanol OR drinking). An overview of the search strategy is presented in Online Resource 2. We restricted our review to English studies, owing to translation of non-English language studies and lack of resources for review. The references of all selected articles were manually searched to identify any additional relevant studies. The decision whether an identified article would be eligible for the review was made prior to initiating the search.

Two independent reviewers (Y.B.H. and K.T.Y.) first screened the titles and abstracts to identify the relevant investigations. A third reviewer (K.K.H.) settled discrepancies between these two reviewers. Population-based epidemiological studies that investigated the association between alcohol intake and the risk of ONFH, including cross-sectional studies, case-control studies, and cohort studies, were included. We also included articles that reported adjusted effect estimates (OR) and 95% confidence intervals (CIs) for comparisons of different categories of alcohol intake. We excluded articles that involved subjects younger than 18 years [15], review articles, basic science articles, comments, letters, and protocols.

Outcome measure and data extraction

The primary outcome of interest was the rate of ONFH. Drinkers were defined as those who consumed more than 6.4 g (8 mL) of alcohol per week [8]. Drinking habits were classified into three categories: never, former, and current. With respect to alcohol intake, average drinking consumption (g/week) and cumulative drinking (drink-years) were extracted. The cumulative amount of drinking (drink-years) was calculated as follows: drink-years = weekly ethanol consumption (g)/7 × the total years of drinking [12].

For every eligible study, the following data were also extracted by two independent reviewers: the first author's name, the year of publication, enrollment period, study design, sample size, mean age, percentage of male patients, covariates, and patient demographics. Then, all data were entered in a spreadsheet. For studies that reported several multivariable-adjusted ORs, we selected the effect estimate that was maximally adjusted for potential confounders.

Quality assessment

The Newcastle-Ottawa Scale was used to assess the quality of the enrolled studies. This tool comprises three parameters: selection, comparability, and outcome [16]. Each parameter consists of subcategorized questions: selection (a maximum of four stars), comparability (a maximum of two stars), and exposure or outcome (a maximum of three stars). A study can be awarded a maximum of nine stars, indicating the highest quality. Two of the authors (Y.B.H. and K.T.Y.) independently evaluated the quality of all the studies (Online Resource 3).

Data synthesis and analysis

We examined the relationship between alcohol intake and the risk of ONFH based on the effect estimate (relative risk, odds ratio, or hazards ratio) and its 95% CI in each study. Using a comparative meta-analysis, we evaluated the association between the habit of alcohol intake (never, former, or current) and the risk of ONFH. Because no heterogeneity was found, we reported the data from a fixed-effect model [17].

We conducted a two-stage dose-response random-effects meta-regression analysis [18, 19] and estimated the dose-response relationship curve by taking into account the covariance among risk estimates for different exposure categories [18]. A potential non-linear relation between alcohol intake and ONFH risk was investigated using restricted cubic splines with four knots at fixed percentiles (5, 35, 65, and 95%) of the exposure distribution [18, 19]. This method requires stating the distribution of cases and non-cases or person-time and the OR with its CIs for at least three quantitative exposure categories. For this reason, a study that reported only two exposure categories was excluded from this meta-analysis [20]. The midpoint of each exposure category was assigned to each corresponding risk estimate. When the upper category was open-ended, the midpoint between the upper boundary value and the midpoint value of the preceding category was

assigned to the risk estimate. Likewise, when the lower category was open-ended, the midpoint between the lower boundary value and the midpoint value of the next category was assigned to the risk estimate. We assigned a null value to the lowest category, composed by never drinkers in all the studies.

Sensitivity analyses were conducted by stratifying for study design and by excluding one study at the time to evaluate if results were particularly influenced by single studies.

In all meta-regression models, statistical heterogeneity between studies was evaluated with the Cochran's Q-test and the I^2 statistic. We assessed publication bias with Begg's funnel plot [21] and Egger's test [22]. All analyses were performed using STATA (version 14.0; Stata Corporation, College Station, TX, USA). This study was exempted from institutional review board (IRB) review because it did not involve human subjects.

Results

Literature selection

The selection process of the studies is shown in Fig. 1. Five studies were finally selected. All studies were from Japan [7, 8, 11, 12, 23] and involved a total of 1251 subjects. The general characteristics of the five studies are presented in Table 1. All of the five studies showed a significant dose-response relationship.

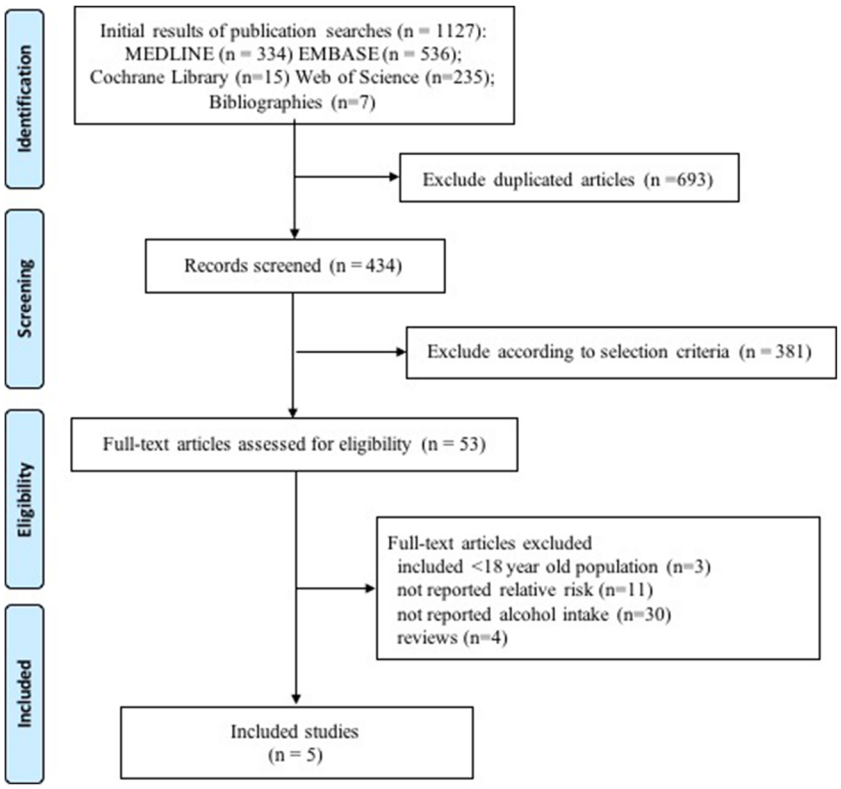

Fig. 1 Flow diagram of the literature search and study selection process

Drinking habits and the risk of ONFH

Two studies reported the OR of the current drinking habit into subcategory: occasional (at least once a week) and regular (daily) categories [7, 8]. Thus, the meta-analysis was performed using the ORs from occasional drinking and regular drinking from these two studies. Former alcohol intake was marginally associated with an increased risk of ONFH (OR, 2.63; $p = 0.055$; Fig. 2). Current alcohol intake was significantly associated with an increased risk of ONFH on occasional drinking (OR, 3.63; $p < 0.001$; Fig. 2) and on regular drinking (OR, 5.90; $p < 0.001$; Fig. 2). There was no significant heterogeneity across the five studies. A publication bias was found in the analysis of current occasional drinking. However, the OR decreased after adjustment for the publication bias using the Duval and Tweedie trim and fill method (Online Resource 4).

Dose-response meta-analysis

We first assumed a linear-response model for the association between the amount of alcohol consumption and the risk of ONFH. The risk of ONFH increased by 35.3% for every 100 g/week (exp(b) = 1.353, $p < 0.001$) and by 44.1% for every 500 g drink-years (exp(b) = 1.441, $p < 0.001$) (Table 2). Then, we allowed departure from linearity by fitting a restricted cubic spline model. We found a statistically significant departure from linear association between alcohol

Table 1 Characteristics of included individual studies

Study name	Country	Study design	Assessment of exposure	Male percentage	Mean age (years)	Categories (average alcohol consumption)	Sample size (disease/control)	Covariates that were adjusted in multivariate model	NOS score
Fukushima 2013	Japan	Multicenter case-control	Self-administered questionnaire	44/71 (62%)	55	None <160 g (week) vs none >160 g (week) vs none	26/94 17/67 28/66	Sex, age, steroid use smoking, liver disease, hyperlipidemia, gout	9
Sakata 2003	Japan	Single center case-control	Self-administered questionnaire	34/43 (79%)	48	None <320 g (week) vs none >320 g (week) vs none	9/22 7/35 27/29	Sex, age, BMI, occupation, genotype, smoking, liver disease, green-tea drinking	9
Shibata 1996	Japan	Multicenter case-control	Self-administered questionnaire	64/64 (100%)	49	None <320 g (week) vs none <480 g (week) vs none <640 g (week) vs none	7/66 6/13 15/21 36/28	Sex, age, BMI, occupation, BMI, smoking, liver disease, flushing pattern	8
Hirota 1993	Japan	Multicenter case-control	Self-administered questionnaire	71/118 (61%)	48	None <320 g (week) vs none <800 g (week) vs none >800 g (week) vs none	27/97 24/87 49/45 18/7	Occupation, BMI, smoking, liver dysfunction	8
Matsuo 1988	Japan	Multicenter case control	Patient interview	94/112 (83%)	43	None <320 g (week) vs none <800 g (week) vs none >800 g (week) vs none	19/64 29/66 49/31 15/5	Sex, age, BMI, occupation, smoking, liver disease	9

NOS Newcastle-Ottawa scale, *BMI* body mass index

intake and ONFH risk (Fig. 3). The non-linear dose-response trend showed a statistically significant increased risk of developing ONFH with increasing alcohol intake to 560 g/week (Table 3), and then the slope of risk slightly decreased with a concave downward pattern (Fig. 3a). The non-linear dose-response trend showed a statistically significant increased risk of developing ONFH with increasing number of total drinking years up to 2240 g drink-years (Table 3), and then the slope of risk slightly decreased (Fig. 3b) There was no publication bias across ORs (Online Resource 5).

Sensitivity analysis

The results of the sensitivity analysis, by excluding each one study from the pool of the five studies, were similar to the results of our overall analysis, and the dose-response relationship consistently showed a non-linear trend (Online Resource 6).

Discussion

Excessive alcohol intake has been known as the second leading risk factor for ONFH next to steroids [5]. Femoral head osteonecrosis remains as an intractable disease, and medical efforts regarding ONFH have mainly focused on treatment rather than prevention [24, 25]. The majority of clinicians still endeavor to warn the effect of alcohol on ONFH, but the exact relationship between dose and risk is not revealed yet. In our study, both current consumption and cumulative amount are positively associated with ONFH, showing a concave downward pattern.

Similar to the effects of corticosteroids, alcohol increases adipogenesis, which increases intraosseous pressure, causing a disruption of blood flow to the femoral head while inhibiting osteogenesis and angiogenesis [9]. In vitro studies showed that alcohol induces the differentiation of marrow stromal cells into adipocytes in a dose-dependent manner [26]. However, unlike the effect of steroids on stromal cells, alcohol-treated cells did not show increases in peroxisome proliferator–activated receptor-γ expression, which suggests that the exact molecular mechanisms may differ between these two important risk factors [27, 28].

Although steroid and alcohol are well-known risk factors, genetic predilections play important roles in the pathogenesis of ONFH. The proportion of patients with alcohol-related ONFH is higher in East Asian populations than Western. Aldehyde dehydrogenase 2 (ALDH2) is a key enzyme in alcohol metabolism that oxidizes acetaldehyde to non-toxic acetic acid. The enzyme is coded by the *ALDH2* gene, which is commonly polymorphic in East Asian populations, with a prevalence of the inactive allele variant ALDH2*2 [29]. Those with inactive ALDH2 are likely to experience acetaldehydemia, which could lead to lipodystrophy [30].

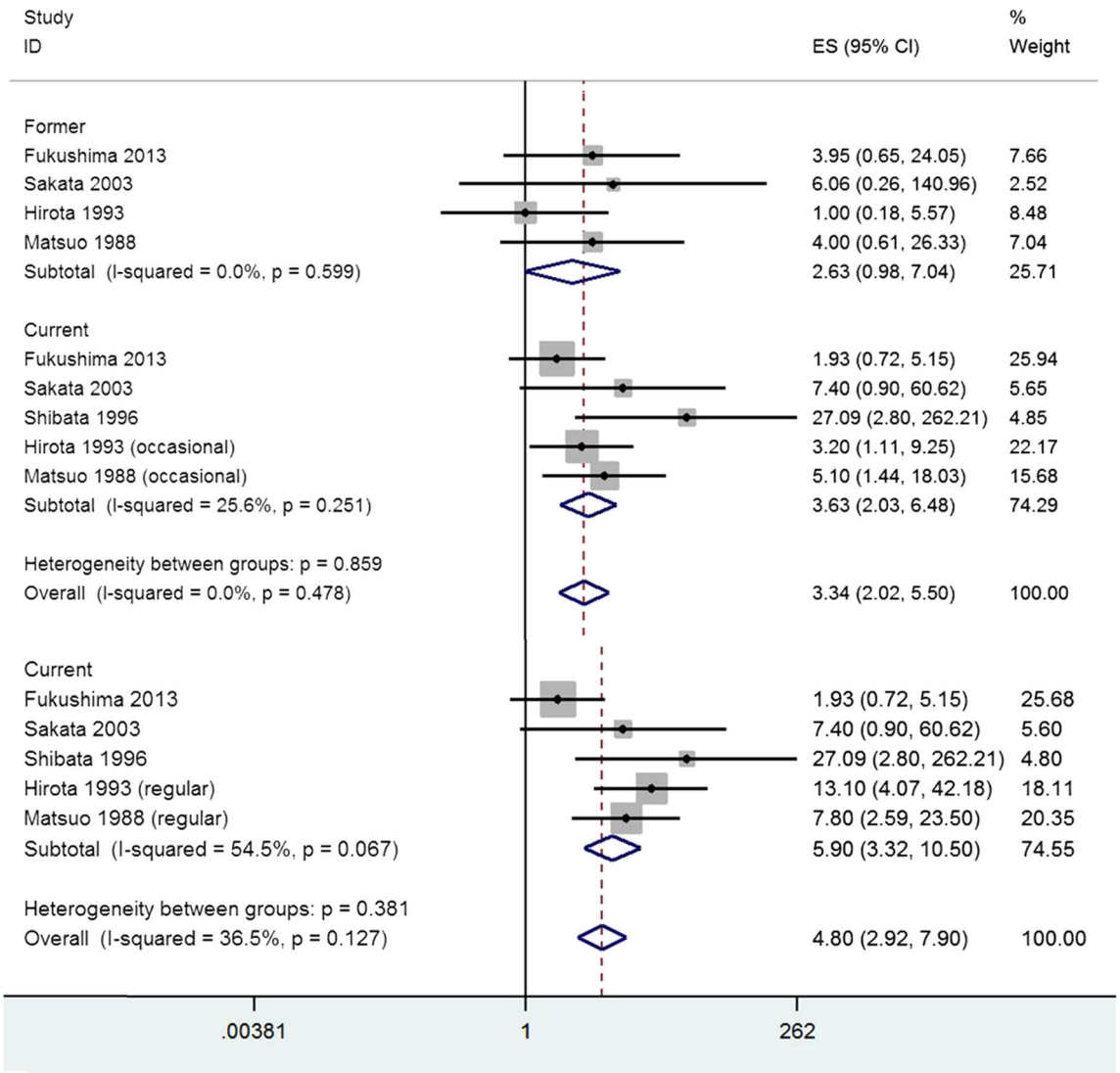

Fig. 2 Summary of the odds ratio of the association between the risk of osteonecrosis of the femoral head and drinking habit

Meanwhile, a protective effect of ALDH2 deficiency against alcohol addiction was reported because ALDH2 deficiency accumulates acetaldehyde, which induces an unpleasant feeling. The unpleasant feeling is a strong deterrent against heavy drinking and alcoholism [6].

In our study, regular (daily) drinkers had a higher risk for ONFH than occasional drinkers (OR, 5.90 versus 3.63). The disease involves an evolutionary process—if the duration of ischemia was temporary and shorter than the threshold for complete osteocytic death, the ischemic lesion does not progress to osteonecrosis [31]. A daily pattern of drinking seems to make fall a vicious cycle before fibrinolysis or reparative angiogenesis occurs [32]. Although the pattern measures have not been included in many alcohol-disease epidemiologic studies, not only volume of consumption but also patterns of drinking were found to be an additional influencing factor [33].

Table 2 Overall statistics for dose-response meta-analysis of ONFH and alcohol intake in linear model

Model	Variable	Odds ratio	95% CI		*p* for trend	*p* for non-linearlity	*p* for heterogenity
			Low	High			
Greenland and Longnecker	Average consumption	1.0035	1.0024	1.0047	<0.001	0.030	0.46
	Total consumption	1.00073	1.00051	1.0094	<0.001	0.044	0.001

Q homogeneity test

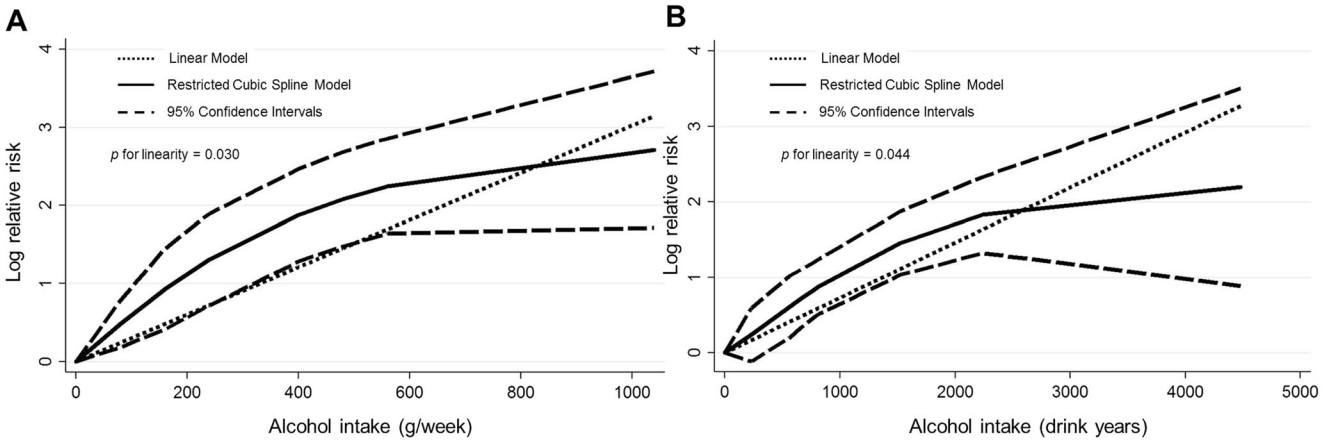

Fig. 3 Dose-response relations between alcohol intake and odds ratios for the osteonecrosis of the femoral head: **a** average and **b** total consumption. Data were modeled with fixed-effects restricted cubic spline models with four knots and using the Greenland and Longnecker method to estimate the covariances of multivariable-adjusted relative risks. *Lines with long dashes* represent the pointwise 95% confidence intervals for the fitted non-linear trend (*solid line*). *Lines with short dashes* represent the linear trend

Our dose-response meta-analysis shows an ever-increasing pattern, that is, the higher the alcohol intake, the higher risk of ONFH. The risk of heart disease or stroke between alcohol intake has shown a J-shaped correlation (i.e., initially decreases, then steadily increases) [34–36]. The decreased risk of cardiovascular disease in light alcohol intake is associated with increased high-density lipoprotein cholesterol levels [37] or decreased plasma fibrinogen levels and platelet aggregation in low alcohol concentration [38]. However, the pathogenesis of ONFH is more multifactorial [5]. Besides hemostatic abnormalities, decreased bony turnover [10], adipocyte hypertrophy [39], and higher bone marrow pressure [40] contribute to the development of ONFH. A different pattern of correlation between alcohol intake and ONFH might result from the variability of underlying risk factors.

Steroid use can be a critical confounding factor when evaluating the effect of alcohol intake for ONFH. In this analysis, four studies had included patients without history of systemic corticosteroid use as selection criteria [7, 8, 12, 23]. One study investigated the possible interactions between alcohol intake and oral corticosteroid use [11]. However, no combined effect of alcohol intake and steroid use was observed, and there was no further increase in the OR of patients who had both alcohol intake and steroid use [11]. The added effect of alcohol intake was too small to make any significant difference in the presence of the overwhelming effect of steroids in the development of ONFH.

Although the estimated proportion of drinkers among ONFH patients is high, the reverse is not. The incidence of ONFH has been reported between 0.3 and 5.0% among patients who were treated for alcoholism [41, 42]. The role of an underlying genetic predisposition in the development of ONFH in these patients has not been fully elucidated but could explain why some chronic users of alcohol do not acquire the disease.

To date, no universal definition regarding alcohol-induced ONFH was established. In some studies, alcohol overuse was defined as consumption of pure alcohol >400 mL/week [43] or >400 mL/week for at least 6 months [44]. However, the risk of ONFH increased with even lower alcohol consumption in our analysis. The critical dose of alcohol necessary to induce ONFH remains unknown, and the determination of the proper dosage of alcohol is needed, in view of public health. Based on our analysis, clinicians could assess the risk of ONFH according to alcohol intake through a more detailed approach.

The limitations of our study are as follows. First, all case-control studies used to determine the factors associated with ONFH came from a single country (Japan). However, the

Table 3 Odds ratios (OR) and 95% confidence intervals (CI) for categories of average intake of alcohol in non-linear model

Average intake (g/week)	OR in non-linear model	Cumulative intake (g drink-year)	OR in non-linear model
80	1.62 (1.20–2.19)	220	1.26 (0.89–1.77)
160	2.54 (1.52–4.25)	660	2.04 (1.39–3.01)
240	3.71 (2.05–6.67)	820	2.40 (1.67–3.46)
400	6.51 (3.60–11.78)	1620	4.27 (2.81–6.49)
560	9.46 (5.14–17.42)	2240	6.22 (3.76–10.29)
1040	15.06 (5.53–41.06)	4480	8.98 (2.43–33.27)

development of ONFH cannot be tested in randomized experiments, and a case-control study is particularly suited for healthcare interventions of low incidence disease, and the study design and questionnaires used to obtain a detailed history of each subject were very similar between studies. Second, the ONFH can be influenced by many variables other than steroid use, such as underlying diseases, the use of anticoagulants, flushing pattern, history of liver diseases, and occupation. Thus, we have only used adjusted ORs, which were adjusted from several potential confounders that were comparable between studies (Table 1). Third, the OR can vary depending on the type of alcohol (liquid, wine, or beer), but it could not be evaluated in our analysis. Fourth, the size of ONFH is an important factor, but the relationship between size and alcohol intake could not be evaluated and also there was a lack of effort to contact the original authors.

Based on our meta-analysis, current drinking habit significantly increased the risk of ONFH and the risk was markedly pronounced among those who regularly drink. Moreover, the dose-response meta-analysis suggests that the risk of ONFH increased by 35.3% for every 100 g/week and by 44.1% for every 500 g drink-years. Future studies should focus on the cut-off value of alcohol consumption to prevent alcohol-induced ONFH.

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Compliance with ethical standards

Disclosures None.

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