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Short Report

Lifetime alcohol intake and risk of non-Hodgkin lymphoma: findings from the Melbourne Collaborative Cohort Study

Running title: Alcohol intake and non-Hodgkin lymphoma

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Running title: Alcohol intake and risk of non-Hodgkin lymphoma

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Keywords: Cohort study; lifetime alcohol intake; non-Hodgkin lymphoma

Abbreviations: BL, Burkitt's lymphoma; CI, confidence interval; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HR, hazard ratio; ICD-O-3, International Classification of Diseases for Oncology; MCCS, Melbourne Collaborative Cohort Study; NHL, non-Hodgkin lymphoma; OR, odds ratio; VCR, Victorian Cancer Registry

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Novelty and Impact

Ethanol in alcoholic beverages is a carcinogen linked to several cancers but findings for non-Hodgkin lymphoma (NHL) from cohort studies thus far have been inconsistent. While most studies have used intake around the time of study enrolment, the present study captured alcohol intake from age 20 onwards. We did not observe a dose-dependent association between lifetime alcohol intake and NHL risk. HR for beer was 0.91 (95% CI: 0.83-1.00) per 10 g/day increment in intake.

Abstract

Cohort studies have reported inconsistent evidence regarding alcohol intake and risk of non-Hodgkin lymphoma (NHL), mostly based on alcohol intake assessed close to study enrolment. We examined this association using alcohol intake measured from age 20 onwards. We calculated usual alcohol intake for 10-year periods from age 20 using recalled frequency and quantity of beverage-specific consumption for 37,990 participants aged 40-69 years from the Melbourne Collaborative Cohort Study. Cox regression was performed to derive hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between alcohol intake (g/day) and NHL risk. After a mean follow-up of 19.3 years, 538 NHL cases were diagnosed. Approximately 80% of participants were either lifetime abstainers or consumed below 20 g of ethanol/day. All categories of lifetime alcohol intake were associated with about 20% lower incidence of NHL compared with lifetime abstention, but there was no evidence of a trend by amount consumed (HR = 0.97 per 10 g/day increment in intake, 95% CI: 0.92-1.03; *p* value=0.3). HRs for beer, wine and spirits were 0.91 (95% CI: 0.83-1.00; *p* value=0.05), 1.03 (95% CI: 0.94-1.12; *p* value=0.6) and 1.06 (95% CI: 0.83-1.37; *p* value=0.6), respectively, per 10 g/day increment in lifetime intake. There were no significant differences in associations between NHL subtypes. In this low-drinking cohort, we did not detect a dose-dependent association between lifetime alcohol intake and NHL risk.

Introduction

Ethanol in alcoholic beverages is a carcinogen causally-linked to cancers of the oral cavity, pharynx, larynx, esophagus, liver, colon, rectum and female breast.[1] In 2007, the World Health Organization Expert Committee concluded that, for non-Hodgkin lymphoma (NHL), there is 'evidence suggesting lack of carcinogenicity' for alcohol drinking,[1] largely based on evidence from a pooled analysis of case-control studies which reported an inverse association between alcohol drinking and NHL (odds ratio, OR = 0.83, 95% confidence interval, CI: 0.76-0.89 compared with non-drinking) but no decrease in risk with increasing alcohol intake.[2] A limited number of cohort studies, which only assessed alcohol intake close to study enrolment, have examined the association between alcohol intake and NHL since then and have reported either a lower risk[3-5] or no association.[6] Alcohol intake is likely to vary over time and intake over time is thought to correlate more closely with chronic outcomes.[7] Further, current abstainers may potentially include former drinkers who have quit drinking due to ill health (*sick quitters*); including them in the reference category could underestimate an association between alcohol intake and NHL. One cohort study that assessed alcohol intake at ages 18-22, 30–35 and during the year before study entry reported no association between drinking and B-cell NHL.[8]

In the present study, using lifetime alcohol intake for participants of a prospective cohort study, we have examined the association between NHL and alcohol intake, including analyses by subtypes of NHL and for beverage-specific intake.

Methods

Study population

The Melbourne Collaborative Cohort Study (MCCS) is a prospective cohort study of 41,514 people (99.2% aged 40-69 years; 58.9% women) recruited during 1990-94 from Melbourne.[9] We excluded participants aged <40 (n=194) and 70+ years (n=131) at baseline, with a confirmed diagnosis of cancer before baseline (n=1,882), missing or reporting implausibly high alcohol intake (n=381), or extreme values of total energy intake (<1st percentile and >99th percentile) (n=777), or missing data for covariates (n=159), leaving 37,990 for analysis (Figure 1).

Baseline data collection

Information on potential risk factors for NHL including age, sex, country of birth, education, smoking habits, physical activity and previous medical conditions was collected at enrolment into the study using a structured interview schedule. A 121-item food frequency questionnaire was used to collect dietary information.[10] Energy intake was estimated from food frequency data, not including energy from alcoholic beverages. Height and weight were measured according to a standard protocol. Baseline residential addresses were used to classify participants into quintiles of an area-based measure of socioeconomic status.[11]

Ascertainment of lifetime and current alcohol intakes

Participants were asked at baseline if they had ever drunk at least 12 alcoholic drinks in a year. Those who had ('non-lifetime abstainers') were then asked about their usual frequency of consumption and usual quantity consumed per drinking occasion for beer, wine and spirits separately during 10-year age periods commencing at age 20, up to the decade of their age at

enrolment into the study. Usual intake within each age period in grams per day for each beverage type was calculated by multiplying intake frequency by quantity and standard amount of alcohol per container using Australian food composition tables.[12] Alcohol intake for each age period in grams per day was calculated as the sum of intake from the three beverage types. Current alcohol intake in grams per day was obtained from intake for the age period encompassing study enrolment. Beverage-specific total intakes within age periods were summed to obtain their total lifetime intakes in grams. The usual lifetime alcohol intake in grams per day was derived by dividing the total lifetime intake by the total number of days within the age intervals up to study enrolment. Usual lifetime alcohol intake was categorized as follows: lifetime abstainers (reference category: participants who did not report any consumption of alcoholic beverages at each age decade during their lifetime, i.e. they had both lifetime and current alcohol consumption equal to 0 g/day), >0-19, 20-39 and ≥40 g/day.

Cohort follow-up and ascertainment of cases and deaths

Cases and vital status were ascertained through the Victorian Cancer Registry (VCR), the Victorian Registry of Births, Deaths and Marriages, the National Death Index and the Australian Cancer Database.

Classification of NHL and its subtypes

We used the classification of the World Health Organization[13-15] and guidelines from the InterLymph Pathology Working Group[16, 17] to define incident cases of NHL (defined as men and women with a first hematopathological diagnosis of NHL) and its main subtypes. The following 3rd Revision of the International Classification of Diseases for Oncology (ICD-O-3) codes for NHL were captured by VCR: 9590, 9591, 9597, 9670, 9671, 9673, 9675, 9679, 9680, 9684, 9689, 9690, 9691, 9695, 9698, 9699, 9700, 9701, 9702, 9708, 9709, 9714, 9718,

9719, 9727, 9823. The codes for subtypes were as follows: diffuse large B-cell lymphoma (DLBCL) = 9679, 9680, 9684; follicular lymphoma (FL) = 9690, 9691, 9695, 9698; chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) = 9670, 9823 (unclassified NHL codes given in Supplementary Table 1 according to cell line of origin). In-situ lesions diagnosed during follow-up were ignored.

Statistical analysis

Cox regression with age as the time axis[18] was performed to calculate HRs and 95% CIs for lifetime and current alcohol intake and beverage-specific intakes in relation to NHL. Follow-up began at baseline attendance and continued until diagnosis of first NHL, death, date of leaving Victoria or 31 August 2014, whichever came first. Dose-response relationships between lifetime alcohol intake (as a continuous variable) and NHL incidence were examined by comparing the log-likelihoods of the models that included alcohol as a linear term only and as restricted cubic splines (four knots).[19] We fitted interaction terms to test for differences in associations by sex and smoking status. To test for heterogeneity in the HRs across subtypes of NHL, Cox regression models were fitted using a competing risks method.[20] A causal diagram (directed acyclic graph) and existing evidence were used to determine confounding variables to be included in the multivariable-adjusted models. The variables in the final models included sex, education (primary school, some high/technical school, completed high/technical school, completed tertiary degree/diploma), socioeconomic status (quintiles ranging from most to least disadvantaged), smoking (never, former, current), body mass index (continuous) and energy from food (continuous), and all models were stratified by country of birth (Australia/New Zealand/United Kingdom, Italy/Greece). A secondary analysis for beer, wine and spirits was mutually adjusted for beverage-specific intakes. The model for current alcohol intake (continuous variable) included an additional

indicator variable to assess risk for former drinkers (participants with a current alcohol intake equal to 0 g/day but a lifetime alcohol intake of >0 g/day). Each model was examined for outliers and influential points. Tests based on Schoenfeld residuals showed no evidence that proportional hazard assumptions were violated. Nested models were compared using the likelihood ratio test. Wald tests from Cox regression models were used to assess linear trends for a 10 g/day increment in alcohol intake and for intake categories as a continuous measure. All statistical tests were two-sided, and *P*-values less than 0.05 were considered statistically significant. All statistical analyses were performed using Stata 14.1 (StataCorp, College Station, TX).

Results

By the end of follow-up (average 19.3 years), 538 incident cases of NHL were diagnosed, 1,420 participants had left Victoria and 7,747 had died. Among the NHL cases, 149 had DLBCL (27.7%), 130 had CLL/SLL (24.2%) and 99 had FL (18.4%). Out of all participants included in the study, 28.8% were lifetime abstainers and 50.7% drank below 20 g/day during lifetime. The mean lifetime alcohol intake for non-abstainers was 16.7 g/day (standard deviation = 18.5; range = 0.004-185.6). Characteristics of participants and NHL cases are given in Table 1.

A 10 g/day increment in lifetime alcohol intake was not associated with NHL incidence (HR = 0.97, 95% CI: 0.92-1.03; *p* for trend=0.3) (Table 2). This finding did not differ between men (HR = 0.97 per 10 g/day increment in intake, 95% CI: 0.91-1.04) and women (HR = 0.96 per 10 g/day increment in intake, 95% CI 0.84-1.11) (*p* for interaction = 0.9). We observed HRs of 0.91 (95% CI: 0.81-1.01), 1.00 (95% CI: 0.93-1.08) and 0.97 (95% CI: 0.86-1.11) for never, former and current smokers, respectively, per 10 g/day increment in lifetime intake (*p* for interaction = 0.3). When categories of lifetime alcohol intake were used in the model, HRs of approximately 0.80 were observed for all levels of intake compared with lifetime abstention (*p* for trend=0.1) (Table 2). The model with the cubic splines did not fit significantly better than a model with a single linear term for lifetime intake (*p* for difference between models=0.1). There was weak evidence of an inverse association with beer intake (HR = 0.91 per 10 g/day increment in intake, 95% CI: 0.83-1.00; *p* value=0.05) but not for other beverages (Table 2). The HRs for beer, wine and spirits did not change in a mutually adjusted model.

Findings for a 10 g/day increment in current alcohol or beer intake did not differ materially from results for lifetime intake [HR = 0.97 for alcohol, 95% CI: 0.92-1.02; *p* for

trend=0.2 and HR = 0.90 for beer, 95% CI: 0.81-1.00; *p* for trend=0.05]. The HR for former drinkers was 0.90 (95% CI: 0.67-1.21; *p* for trend=0.5).

We did not observe a significant difference in association by subtypes of NHL in relation to lifetime alcohol intake ($p_{homogeneity}$=0.7 using intake as a continuous variable) or according to the specific beverage type (Table 2). An inverse association observed for CLL/SLL using lifetime alcohol intake categories was not evident for a 10 g/day increment in intake (Table 2).

Discussion

NHL has not been classified as a cancer that is causally linked to ethanol in alcoholic beverages[1] and, in fact, meta-analyses of published studies have highlighted a potential protective effect for NHL.[2, 21] In the present study, evidence for a dose-dependent association between lifetime alcohol intake and the risk of NHL was not observed. There were no significant differences in association between NHL subtypes.

The study has several strengths including the availability of lifetime alcohol intake data (from age 20) which correlates better with a chronic process such as carcinogenesis.[7] Distinguishing lifetime abstainers and former drinkers helps minimize contamination of abstainers with *'sick'* quitters to some extent. Other strengths include the prospective nature of the study, the near complete follow-up of cases through the population cancer registry, the low rates of attrition, and the availability of a range of demographic, clinical and lifestyle data. Limitations include measurement error due to respondents having to summarize their frequency and quantity of alcoholic beverage intake for 10-year age intervals into single 'usual' values, the potential for present intake to influence recall of past intake and under-reporting of past intake, the influence of confounding by unmeasured factors such as family history of NHL (MCCS only collected information on family history of cancer in aggregate), and effects from any changes in alcohol intake after the baseline assessment. Cautious interpretation of findings is also warranted when analyses involve relatively small number of cases for NHL subtypes.

A pooled analysis of case-control studies that included 6,492 cases and 8,683 controls showed an inverse association between alcohol drinking and NHL [e.g. OR = 0.87 for ≥28 servings/week (approximately ≥40 g/day), 95% CI: 0.76-0.99, compared with non-drinking] but found no evidence of a consistent, dose-dependent decrease in NHL risk with increasing

alcohol intake (*p* for linear trend using intake categories=0.97).[2] In contrast to our results, the inverse association between drinking and NHL was not limited to a particular beverage type in the pooled analysis and was observed consistently for only Burkitt lymphoma (BL), DLBCL and FL, with the lowest risk observed for BL (OR = 0.51 for ever drinking, 95% CI: 0.33-0.77, compared with abstention).[2] No cases of BL were available for the present analysis. A more recent meta-analysis of 8 cohort studies reported a pooled relative risk of 0.96 (95% CI: 0.88–1.04) for drinking compared with abstention.[21] After combining these findings with those from 21 case-control studies, the meta-analysis reported negative associations for DLBCL and FL, but not for CLL/SLL, and for both men and women.[21] The National Institutes of Health-former American Association of Retired Persons Diet and Health Study, which reported a HR of 0.77 (95% CI: 0.59-1.00) for an alcohol intake of >28 drinks/week compared with abstention for overall NHL risk,[3] did not detect a discernible difference in risk according to main NHL subtypes or beverage type although statistically significant associations were limited to DLBCL and beer intake.[3] Similarly, the Million Women Study, which observed a dose-dependent negative association between alcohol intake and NHL (*p* for trend=0.001) among women in United Kingdom, did not detect a difference in association between wine drinkers and drinkers of other beverages.[4] A dose-dependent negative association between alcohol intake and NHL (*p* for trend=0.024) was also observed in a Japanese cohort of men and women, with a HR of 0.47 (95% CI: 0.25-0.89) for an intake of ≥300 g/week compared with occasional drinking.[5] The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, which did not detect an association between alcohol intake and NHL overall, reported a HR of 0.37 for DLBCL for an intake of ≥14 drinks/week (95% CI: 0.16-0.87) compared with <1 drink/week, although only 7 cases of DLBCL drank ≥14 drinks/week, along with weak evidence of an inverse relationship for beer intake (*p* for trend=0.077) but not for wine or liquor intakes.[6]

Findings from several cohort studies that have mostly assessed drinking close to baseline report a potential inverse association between alcohol intake and NHL risk although it has not been seen consistently whether a particular level of intake, beverage type or NHL subtype is involved. Authors of the California Teachers Study, which assessed long term alcohol intake, did not find evidence of an inverse association between alcohol intake and NHL risk but observed an increased risk of B-cell NHL for former drinkers.[8] They speculate that this may have been caused by cessation of drinking by those who were experiencing general ill-health more than 3 years prior to study enrolment but not due to intolerance or other preclinical symptoms of lymphoma.[8] We did not observe an association for former drinkers in the present study.

Possible biological mechanisms involved in a potential relationship between low-dose alcohol intake and NHL risk thus far remain largely speculative. Immunomodulatory effects of alcohol vary according to intake level: heavy drinking may impair immune function whereas light-to-moderate intake may improve it.[22] On the other hand, antioxidants such as flavonoids in beer or resveratrol in wine and enhanced insulin sensitivity due to alcohol may also have a role in a potential association.[23] Another phenolic compound found in beer is xanthohumol which has shown cancer preventive potential.[24] Moreover, low-dose chronic exposure to ethanol has also been shown to inhibit mammalian target of rapamycin (mTOR) phosphorylation and subsequent signaling events leading to a decrease in the availability of proteins associated with the translation initiation complex and a repression of global cap-dependent synthesis in lymphoma cell lines, and to inhibit lymphoma tumor formation in an *in vivo* xenograft mouse model.[25]

In summary, in this cohort where over three-quarters of participants were either lifetime abstainers or consumed below 20 g of ethanol/day, we did not detect a dose-dependent association between lifetime alcohol intake and NHL risk. Future studies are needed to

establish whether low levels of drinking or beer intake has an inverse association with NHL risk.

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Ethics

The study protocol was approved by the Cancer Council Victoria's Human Research Ethics Committee. Participants gave written informed consent to participate and for investigators to obtain access to their medical records.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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Table 1. Baseline characteristics of participants and non-Hodgkin lymphoma cases in the Melbourne Collaborative Cohort Study

	All participants (n=37,990)				NHL cases (n=538)
	Lifetime alcohol intake				
	Abstention (n=10,953)	>0-19 g/day (n=19,247)	20-39 g/day (n=5,008)	≥40 g/day (n=2,782)	
Age at baseline, mean (SD), years	56.7 (8.1)	54.6 (8.7)	54.2 (8.7)	55.4 (8.6)	58.8 (8.0)
Sex, n (%)					
Male	2,209 (20.2)	7,261 (37.7)	3,628 (72.4)	2,484 (89.3)	242 (45.0)
Female	8,744 (79.8)	11,986 (62.3)	1,380 (27.6)	298 (10.7)	296 (55.0)
Country of birth, n (%)					
Australia/New Zealand/UK	7,133 (65.1)	16,027 (83.3)	3,802 (75.9)	1,906 (68.5)	414 (76.9)
Italy/Greece	3,820 (34.9)	3,220 (16.7)	1,206 (24.1)	876 (31.5)	124 (23.1)
Education, n (%)					
Primary school	3,391 (31.0)	2,449 (12.7)	840 (16.8)	665 (23.9)	110 (20.4)
Some high/technical school	4,556 (41.6)	7,354 (38.2)	1,537 (30.7)	969 (34.8)	214 (39.8)
Completed high/technical school	1,736 (15.8)	4,330 (22.5)	1,155 (23.0)	630 (22.7)	116 (21.6)
Completed tertiary degree/diploma	1,270 (11.6)	5,114 (26.6)	1,476 (29.5)	518 (18.6)	98 (18.2)
Socioeconomic status, n (%)					
Quintile I (most disadvantaged)	1,961 (17.9)	2,424 (12.6)	617 (12.3)	510 (18.3)	87 (16.2)
Quintile II	2,739 (25.0)	3,541 (18.4)	964 (19.3)	641 (23.0)	127 (23.6)
Quintile III	2,194 (20.0)	3,440 (17.9)	868 (17.3)	505 (18.2)	97 (18.0)
Quintile IV	2,067 (18.9)	4,182 (21.7)	1,045 (20.9)	524 (18.8)	93 (17.3)
Quintile V (least disadvantaged)	1,992 (18.2)	5,660 (29.4)	1,514 (30.2)	602 (21.7)	134 (24.9)
Smoking, n (%)					
Never	8,506 (77.7)	11,062 (57.5)	1,762 (35.2)	690 (24.8)	311 (57.8)
Former	1,543 (14.1)	6,266 (32.5)	2,480 (49.5)	1,489 (53.5)	175 (32.5)
Current	904 (8.2)	1,919 (10.0)	766 (15.3)	603 (21.7)	52 (9.7)
Lifetime alcohol intake (g/day), n (%)					
Abstention	-	-	-	-	181 (33.6)
>0-19	-	-	-	-	250 (46.5)
20-39	-	-	-	-	68 (12.6)
≥40	-	-	-	-	39 (7.3)
Energy intake from food, mean (SD), kJ/day	8,620 (3,103)	8,780 (2,970)	9,008 (3,078)	9,003 (3,197)	8,833 (3,129)
Body mass index, mean (SD), kg/m^2	27.7 (5.0)	26.3 (4.2)	26.9 (3.8)	27.8 (3.9)	27.0 (4.6)

NHL, non-Hodgkin lymphoma. SD, standard deviation.

Table 2. Hazard ratios (HR) and 95% confidence intervals (CI) for non-Hodgkin lymphoma and main subtypes according to lifetime alcohol intake for participants in the Melbourne Collaborative Cohort Study

	NHL			NHL subtypes								$p_{heterogeneity}$[b]
				DLBCL		FL		CLL/SLL		Other		
	Cases (%)	HR (95% CI)	*p* for trend[a]	Cases (%)	HR (95% CI)	Cases (%)	HR (95% CI)	Cases (%)	HR (95% CI)	Cases (%)	HR (95% CI)	
Per 10 g/day increment	538 (100.0)	0.97 (0.92-1.03)	0.3	149 (100.0)	0.99 (0.90-1.09)	99 (100.0)	0.93 (0.82-1.07)	130 (100.0)	0.94 (0.83-1.05)	160 (100.0)	1.00 (0.91-1.10)	0.7
Intake categories (g/day)			0.1									
Abstention	181 (33.6)	1		52 (34.9)	1	35 (35.4)	1	46 (35.4)	1	48 (30.0)	1	
>0-19	250 (46.5)	0.81 (0.66-0.99)		62 (41.6)	0.70 (0.47-1.04)	45 (45.4)	0.74 (0.46-1.18)	61 (46.9)	0.70 (0.47-1.06)	82 (51.2)	1.07 (0.73-1.57)	
20-39 for NHL / ≥20 for NHL subtypes	68 (12.6)	0.79 (0.58-1.08)		35 (23.5)	0.95 (0.57-1.58)	19 (19.2)	0.98 (0.51-1.88)	23 (17.7)	0.48 (0.27-0.84)	30 (18.8)	0.90 (0.53-1.52)	
≥40	39 (7.3)	0.79 (0.54-1.15)		-	-	-	-	-	-	-	-	
Beverage-specific intake												
Per 10 g/day increment												
Beer	538 (100.0)	0.91 (0.83-1.00)	0.05	149 (100.0)	0.93 (0.79-1.08)	99 (100.0)	0.91 (0.75-1.11)	130 (100.0)	0.92 (0.78-1.09)	160 (100.0)	0.88 (0.75-1.05)	0.9
Wine	538 (100.0)	1.03 (0.94-1.12)	0.6	149 (100.0)	1.07 (0.93-1.24)	99 (100.0)	0.94 (0.75-1.17)	130 (100.0)	0.89 (0.72-1.09)	160 (100.0)	1.11 (0.98-1.27)	0.2
Spirits	538 (100.0)	1.06 (0.83-1.37)	0.6	149 (100.0)	0.93 (0.51-1.70)	99 (100.0)	0.83 (0.36-1.92)	130 (100.0)	1.19 (0.84-1.68)	160 (100.0)	1.13 (0.77-1.65)	0.8

Adjusted for sex, education, socioeconomic status, smoking, body mass index, energy intake from food, stratified by country of birth, and age as the time variable in Cox model.

[a]Wald test from Cox regression models assessing linear trends for a 10 g/day increment in alcohol intake and for intake categories as a continuous measure.

[b]Test of homogeneity comparing associations for NHL subtypes.

DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; NHL, non-Hodgkin lymphoma.

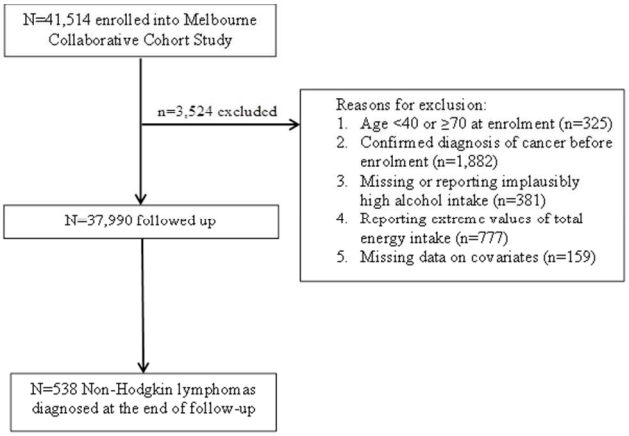

Figure 1. Flow diagram showing selection of participants.

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