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ARTICLE

Eighteen-year alcohol consumption trajectories and their association with risk of type 2 diabetes and its related factors: the China Health and Nutrition Survey

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Abstract

Aims/hypothesis Alcohol consumption levels frequently fluctuate over the life course, but studies examining the association between alcohol consumption trajectories and type 2 diabetes are limited. This study aims to investigate the association of alcohol consumption trajectories with the risk of type 2 diabetes and its related factors.

Methods Weighted longitudinal data were obtained for 12,186 adults who completed a questionnaire about alcohol consumption and diabetes status as part of the China Health and Nutrition Survey (1993–2011). Participants were designated into subgroups based on alcohol consumption trajectory, and subgroup analyses included 5436 individuals who were tested for specified diabetes-related factors. Light alcohol consumption was defined as fewer than seven standard drinks per week; moderate as 7–21 drinks per week; and heavy as more than 21 drinks per week. Latent class trajectory modelling was used to identify different alcohol consumption trajectories by sex. Multivariate Cox regression models and general linear regression models were used to assess association of trajectories with type 2 diabetes and its related factors.

Results Compared with stable abstainers (individuals who never drank alcohol), two trajectories in men showing reduction to moderate or light levels after heavy alcohol consumption during early adulthood were significantly associated with increased risk of type 2 diabetes (HR 1.66 [95% CI 1.18, 2.33]; HR 1.93 [95% CI 1.01, 3.70]), while no significant association between trajectories and risk of type 2 diabetes was observed in women ($p_{\text{for trend}} = 0.404$). Triacylglycerol, HDL-cholesterol (HDL-C), uric acid and high sensitivity C-reactive protein were significantly higher in these two trajectories than other trajectories in men (all $p < 0.05$), while only HDL-C showed significant increasing trends in women. Trajectories showing light–stable, or increase to moderate, levels were not associated with reduced risk of type 2 diabetes.

Conclusions This study indicated that heavy alcohol consumption in early adulthood is significantly associated with increased risk of type 2 diabetes and higher levels of its biomarkers throughout adulthood in men. Gradually reducing alcohol consumption to moderate levels may not make a difference, which demonstrates the importance of alcohol intervention strategies in early adulthood. Although association between alcohol consumption and increased HDL-C levels has been observed, the results of this study did not support the hypothesis regarding the protective effect of moderate alcohol consumption on risk of type 2 diabetes in the Asian population.

Data availability Data from China Health and Nutrition Survey was used in this study, which can be downloaded at www.cpc.unc.edu/projects/china.

Keywords Alcohol · Risk factors · Trajectory · Type 2 diabetes mellitus

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Research in context

What is already known about this subject?

- An association between heavy alcohol consumption and increased risk of type 2 diabetes has been reported; however, the relationship between moderate alcohol consumption and reduced risk of type 2 diabetes remains controversial
- Alcohol consumption levels fluctuate over time with disparate trajectories over the adult life course
- Recent studies have focused efforts on establishing long-term trajectories of alcohol consumption, and demonstrate that different trajectories have distinct patterns in relation to the metabolic syndrome and cardiovascular disease throughout the adult life course

What is the key question?

- Is the trajectory of alcohol consumption throughout adulthood associated with risk of type 2 diabetes, and if so, how?

What are the new findings?

- Heavy alcohol consumption in early adulthood is significantly associated with an increased risk of type 2 diabetes and higher levels of its biomarkers throughout adulthood in men, and gradually reducing alcohol consumption to moderate levels may not make a difference
- Although an association between alcohol consumption and increased HDL-C levels has been observed, the results of this study did not support the hypothesis regarding the protective effect of moderate alcohol consumption on risk of type 2 diabetes or its biomarkers in men and women

How might this impact on clinical practice in the foreseeable future?

- This study emphasises the importance of alcohol intervention strategies in early adulthood for the prevention of type 2 diabetes and highlights the need for additional research to evaluate the net balance of health impacts from light or moderate alcohol consumption

Abbreviations

CHNS	China Health and Nutrition Survey
HDL-C	HDL-cholesterol
hs-CRP	High sensitivity C-reactive protein
LCTM	Latent class trajectory modelling
MET	Metabolic equivalent
PAL	Physical activity level

Introduction

Alcohol consumption is one of the biggest public health challenges facing modern society and is ranked as the world's third largest risk factor for disease burden [1]. Although adverse health effects of heavy alcohol consumption on type 2 diabetes have been abundantly documented, protective health effects of moderate alcohol consumption still remain controversial [2–4].

Previous observational studies have used non-drinkers as the unexposed reference category, but non-drinkers are by no means homogeneous, encompassing both never and former drinkers [5, 6]. This may therefore lead to misestimation of the risk of type 2 diabetes among moderate alcohol consumers as former drinkers are likely to be in poorer health and have higher rates of mortality than moderate drinkers and abstainers [7]. Further, these studies frequently adopted single baseline measures of alcohol intake, ignoring variation of alcohol consumption over time [8–11]. Recent studies have focused efforts on establishing long-term trajectories of alcohol consumption, and demonstrated that different trajectories have distinct patterns in relation to the metabolic syndrome, cardiovascular disease and its intermediate markers [12–16]. A French cohort study in women using trajectory analysis demonstrated a potential beneficial cumulative effect of moderate wine consumption on type 2 diabetes [17]. However, an association between alcohol consumption trajectory throughout the adult life course and type 2 diabetes has not yet been reported in the Asian population. Establishing this association may increase the knowledge base, and therefore the understanding, surrounding the alcohol–diabetes relationship, and provide evidence-based lifestyle recommendations to assist in the prevention of type 2 diabetes.

With fast economic development and a parallel rise in average income level, alcohol consumption in China is increasing faster than in other parts of the world [18], presenting a unique model for drinking-pattern change, and providing sufficient variation in the form of alcohol consumption trajectories to investigate a potential differential association with type

2 diabetes. Therefore, using latent class trajectory modelling (LCTM) to characterise alcohol consumption trajectories over 18 years with weighted longitudinal data from China, this study aims to examine the association of alcohol consumption trajectories with risk of type 2 diabetes and its biomarkers.

Methods

The China Health and Nutrition Survey The China Health and Nutrition Survey (CHNS) is a nationwide survey designed to investigate health and nutritional status in Chinese populations, and to reflect national age–sex–education profiles [19–21]. The study sample was drawn from 228 communities from nine diverse provinces in China and involved eight surveys undertaken between 1991 and 2011 [22]. By 2011, these provinces in the CHNS represented 47% of the Chinese population based on the 2010 census. Each survey maintained the desired range of economic and demographic variables; however, it is complex to calculate response rates and attrition in each survey, because the participants who were lost to follow-up in one survey year may have participated in a later survey, and new participants have been recruited as replenishment samples since 1997 [19]. The survey protocols, instruments, and the process for obtaining informed consent were approved by the Institutional Review Committees of the University of North Carolina at Chapel Hill, NC, USA, and the China National Institute of Nutrition and Food Safety at the Chinese Center for Disease Control and Prevention, Beijing, China. All participants provided written informed consent prior to the surveys.

Study population As data on quantity of alcohol consumption were not collected in the 1991 surveys, the present study sample included adults aged over 18 years in seven surveys undertaken between 1993 and 2011. By the end of 2011, there were 35,703 participants in the CHNS. The following individuals were excluded: 13,133 participants who were less than 18 years old in the first survey; 111 participants who were pregnant; 7982 who participated in only one survey; 1204 participants where information on type 2 diabetes was not provided; and 1087 who participated in their first survey before 1991 with only one follow-up visit. The number of visits including alcohol consumption measures ranged from two to seven measurement surveys (two visits, $n = 2417$; three visits, $n = 1547$; four visits, $n = 1639$; five visits, $n = 1423$; six visits, $n = 1817$; seven visits, $n = 3343$; median = 4.7 visits; total $N =$ 12,186 participants across 57,449 observations).

Questionnaire survey Detailed in-person interviews were administered by trained personnel using a structured questionnaire to collect information on demographic characteristics, dietary habits, lifestyle, physical condition and anthropometric characteristics. Dietary assessment was based on a combination of three consecutive days of detailed food consumption information. The food consumption information was transformed to food groups based on nutrient profiles designed for the 2002 China National Nutrition Survey [23]. Current smoking was defined as a positive answer to the question 'do you still smoke cigarettes or a pipe?', and alcohol consumption was measured using the question, 'During the past year, what was your consumption (frequency and quantity) of beer, liquor and wine?' Based on the US National Institute on Alcohol Abuse and Alcoholism guidelines, a standard drink for the purposes of the present study contains about 14 g of alcohol [24]. Light alcohol consumption was defined as <7 standard drinks per week; moderate as 7–21 standard drinks per week; and heavy as >21 drinks per week [25]. Physical activity level (PAL) was defined as the combination of occupational activity and home activity, as previously reported [26]. The total metabolic equivalents (METs) of physical activity were calculated as MET-h per week. Urbanicity was defined using a multidimensional 12-component urbanisation index capturing community-level physical, social, cultural and economic environments [27].

Anthropometric measurements and biochemical analyses At each survey, height was measured without shoes to the nearest 0.2 cm using a portable SECA stadiometer (SECA, Hamburg, Germany). Weight was measured without shoes and in light clothing to the nearest 0.1 kg using a calibrated beam scale. In the 2009 survey, a 12 ml blood sample was collected after overnight fasting. Serum glucose was tested using the glucose oxidase method (Randox, Crumlin, UK). Whole blood HbA_{1c} HPLC analysis (model HLC-723G7; Tosoh, Tokyo, Japan) generated continuous outcomes for HbA_{1c}. Triacylglycerol was measured using glycerol-phosphate oxidase (GPO-PAP) method (Kyowa, Tokyo, Japan). HDL-cholesterol (HDL-C) was measured using enzymatic methods (Kyowa). High sensitivity C-reactive protein (hs-CRP) was measured using the immunoturbidimetric method (Denka Seiken, Tokyo, Japan), and uric acid was measured using enzymatic Colorimetric method (Randox).

Outcome measures Type 2 diabetes was identified by self-reports of a history of diabetes diagnosis, and/or fasting blood glucose ≥7.0 mmol/l, and/or HbA_{1c} ≥40 mmol/mol (6.5%), and/or receiving treatment for diabetes. Detailed information on treatment for diabetes included six sections: (1) special diet; (2) weight control; (3) oral medication; (4) insulin injection; (5) Chinese traditional medicine; (6) home remedies. Data for incidence of self-reported type 2 diabetes were first collected in 1997, and subsequently in 2000, 2004, 2006, 2009 and 2011. Fasting blood glucose and HbA_{1c} were also used to identify incident diabetes cases in the 2009 survey. Total incident type 2 diabetes cases were 767.

Statistical analysis All statistical analyses were performed using R 3.4.3 (www.r-project.org/). A two-sided p value <0.05 was considered statistically significant. Alcohol consumption was normalised by Tukey transformation to improve the normality of the distribution.

LCTM was used to identify alcohol consumption trajectories using the R package lcmm with a censored normal model [28]. Participants were grouped by sex—six classes of men and four of women—and changes in alcohol consumption were modelled by these groups, with a variety of different order polynomials. We used statistically rigorous criteria to determine best fit: (1) using lowest Bayesian information criterion; and (2) inclusion of at least 2% of the sample population within each trajectory class. Once trajectories of alcohol consumption were determined, a nominal categorical variable was created to describe the trajectory classes of each participant, which was then used in Cox multivariate regression models.

Cox multivariate regression models, with age as the time scale, were used to estimate associations between trajectories of alcohol consumption and risk of type 2 diabetes. HRs and 95% CI were calculated by sex. Time at entry was age at the beginning of follow-up (in 1993), and exit time was age when participants were diagnosed with diabetes, were lost to follow-up, or were censored at the end of the follow-up period, whichever came first. Models were adjusted for age, education level, province, rural or city status, smoking status, physical activity, energy intake including levels of fat, fruit and vegetable consumption, BMI, history of cardiovascular disease and urbanicity index. When data for covariates were missing for fewer than 5% of participants, we replaced the missing values with the median values.

After participants were classed into different alcohol consumption trajectories, subgroup analysis was performed in 5436 participants who had a blood sample taken in 2009 by using the alcohol consumption trajectory classes modelled in the total sample. Generalised linear models were performed to test differences in baseline characteristics of continuous variables and biomarkers measured in 2009 across trajectories of alcohol consumption by sex with adjustment for the above covariates. χ^2 test was used to measure differences in baseline characteristics of dichotomous variables.

After a significant association between alcohol consumption trajectories and risk of type 2 diabetes was established, and differences in biomarkers across different classes of trajectories were confirmed, a mediation analysis model was constructed to examine whether association between alcohol consumption trajectories and risk of type 2 diabetes was mediated by these biomarkers with adjustment for the above covariates. Mediation analysis was performed using R package lavaan [29].

Four sensitivity analyses were conducted in this study. The first analysis was performed to obtain 95% percentile bootstrap CIs of HRs in view of the small sample size of some trajectories. The second was to test whether trajectory analysis could provide more information than analyses of single time point or cumulative alcohol consumption. The third analysis was performed to examine whether alcohol consumption trajectory could be influenced by the diagnosis of type 2 diabetes prior to attending the study visit. In total, 323 participants who had been diagnosed with type 2 diabetes before 2009 were excluded, and alcohol consumption trajectories using data from 1993 to 2006 were modelled. After new trajectories were identified, logistic regression models were used to examine association between new trajectories and individuals with type 2 diabetes diagnosed in 2009 and 2011. The fourth analysis used joint longitudinal latent class model with time-to-event outcome to identify trajectories and then automatically link the latent classes with the outcome by survival rate curve [28].

Results

Participant characteristics Characteristics of the study population from the CHNS by survey years are presented in electronic supplementary material (ESM) Table 1. BMI, total dietary fat intake and prevalence of hypertension showed increasing trends across survey years, whereas smoking rate, PAL and total energy intake showed decreasing trends.

Trajectories of alcohol consumption over the adult life course Trajectories of alcohol consumption in men and women are shown in Fig. 1a,b. The first trajectory, labelled 'T0: Abstainers', corresponds to men who never drank alcohol throughout adulthood. The second trajectory, 'T1: Light–stable', corresponds to men who had stable light levels throughout adulthood. The third trajectory, 'T2: Light to moderate', corresponds to men who increased from light to moderate levels throughout adulthood. The fourth trajectory, 'T3: moderate to heavy then decline', corresponds to men who increased to heavy consumption in early adulthood then showed a gradual decline to moderate levels with age. The fifth trajectory, 'T4: heavy and persistent decline', corresponds to men with heavy consumption in early adulthood and whose levels persistently declined with age. The trajectories from T0 to T4 were estimated to include 22.3%, 38.5%, 20.9%, 15.8% and 2.4% of male participants, respectively. For women, the first trajectory, labelled 'T0: Abstainers', corresponds to women who never drank alcohol throughout adulthood. The second trajectory, 'T1: Light–stable', corresponds to women who had stable light levels throughout adulthood. The third trajectory, 'T2: light to moderate then decline', corresponds to women who showed an increase from light to moderate levels in early adulthood and then a decline with age. The trajectories from T0 to T2 were estimated to include 81.0%, 16.6% and 2.3% of female participants, respectively.

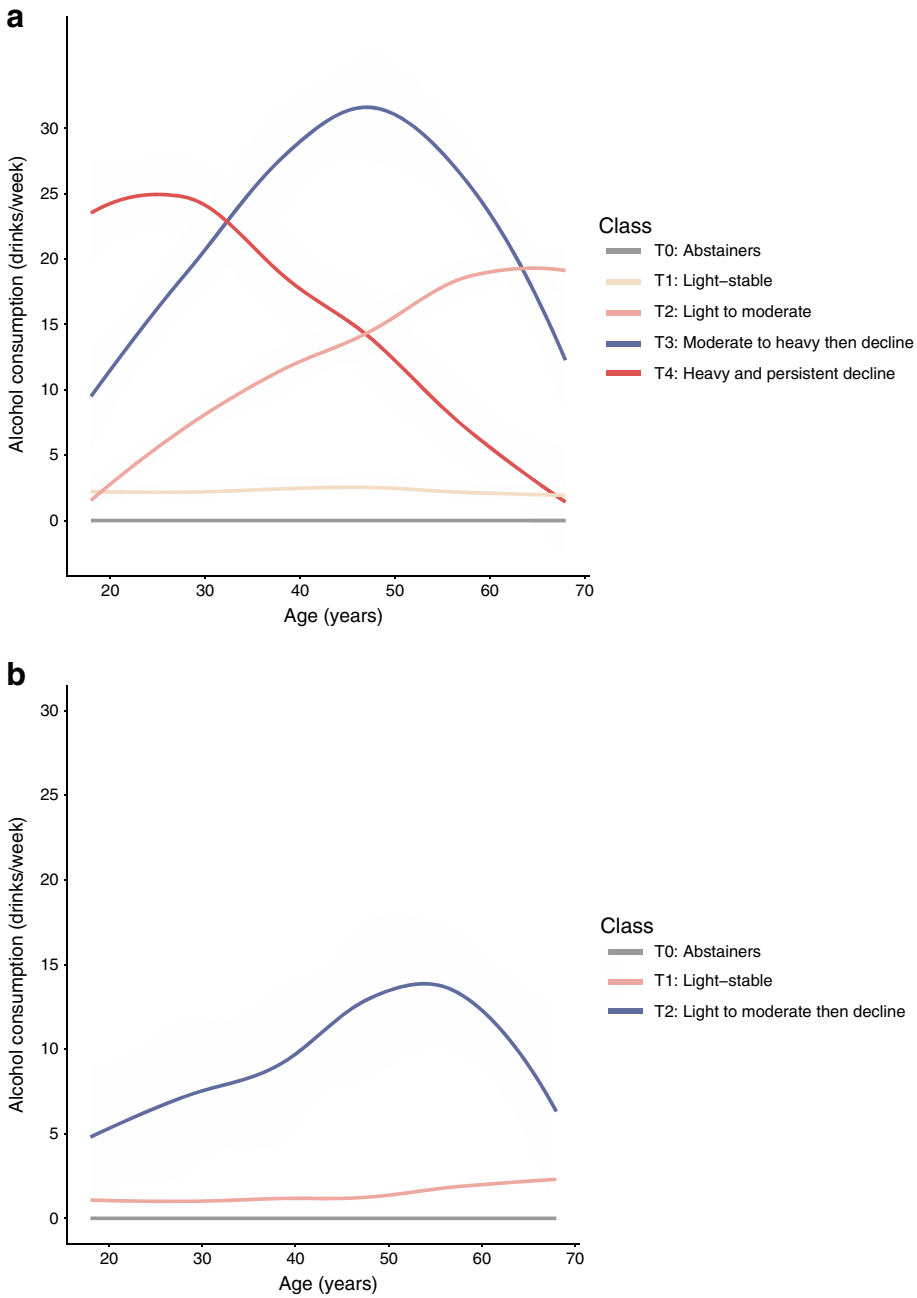

Fig. 1 Trajectories of alcohol consumption in men (**a**; *n*=5617) and women (**b**; *n*=6569) from the CHNS by LCTM

Baseline characteristics by different trajectories of alcohol consumption Table 1 presents the baseline characteristics of study variables by different trajectories of alcohol consumption in men and women. Men in the trajectories labelled 'T3' and 'T4' were younger than in the other three trajectories, and women in the trajectories labelled 'T1' were older than in the other two trajectories. Baseline BMI did not differ significantly across trajectories of alcohol consumption ($p = 0.121$ in men and 0.493 in women), whereas age, total energy intake, fat intake, systolic BP, baseline alcohol consumption and smoking rate varied significantly across different trajectories of alcohol consumption in both men and women (all p for the difference <0.05).

Association between alcohol consumption trajectories and type 2 diabetes Association between alcohol consumption trajectories and risk of type 2 diabetes by sex are presented in Table 2. For men, compared with abstainers, trajectories labelled 'T3' and 'T4' were significantly associated with increased risk of type 2 diabetes (HR 1.66 [95% CI 1.18, 2.33] for T3; HR 1.93 [95% CI 1.01, 3.70] for T4) with adjustment for covariates. For women, compared with abstainers, no association was observed between alcohol consumption trajectories and risk of type 2 diabetes (HR 0.93 [95% CI 0.67, 1.30] for T1; HR 0.40 [95% CI 0.10, 1.60] for T2).

Table 1 Baseline characteristics of study variables by different trajectories of alcohol consumption in men and women

Baseline variable	Trajectories in men						Trajectories in women			
	T0 (*n*=1255)	T1 (*n*=2162)	T2 (*n*=1175)	T3 (*n*=889)	T4 (*n*=136)	*p* value	T0 (*n*=5323)	T1 (*n*=1093)	T2 (*n*=153)	*p* value
Age (years)	37.7 (18.1)	36.7 (14.6)	40.0 (13.1)	33.1 (10.8)	29.1 (11.4)	<0.001	34.7 (16.6)	38.9 (15.0)	35.2 (11.3)	<0.001
BMI (kg/m^2)	22.5 (3.2)	22.3 (3.0)	22.3 (3.0)	22.4 (2.8)	22.1 (2.6)	0.121	22.4 (3.2)	22.4 (3.2)	22.5 (3.0)	0.493
PAL (MET-h /week)	196 (287)	229 (324)	269 (421)	273 (417)	257 (413)	<0.001	253 (371)	256 (401)	278 (447)	0.437
Energy intake (kJ/day)	9966 (2941)	10,920 (3807)	11,204 (3138)	11,447 (3527)	11,330 (3020)	<0.001	9100 (3067)	9401 (2589)	10,229 (4883)	<0.001
Fat intake (g/day)	70.2 (36.0)	72.3 (48.8)	72.8 (39.1)	74.5 (41.1)	67.4 (37.7)	<0.001	64.2 (51.0)	61.7 (36.1)	56.1 (38.2)	0.008
Vegetable intake (g/day)	210 (105)	227 (99)	219 (97)	223 (88)	230 (99)	0.004	198 (91)	215 (96)	230 (91)	<0.001
Fruit intake (g/day)	23.8 (48.8)	16.5 (33.7)	20.9 (39.5)	15.3 (31.9)	13.5 (28.6)	<0.001	24.9 (47.2)	27.1 (44.1)	19.9 (29.6)	0.136
SBP (mmHg)	119.4 (15.9)	117.6 (14.4)	118.0 (15.6)	119.4(13.0)	119.8 (15.8)	<0.001	114.6 (17.3)	112.6 (15.7)	109.2 (13.6)	<0.001
DBP (mmHg)	78.3 (10.1)	77.1 (9.3)	77.5 (10.5)	77.3 (9.8)	75.2 (8.2)	0.192	74.6 (10.5)	73.8 (10.5)	72.5 (8.5)	<0.001
Baseline alcohol consumption (drinks/week)	0	1.6 (4.6)	4.7 (10.6)	9.4 (19.8)	12.7 (20.8)	<0.001	0	1.6 (2.9)	8.1 (12.0)	<0.001
Accumulation alcohol consumption (drinks/week)	0	2.4 (2.3)	9.6 (8.4)	11.7 (5.8)	17.1 (13.1)	<0.001	0	1.0 (1.4)	6.6 (4.4)	<0.001
Wine (drinks/week)	0	0.1 (0.8)	0.2 (1.6)	0.2 (1.1)	0.1 (1.0)	<0.001	0	0.5 (0.3)	0.1 (0.5)	<0.001
Beer (drinks/week)	0	0.3 (1.3)	0.3 (1.9)	0.5 (2.5)	2.3 (9.4)	<0.001	0	0.1 (0.4)	0.1 (0.6)	<0.001
Liquor (drinks/week)	0	1.3 (3.9)	4.2 (10.4)	8.7 (19.1)	10.3 (16.9)	<0.001	0	1.0 (1.7)	7.8 (6.1)	<0.001
Living in city [(*n*, (%)]	475 (37.8)	842 (38.9)	385 (32.8)	288 (32.4)	47 (34.6)	<0.001	1773 (33.4)	511 (46.8)	66 (43.1)	<0.001
Urban index	63.4 (18.7)	59.7 (17.8)	61.0 (18.7)	59.1 (16.6)	57.6 (16.8)	<0.001	60.4 (18.2)	62.2 (18.0)	58.5 (16.4)	<0.001
High school education [(*n*, (%)]	453 (36.1)	322 (27.4)	660 (30.5)	262 (29.5)	31 (22.8)	<0.001	1276 (24.0)	286 (26.2)	37 (24.2)	0.305
Smoking [(*n*, (%)]	368 (29.3)	997 (46.1)	678 (57.7)	527 (59.3)	91 (66.9)	<0.001	143 (2.7)	81 (7.4)	18 (11.8)	<0.001
Hypertension [(*n*, (%)]	183 (14.6)	234 (10.8)	150 (12.8)	88 (9.9)	5.0 (3.7)	0.680	514 (9.7)	93 (8.5)	5 (3.3)	0.063

Continuous data are expressed as mean (SD); where shown, data are *n* (%)

PAL included two aspects: occupational activity and home activity

Hypertension was defined as self-reports of a history of hypertension diagnosis, and/or SBP (systolic BP) ≥140 mmHg, and/or DBP (diastolic BP) ≥90 mmHg, and/or receiving treatment for hypertension

Generalised linear models adjusted for age and χ^2 test were used to probe for differences in continuous variables and dichotomous variables

Table 2 Association between alcohol consumption trajectories and risk of type 2 diabetes by sex

Trajectories	Case/n[a]	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Model 4 HR (95% CI)	Model 5 HR (95% CI)
Men						
Abstainer (T0)	99/1255	1	1	1	1	1
Light–stable (T1)	171/2162	1.24 (0.94, 1.64)	1.34 (1.01, 1.80)	1.26 (0.93, 1.72)	1.22 (0.89, 1.66)	1.25 (0.91, 1.70)
Light to moderate (T2)	104/1175	1.17 (0.91, 1.51)	1.20 (0.92, 1.55)	1.08 (0.82, 1.43)	1.04 (0.78, 1.37)	1.07 (0.81, 1.42)
Moderate to heavy then decline (T3)	86/889	1.71 (1.26, 2.31)	1.86 (1.36, 2.54)	1.72 (1.23, 2.40)	1.61 (1.15, 2.26)	1.66 (1.18, 2.33)
Heavy and persistent decline (T4)	15/136	2.31 (1.33, 4.01)	2.65 (1.51, 4.66)	2.30 (1.26, 4.20)	1.91 (1.01, 3.65)	1.93 (1.01, 3.70)
p for trend		<0.001	<0.001	0.002	0.015	0.013
Women						
Abstainer (T0)	244/5323	1	1	1	1	1
Light–stable (T1)	46/1093	0.88 (0.64, 1.20)	0.97 (0.69, 1.34)	0.92 (0.66, 1.28)	0.92 (0.66, 1.28)	0.93 (0.67, 1.30)
Light to moderate then decline (T2)	2/153	0.36 (0.10, 1.45)	0.40 (0.10, 1.62)	0.27 (0.10, 1.21)	0.25 (0.10, 1.17)	0.40 (0.10, 1.60)
p for trend		0.266	0.436	0.214	0.197	0.404

Model 1 was adjusted by age

Model 2 was further adjusted by smoking, education, urban or rural status, province status, metabolic equivalent hours

Model 3 was further adjusted by BMI

Model 4 was adjusted by all variables in model 3, with further adjustment for total energy intake, fat intake, fruit intake, vegetable intake and baseline alcohol consumption levels

Model 5 was adjusted by all variables in model 3, with further adjustment for urbanity index and history of cardiovascular disease

[a] Number of type 2 diabetes cases/number of participants with this trajectory

Trajectories of alcohol consumption and biomarkers of type 2 diabetes Differences for biomarkers across alcohol consumption trajectories classes are shown in Table 3. For men, fasting glucose, triacylglycerol, HDL-C, uric acid and hs-CRP in the two trajectories (T3 and T4) were higher than the other three trajectory classes (T0, T1 and T2) (all $p_{\text{for trend}} < 0.05$). HbA_{1c} in these two trajectories showed non-significant higher trends than the other three trajectories classes ($p_{\text{for trend}} = 0.445$). For women, HDL-C significantly increased across the three alcohol consumption trajectories ($p_{\text{for trend}} < 0.001$). Fasting glucose, HbA_{1c}, uric acid and hs-CRP showed non-significant increasing trend across the three trajectory classes ($p_{\text{for trend}} > 0.05$).

Mediation analysis Figure 2 shows mediation effects of triacylglycerol, HDL-C, uric acid and hs-CRP on the association between trajectories and risk of type 2 diabetes in men. The direct effect of alcohol consumption trajectories was estimated at 0.33. The β_1 to β_8 were used to calculate the overall indirect effect for these factors respectively ($\beta_{ind} = 0.073$ for triacylglycerol, −0.097 for HDL-C and 0.040 for uric acid; both $p < 0.05$). The percentages of the total effect mediated by

Table 3 Difference for type 2 diabetes-related factors across alcohol consumption trajectories in men and women

Factors	Men						Women			
	T0	T1	T2	T3	T4	p value	T0	T1	T2	p value
FPG (mmol/l)	5.49(1.68)	5.48(1.52)	5.52(1.52)	5.90(1.70)	5.72(2.23)	0.045	5.26(1.28)	5.32(1.42)	5.44(1.44)	0.240
HbA_{1c} (mmol/mol)	38.7(10.8)	38.3(8.8)	38.3(10.1)	38.8(11.8)	39.3(10.8)	0.468	37.8 (8.8)	37.7(13.5)	38.4(10.4)	0.473
HbA_{1c} (%)	5.67(1.08)	5.63(0.80)	5.64(0.92)	5.71(0.98)	5.80(0.98)	0.445	5.61(0.81)	5.57(0.60)	5.65(0.66)	0.480
TG (mmol/l)	1.67(1.73)	1.82(1.71)	1.90(1.73)	2.06(1.92)	2.14(1.98)	0.025	1.57(1.19)	1.42(1.23)	1.50(1.13)	0.230
HDL-C (mmol/l)	1.30(0.42)	1.37(0.49)	1.45(0.64)	1.53(0.54)	1.59(0.92)	<0.001	1.47(0.39)	1.49(0.38)	1.67(0.90)	<0.001
UA (μmol/l)	354(130)	347(109)	356(118)	370(107)	378(93.2)	0.001	264(79)	271(82)	277(89)	0.163
hs-CRP (nmol/l)	24.7(52.9)	29.6(66.0)	27.0(60.0)	25.7(65.2)	57.7(78.1)	0.037	21.4(50.5)	20.2(38.1)	26.3(70.1)	0.521

Generalised linear model was used to probe for differences across different trajectories with adjustment for age, smoking rate, education, urban or rural status, province status, metabolic equivalent hours and BMI

Data are mean (SD)

FPG, fasting plasma glucose; TG, triacylglycerol; UA, uric acid

triacylglycerol, HDL-C and uric acid were estimated at 22.1%, −29.4% and 12.1%.

Sensitivity analysis A detailed description of the results of sensitivity analyses can be found in ESM Methods. In brief, ESM Table 2 suggests that imbalanced sample distribution by trajectories probably did not influence the association between trajectories and risk of type 2 diabetes. Second, ESM Table 3 shows that using alcohol consumption measured using single time point probably bias the association between alcohol and type 2 diabetes as alcohol consumption measured in the 1993 survey was not significantly associated with type 2 diabetes. Moreover, ESM Table 4 indicates that alcohol consumption trajectories probably influence the association between cumulative amount of consumption and risk of type 2 diabetes. Third, ESM Fig. 1 shows that the original trajectories in men, with the exception of class T4, were not influenced by diagnosis of type 2 diabetes prior to attending the study visit. The trajectory showing a persistent increase from moderate to heavy levels throughout early adulthood followed by gradual decrease to moderate levels was still significantly associated with increased risk of type 2 diabetes, which was consistent with the findings in Fig. 1 and Table 3 (ESM Table 5). Fourth, alcohol consumption trajectories with time-to-event type 2 diabetes and survival rate curve of these trajectories were presented in ESM Fig. 2. The trajectory with high risk of type 2 diabetes showed varying trends similar to the original trajectory.

Discussion

In this study, using longitudinal data gathered over 18 years from China, we observed that two trajectories with heavy alcohol consumption in early adulthood were significantly associated with increased risk of type 2 diabetes throughout late adulthood in men. The two trajectories had higher fasting glucose, triacylglycerol, HDL-C, uric acid and hs-CRP than other trajectories. Further, triacylglycerol, HDL-C and uric acid partially mediated the association between trajectories and type 2 diabetes. Associations between alcohol consumption trajectories and risk of type 2 diabetes were not observed in women.

One of the two trajectories mentioned above showed a persistent increase to heavy alcohol consumption during early adulthood followed by gradual decrease to moderate levels, suggesting that despite gradual decrease to moderate alcohol consumption with age, persistent increased alcohol consumption to heavy levels during early adulthood is still significantly associated with increased risk of type 2 diabetes. Compared with previous studies with longitudinal assessments of drinking between two measurement time points [30], this study emphasised the harmful effects of alcohol consumption in early adulthood and the importance of capturing more alcohol consumption variation over the adult life course. This observation was partially supported by a previous study which reported that lifetime drinking intensity independent of current drinking status is significantly associated with increased prevalence of the metabolic syndrome [12]. The other trajectory with high risk of type 2 diabetes showed heavy levels in early adulthood with persistent decrease to light levels with age. However, after excluding participants diagnosed with type 2 diabetes during the surveys, this trajectory cannot be identified. This observation probably suggested that those with type 2 diabetes would exhibit persistently higher levels of alcohol consumption prior to diagnosis, which was consistent with a previous study showing that reductions of alcohol consumption were apparent only after diagnosis of type 2 diabetes [31], both demonstrating that drinking behaviour probably differed before and after diagnosis of type 2 diabetes.

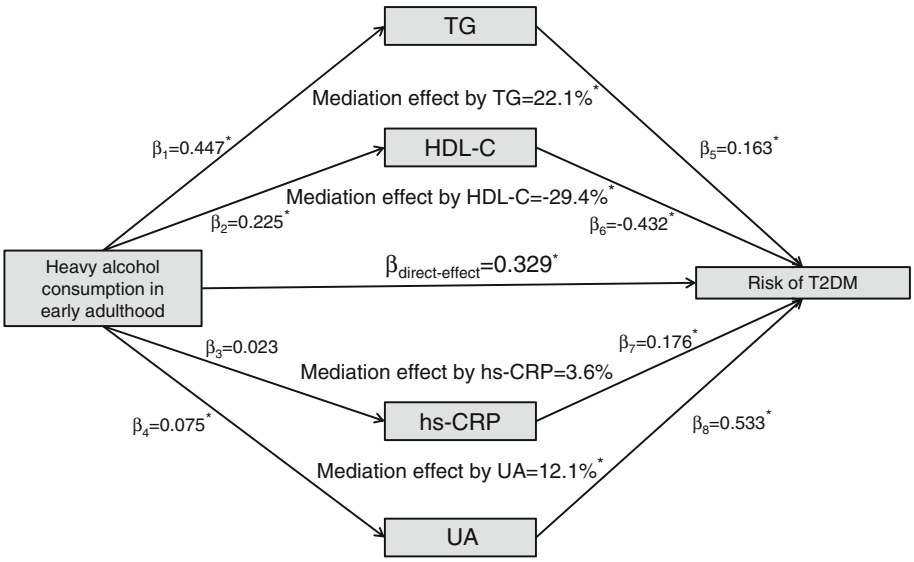

Fig. 2 Mediation effects of triacylglycerol, HDL-C, hs-CRP and uric acid on the association between alcohol consumption trajectories and risk of type 2 diabetes. Data are standardised regression coefficients with adjustment for covariates; *$p<0.05$ for coefficients different from 0. T2DM, type 2 diabetes mellitus; TG, triacylglycerol; UA, uric acid

Subgroup analyses for differences of biomarkers in men indicated that heavy alcohol consumption in early adulthood was probably associated with higher fasting glucose, triacylglycerol, HDL-C, uric acid and hs-CRP in later adulthood, indicating that reduction of alcohol consumption after heavy levels in early adulthood probably did not reverse the effects of ethanol on these biomarkers. Further, triacylglycerol, HDL-C and uric acid partially mediated the association between trajectories and type 2 diabetes, suggesting that increase to heavy alcohol consumption in early adulthood was associated with increased risk of type 2 diabetes partially through increasing triacylglycerol and uric acid. Cell and animal studies may provide potential mechanisms of these mediation effects. Previous studies have suggested that alcohol consumption could induce hypertriacylglycerolaemia through increasing VLDL secretion and non-esterified fatty acid fluxes from adipose tissue to the liver [32], and induce hyperuricaemia through increasing urate synthesis by enhancing the turnover of adenine nucleotides [33]. Both hypertriacylglycerolaemia and hyperuricaemia have been reported to be associated with type 2 diabetes through inducing insulin resistance and beta cell dysfunction as described in previous studies [34, 35]. Although HDL-C showed a significant mediation effect in the opposite direction to the direct effect, the mediation effect was relatively smaller than the direct effect, suggesting that increased HDL-C probably did not compensate for the harmful effect of heavy alcohol consumption in early adulthood on the development of type 2 diabetes.

Unlike the results of the men's trajectory classes, alcohol consumption trajectories with higher alcohol consumption level throughout the adult life course in women were not associated with increased risk of type 2 diabetes, and its biomarkers, with the exception of HDL-C, showed non-significant increasing trends in women. There are several possible explanations for these contrasting results. First, in this general population, there were significantly fewer female than male drinkers; therefore, we surmise that the smaller sample size may have resulted in the non-significant results. Second, although the trajectory with higher alcohol consumption levels in women showed a pattern similar to that noted for one of the higher risk trajectories in men, the peak of this trajectory in women was significantly lower than that for men, and the highest level of alcohol consumption in men was approximately twice as high as that in women. The relatively low alcohol consumption levels in women may also have led to the non-significant results.

Further, light–stable and increase from light to moderate levels were not associated with reduced risk of type 2 diabetes in either men or women, indicating that there was likely no protective effect of light or moderate alcohol consumption on type 2 diabetes. Although it has been reported that light or moderate alcohol consumption is associated with reduced risk of type 2 diabetes in previous studies [2, 3, 36], it has been suggested that when using a strictly defined never-drinking category, moderate consumption relative to never drinkers was likely associated with no reduction in risk of type 2 diabetes [37], which partially supported the results in this study. In addition, moderate alcohol consumption in the Asian population tends not to be associated with reduced risk of type 2 diabetes based on current research [38–40].

This study is the first on this subject area conducted in an Asian population with a relatively large cohort size and long follow-up duration. It does, however, have certain limitations. First, this study included only Asian participants, which is likely to limit the generalisability of our findings to other ethnic populations. Second, as in any observational study, it is limited by the possibility of residual confounding and measurement error, such as the determinants of alcohol consumption, the presence of which would affect the accuracy of estimates in this study. Third, this study did not exclude individuals with type 2 diabetes at baseline. However, the prevalence rate in the 1997 survey was 0.8%, and we therefore expected that prevalent type 2 diabetes cases in the 1993 survey would have been extremely low, and probably did not influence the results in this study. Further, the diagnosis of type 2 diabetes was mainly based on self-report with only blood samples used in the 2009 survey, leading to incident cases being higher in the 2009 survey than other surveys, and the incidence of type 2 diabetes relatively low throughout the CHNS, which may bias the Cox model results for time-event estimation. Moreover, this study distinguished participants' diabetes type from their at diagnosis of diabetes: previous studies using CHNS data have reported that mean age of onset of type 1 diabetes was 9.6 ± 3.5 years [41]; as mean age of onset of all types of diabetes was 53.7 ± 11.1 years in the present study, we may therefore expect that type 1 diabetes has only a slight influence on the results. Fourth, this study did not establish a trajectory for frequency of alcohol consumption as the frequency information was measured with categorical variables rather than continuous variables. Further studies including frequency of alcohol consumption would provide more information on this subject.

In conclusion, this study emphasises the harmful effect of heavy alcohol consumption during early adulthood on the development of type 2 diabetes, highlighting that alcohol intervention strategies should be implemented in early adulthood. Further, although association between alcohol consumption and increased HDL-C levels has been observed, results of this study did not support the hypothesis regarding the protective effect of moderate alcohol consumption on type 2 diabetes or its biomarkers. Additional study is needed to evaluate the net balance of health impacts from light or moderate alcohol consumption.

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Data availability Data from China Health and Nutrition Survey was used in this study, which can be downloaded at www.cpc.unc.edu/projects/china

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Contribution statement TH, CS and YL conceived the idea. TH and WD designed the study and wrote the original manuscript. TH and SZ wrote the revised manuscript. WD, XR and CW analysed and interpreted data. TH, SZ and WD performed the validation analyses. All authors critically assessed and reviewed the paper, and approved the version to be published. CS is the guarantor of this work.

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