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Original Contribution

The Association Between Age at Initiation of Alcohol Consumption and Type 2 Diabetes Mellitus: A Cohort Study of 0.5 Million Persons in China

Haoxin Li, Jun Lv, Canqing Yu, Yu Guo, Zheng Bian, Junning Fan, Ling Yang, Yiping Chen, Huaidong Du, Huajun Long, Zengzhi Zhang, Junshi Chen, Zhengming Chen, Tao Huang, and Liming Li* for the China Kadoorie Biobank Collaborative Group

* Correspondence to Prof. Liming Li, Department of Epidemiology and Biostatistics, Peking University Health Science Center, 38 Xueyuan Road, Beijing 100191, China (e-mail: lmlee@vip.163.com); or Prof. Tao Huang, Department of Epidemiology and Biostatistics, School of Public Health, Peking University Health Science Center, 38 Xueyuan Road, Beijing 100191, China (e-mail: huangtao@bjmu.edu.cn).

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It is well known that alcohol consumption is associated with type 2 diabetes mellitus. However, the association of age at initiation of alcohol consumption and duration of alcohol drinking with type 2 diabetes mellitus among Chinese adults is not fully understood. This study was based on data from the China Kadoorie Biobank, which included 512,712 participants aged 30–79 years who were living in China in 2004–2008. A Cox proportional hazards model was used to estimate the association of AAI and drinking duration with type 2 diabetes. After adjustment for potential covariates, ages at alcohol initiation (AAIs) of 18.1–29.0 years, 29.1–39.0 years, and >39.0 years were associated with 22% (95% confidence interval (CI): 14, 30), 25% (95% CI: 17, 33), and 32% (95% CI: 24, 39) lower hazards of type 2 diabetes compared with abstaining, respectively. Drinking durations of <10.1 years, 10.1–20.0 years, and 20.1–30.0 years were associated with a lower risk of type 2 diabetes, compared with abstaining. Among current (weekly) drinkers, AAI <18.1 years and drinking duration >30.0 years were associated with 18% (95% CI: 4, 33) and 20% (95% CI: 3, 40) higher hazards of type 2 diabetes, compared with AAI 18.1–29.0 years and drinking duration <10.1 years, respectively. In conclusion, late AAI and a short drinking duration were associated with a lower risk of type 2 diabetes in this large prospective cohort study of Chinese adults, but early AAI and long drinking duration were not.

alcohol; alcohol consumption; Chinese; cohort studies; drinking duration; type 2 diabetes

Abbreviations: AAI, age at alcohol initiation; BMI, body mass index; CI, confidence interval; CKB, China Kadoorie Biobank; HR, hazard ratio; MET, metabolic equivalent of task.

Alcohol, one of the most popular drinks in the world, has been shown to contribute to serious disease burden (1). Globally, 5.1% of the global burden of disease and injury are attributable to alcohol consumption (2). Previous studies found that high intake of alcohol was directly or indirectly associated with type 2 diabetes mellitus, while moderate drinking might decrease the risk of type 2 diabetes (3–5). In animal experiments, it was found that chronic alcohol consumption was associated with damage to the pancreas and development of diabetes, owing to pancreatic β-cell dysfunction and apoptosis (6–8).

Some previous studies showed that early age at initiation of alcohol consumption, defined as age at alcohol initiation (AAI) less than 18 years, and long duration of alcohol drinking increased the risk of alcohol-use disorders, heavy drinking, and alcohol dependence (9, 10). In the United States, the National Epidemiologic Survey on Alcohol and Related Conditions found that the incidence of alcohol dependence for AAI less than 15 years was 1.38 times higher than that for AAI greater than 18 years (11). Alcohol dependence was associated with higher body mass index (BMI), more cigarette smoking, and a lower level of physical activity,

which are associated with higher risk of metabolic diseases in Western populations (11–13). However, the direct association of AAI and drinking duration with type 2 diabetes in China is largely unclear.

Therefore, in the present study, we tested our hypothesis that AAI and drinking duration contribute to the risk of developing type 2 diabetes, independent of daily alcohol consumption, among 0.5 million participants in a prospective Chinese cohort study, the China Kadoorie Biobank (CKB).

METHODS

Study population

Details on the CKB cohort and characteristics of the study participants have been published previously (14). Briefly, the CKB is a prospective cohort study which included 512,712 participants aged 30–79 years from 5 urban areas (Harbin, Qingdao, Suzhou, Liuzhou, and Haikou) and 5 rural areas (Gansu, Henan, Sichuan, Zhejiang, and Hunan) in China during 2004–2008. The study areas were chosen according to local disease patterns, exposure to certain risk factors, population stability, quality of death and disease registries, and local commitment and capacity. Baseline questionnaire information was entered directly by trained staff into a laptop-based data entry system developed with built-in functions to avoid missing items and to minimize logical errors during data collection. Trained staff measured weight and height using calibrated instruments. The Ethical Review Committee of the Chinese Center for Disease Control and Prevention (Beijing, China) and the Oxford Tropical Research Ethics Committee of the University of Oxford (Oxford, United Kingdom) approved the study protocol.

In our study, we excluded persons with self-reported diagnoses of heart disease ($n = 15{,}472$), stroke ($n = 8{,}884$), cancer ($n = 2{,}577$), and diabetes or screen-detected diabetes ($n = 30{,}299$), defined as a measured fasting blood glucose concentration of 7.0 mmol/L or a random blood glucose concentration of 11.1 mmol/L at baseline, as well as persons who had missing data for BMI ($n = 2$) or appeared ineligible (e.g., AAI > age; $n = 24$). After these exclusions, the analysis included 461,013 participants.

Assessment of alcohol consumption

Our baseline questionnaire asked participants to report how often they had consumed alcohol during the previous 12 months (never or almost never; occasionally; only in certain seasons; every month but less than weekly; usually at least once a week). Those who had not consumed alcohol weekly in the past 12 months were asked whether there had been a period of at least 1 year prior to that when they had consumed some alcohol at least once a week. Participants who had consumed alcohol weekly in the past 12 months were further asked about the age at which they had started drinking weekly; how many days in a typical week they drank alcohol (1–2, 3–5, or 6–7 days/week); the types of beverages consumed (beer, grape wine, rice wine, weak spirits (<40% ethanol content), or strong spirits (≥40% ethanol content)); and amounts of alcohol consumed (reported as number of small (250 mL) or large (640 mL) bottles for beer and as number of liang (50 g) for wine and spirits); indicators of problem drinking in the past month (drinking in the morning; being unable to work or do anything due to drinking; being depressed, being irritated, or losing control because of drinking; being unable to stop drinking; shaking when stopping drinking). Problem drinking was defined as having any 1 of the indictors of problem drinking. We also calculated duration of alcohol drinking (drinking duration = baseline age − AAI). Quality control survey data were available for 15,728 participants (3.1%) at baseline. There was good agreement between the baseline and quality control survey for alcohol drinking (weighted κ coefficient = 0.79).

For our study, participants were classified into 4 main categories: Abstainers were defined as persons who had never or almost never consumed alcohol in the past 12 months and had not drunk alcohol weekly in the past; occasional drinkers were defined as those who had consumed alcohol occasionally, in certain seasons, or every month but less than weekly in the past 12 months (regardless of whether they had drunk weekly in the past); ex-drinkers were defined as those who had never or almost never consumed alcohol in the past 12 months but had drunk weekly in the past; and current drinkers were defined as those who had usually consumed alcohol at least once a week during the past 12 months. Further, according to AAI or drinking duration (years), the weekly drinkers were separately divided into 4 groups according to AAI (<18.1 years, 18.1–29.0 years, 29.1–39.0 years, or >39.0 years) and drinking duration (<10.1 years, 10.1–20.0 years, 20.1–30.0 years, or >30.0 years). Binge drinking was defined as usual or occasional consumption of ≥60 g of pure ethanol among current drinkers (2).

Assessment of other covariates

Information on other sociodemographic characteristics and lifestyle factors was collected through an interviewer-administered electronic questionnaire. Questions about tobacco included the frequency, type, and amount of tobacco smoked per day for ever smokers and years since quitting and reason for quitting for former smokers. By using a short qualitative food frequency questionnaire, we assessed habitual intakes of foods from 12 conventional food groups in the past 12 months. The reliability and validity of the food frequency questionnaire were 0.62–0.90 and 0.60–0.90, respectively, for all food categories (15). We also assessed physical activity by asking participants about the usual type and duration of their activities in occupational, commuting, domestic, and leisure-time-related domains in the past 12 months. We multiplied the metabolic equivalent of task value for a particular type of activity by the number of hours spent in that activity per day and summed the metabolic equivalent of task-hours for all activities to derive the daily level of physical activity. BMI was calculated as weight in kilograms divided by squared height in meters, as

measured by trained staff. We validated the reproducibility of the assessment in previous studies (14).

Ascertainment of type 2 diabetes

Cases of type 2 diabetes were ascertained by linking participants to local disease and death registries, starting from the time they enrolled in the study, and to the national health insurance system (14). Trained staff who were blinded to baseline information coded all cases using the *International Classification of Diseases, Tenth Revision*. For our study, type 2 diabetes cases were coded as E11 or E14. Other cases clearly defined as non–type 2 diabetes were excluded. Among participants in our CKB study, who were mostly over 40 years of age, the number of non–type 2 diabetes cases was small, so misclassification of other types of diabetes was minimal. During 2012–2013, clinical research fellows at the Oxford International Coordinating Center of the CKB reviewed medical records to adjudicate the validity of reported diabetes diagnoses in a random sample of 831 cases; 98.6% of the diagnoses were confirmed (14).

Statistical analysis

Numbers of person-years at risk were calculated from the baseline date to the diagnosis of diabetes, death, loss to follow-up, or December 31, 2016, whichever came first. The distributions of AAIs and drinking durations in the total population and at the 10 survey sites of the CKB study were determined.

With age as the time scale, Cox proportional hazards models were used to estimate adjusted hazard ratios for incident type 2 diabetes associated with AAI and drinking duration among all participants and among men and women separately. Results were adjusted for sex; education; marital status; household income; tobacco smoking; physical activity; intakes of red meat, fresh fruits and vegetables, and whole grains; BMI; family history of type 2 diabetes (presence or absence); and menopausal status (for women) and were stratified by age (in 5-year groups) and region (10 areas). Because alcohol consumption is most likely both a confounder and a mediator of the association of AAI and drinking duration with type 2 diabetes (3, 16), we adjusted results for pure ethanol consumption (g/day) only in the final model. No data were missing for the variables. When testing for linear trends across categories, AAI and drinking duration were considered continuous variables. We also tested the association of alcohol-related problems with AAI and drinking duration using logistic regression, adjusted for the same covariates.

Next, we used a restricted cubic spline model to examine the continuous measures of AAI and drinking duration with 3 knots (knot values were 10, 25, and 50 for AAI and 10, 20, and 30 for drinking duration). We compared a model with 3 knots with a model with 4 knots using the log likelihood test, but we found no statistically significant difference between the two in the prediction of the relationship between AAI or drinking duration and risk of incident type 2 diabetes. Therefore, we applied the model with 3 knots. The reference value for AAI was set at 25 years of age, and the reference value for drinking duration was set at 1 year. Because cubic spline models are sensitive to outliers, we included participants with exposures between the first and 99th percentiles, corresponding to AAIs of 10.1–64.9 years and drinking durations of 1.1–59.9 years.

We examined the joint associations of AAI and drinking duration with alcohol consumption, frequency of drinking, BMI, tobacco use, and hypertension in the risk of incident type 2 diabetes. We also assessed the interaction association using a likelihood ratio test comparing models with and without cross-product terms to test multiplicative interaction.

Sensitivity analyses were conducted to ensure the robustness of our results. We excluded patients who received a diagnosis of type 2 diabetes during the first 2 or 4 years of follow-up and participants whose AAI was less than 12 years. In addition, we redefined drinking duration considering the drinking duration of every participant in our cohorts (including ex-drinkers) and then repeated the above analysis. All statistical analyses were carried out using Stata, version 14.2 (Stata Corporation LLC, College Station, Texas).

RESULTS

A total of 461,013 participants, who had a mean age of 51.2 (standard deviation, 10.5) years, were included in the present analysis. The proportion of participants with AAI <18.1 years was 12.93% in the whole population and 1.92% among current (weekly) drinkers (see Web Figure 1, available at https://academic.oup.com/aje. Among the 10 survey sites of the CKB study, participants in Sichuan Province had the highest proportion of AAI <18.1 years. On the contrary, the proportion was lowest in Haikou, which is one of the most southern cities in China (Web Figure 2). The participants who had younger AAI were more likely to drink more alcohol per day, to be male, to be rural residents, to be less educated, to have higher household incomes, and to suffer from hypertension (Table 1).

During a median of 9.8 years (4,549,119 person-years) of follow-up, we identified 15,115 incident cases of type 2 diabetes. After adjustment for potential covariates, AAIs of 18.1–29.0 years, 29.1–39.0 years, and >39.0 years were associated with 17% (95% confidence interval (CI): 11, 23), 21% (95% CI: 13, 29), and 29% (95% CI: 21, 36) lower hazards of type 2 diabetes compared with abstaining, respectively. The association was not markedly changed after further adjustment for ethanol consumption (Table 2). Compared with abstaining, drinking durations of <10.1 years, 10.1–20.0 years, and 20.1–30.0 years were associated with lower risk of type 2 diabetes, with hazard ratios of 0.65 (95% CI: 0.57, 0.74), 0.66 (95% CI: 0.58, 0.74), and 0.72 (95% CI: 0.64, 0.80), respectively. However, a drinking duration greater than 30.0 years was not statistically significantly associated with decreased risk of type 2 diabetes (Table 3). We also repeated the analysis among current drinkers. After adjustment for ethanol consumption and other potential covariates, AAI <18.1 years and drinking duration >30.0 years were associated with 18% (95% CI:

Table 1. Baseline Characteristics of Participants in a Study of Alcohol Drinking and Type 2 Diabetes Risk, by Alcohol Consumption Status and (Among Current Drinkers) Age at Initiation of Alcohol Consumption, China Kadoorie Biobank, 2004–2008[a]

Variable	Alcohol Consumption Category													
	Abstainer (*n* = 208,906)		Occasional Drinker (*n* = 165,209)		Ex-Drinker (*n* = 16,730)		Current Drinker							
							AAI <18.1 Years (*n* = 9,191)		AAI 18.1–29.0 Years (*n* = 31,049)		AAI 29.1–39.0 Years (*n* = 16,397)		AAI >39.0 Years (*n* = 13,531)	
	%	Mean (SE)	%	Mean (SE)	%	Mean (SE)	%	Mean (SE)	%	Mean (SE)	%	Mean (SE)	%	Mean (SE)
Age, years		52.0 (0.01)		49.6 (0.01)		56.1 (0.01)		49.7 (0.01)		49.6 (0.01)		49.7 (0.01)		58.2 (0.01)
Female sex	84.7		51.1		13.4		2.7		3.4		8.7		18.7	
Residence in an urban area	37.7		44.8		38.0		39.6		50.9		56.9		51.6	
Education of middle school or above	47.1		53.0		48.2		41.0		47.3		50.7		51.2	
Household income >20,000 Chinese yuan/year	40.0		45.0		43.0		41.1		44.7		46.6		45.7	
Current smoker	22.4		25.8		26.6		34.3		33.3		33.3		30.3	
Ethanol consumption, g/day		0		0		0		65.4 (0.15)		56.0 (0.09)		48.1 (0.11)		36.4 (0.12)
Physical activity, MET-hours/day		21.6 (0.03)		22.1 (0.03)		20.7 (0.10)		22.1 (0.13)		22.2 (0.07)		22.0 (0.10)		22.9 (0.11)
Body mass index[b]		23.5 (0.01)		23.5 (0.01)		23.9 (0.03)		23.8 (0.03)		23.8 (0.02)		23.7 (0.03)		23.3 (0.03)
Waist circumference, cm		79.5 (0.02)		79.5 (0.02)		80.8 (0.07)		81.1 (0.10)		81.1 (0.06)		81.0 (0.07)		79.4 (0.08)
Waist:hip ratio		0.88 (0.01)		0.87 (0.01)		0.88 (0.01)		0.89 (0.01)		0.89 (0.01)		0.89 (0.01)		0.88 (0.01)

Table continues

Table 1. Continued

Variable	Abstainer (*n* = 208,906)		Occasional Drinker (*n* = 165,209)		Ex-Drinker (*n* = 16,730)		Current Drinker: AAI <18.1 Years (*n* = 9,191)		Current Drinker: AAI 18.1–29.0 Years (*n* = 31,049)		Current Drinker: AAI 29.1–39.0 Years (*n* = 16,397)		Current Drinker: AAI >39.0 Years (*n* = 13,531)	
	%	Mean (SE)	%	Mean (SE)	%	Mean (SE)	%	Mean (SE)	%	Mean (SE)	%	Mean (SE)	%	Mean (SE)
Family history of chronic disease														
Stroke	16.3		18.1		19.9		18.2		18.4		18.7		19.2	
Diabetes	5.5		6.8		7.1		6.9		6.2		6.6		6.7	
Heart attack	2.9		3.2		3.8		2.9		3.2		3.3		3.5	
Hypertension	33.0		28.8		36.6		40.3		39.4		37.6		31.9	

Abbreviations: AAI, age at alcohol initiation; MET, metabolic equivalent of task; SE, standard error.

[a] Mean values and proportions were calculated using multiple linear regression and multinomial logistic regression models which adjusted for age, region, and sex (where appropriate), respectively. All *P* values for heterogeneity and trend across subgroups were less than 0.001.

[b] Weight (kg)/height $(m)^2$.

4, 33) and 20% (95% CI: 3, 40) higher hazards of type 2 diabetes, respectively, compared with AAI 18.1–29.0 years and drinking duration <10.1 years (Table 4). The restricted cubic spline curves of the continuous AAI variable showed an L-shaped association between AAI and the hazard of type 2 diabetes among current drinkers (Figure 1), while the association between drinking duration and the hazard of type 2 diabetes showed a linear trend (Figure 2).

In the subgroup analyses, we found that, compared with abstainers, AAIs of 18.1–29.0 years and 29.1–39.0 years were associated with 16% and 22% lower risks of incident type 2 diabetes, respectively, if daily alcohol consumption was less than 60 g, but the association was not statistically significant in participants with daily alcohol consumption greater than or equal to 60 g. In the subgroups for frequency of drinking, type of alcohol consumed, and binge drinking, we found associations similar to those in our main analyses (Web Table 1). In addition, no linear trend was found in the subgroup analyses for the association between drinking duration and type 2 diabetes (Web Table 2).

We did not find any interaction association of AAI or long drinking duration with frequency of alcohol drinking, daily alcohol consumption, smoking, BMI, or hypertension (Web Figures 3 and 4, Web Tables 3–10).

AAI and drinking duration may be associated with indicators of problem drinking. In logistic regression analysis, participants who could not stop drinking were more likely to have a younger AAI and a longer drinking duration. No other significant trends were found between other indicators of problem drinking and AAI or drinking duration (Web Figures 5 and 6).

We performed sensitivity analysis in which we tested the association of AAI and drinking duration with risk of type 2 diabetes (data not shown). We excluded patients who received a type 2 diabetes diagnosis during the first 2 or 4 years of follow-up and participants whose AAI was less than 12 years. We also redefined drinking duration (considering the duration of every participant in our cohorts). These modifications did not change the estimates noticeably.

DISCUSSION

In this large prospective cohort study based on half a million Chinese, we found an association of AAI and drinking duration with type 2 diabetes that was independent of pure ethanol consumption. Compared with abstention, a later AAI and shorter drinking duration were associated with a decreased risk of type 2 diabetes. However, the association of AAI and drinking duration with type 2 diabetes was less pronounced among the participants with an early AAI and a long drinking duration. We found a similar association when examining different patterns of alcohol drinking. Among current drinkers, we estimated a J-shaped association between AAI and type 2 diabetes and a linear association between drinking duration and type 2 diabetes. Moreover, we did not find any interaction association of AAI and drinking duration with other lifestyle factors.

Few previous studies focused on the direct association between AAI/drinking duration and type 2 diabetes risk, but

Table 2. Risk of Type 2 Diabetes Mellitus According to Alcohol Consumption Status and (Among Current Drinkers) Age at Initiation of Alcohol Consumption, China Kadoorie Biobank, 2004–2008

Alcohol Consumption Category and Age at Alcohol Initiation	No. of Persons	No. of Person-Years	No. of Cases	No. of Cases per 1,000 Person-Years	Model 1[a]		Model 2[b]		Model 3[c]		*P* for Trend[d]
					HR	95% CI	HR	95% CI	HR	95% CI	
Total (n = 461,013)											
Abstainer	208,906	2,059,035	8,141	4.0		1.00		1.00		1.00	
Occasional drinker	165,209	1,641,614	4,194	2.6	0.71	0.68, 0.73	0.89	0.85, 0.93	0.89	0.85, 0.93	
Ex-drinker	16,730	157,873	775	4.9	1.10	1.02, 1.18	0.99	0.92, 1.08	0.99	0.92, 1.08	
Current drinker											
<18.1 years	9,191	90,043	364	4.0	1.13	1.02, 1.25	0.97	0.87, 1.09	0.90	0.79, 1.03	
18.1–29.0 years	31,049	306,884	993	3.2	0.89	0.83, 0.95	0.83	0.77, 0.89	0.78	0.70, 0.86	
29.1–39.0 years	16,397	162,596	465	2.9	0.78	0.71, 0.86	0.79	0.71, 0.87	0.75	0.67, 0.83	
>39.0 years	13,531	131,075	401	3.1	0.63	0.57, 0.69	0.71	0.64, 0.79	0.68	0.61, 0.76	<0.001
Men (n = 189,081)											
Abstainer	37,457	354,855	1,361	3.8		1.00		1.00		1.00	
Occasional drinker	72,769	715,538	1,842	2.6	0.76	0.70, 0.81	0.87	0.81, 0.93	0.87	0.81, 0.93	
Ex-drinker	14,479	135,831	632	4.7	1.18	1.08, 1.30	0.99	0.90, 1.09	0.99	0.90, 1.09	
Current drinker											
<18.1 years	8,869	86,828	346	4.0	1.20	1.07, 1.36	0.97	0.86, 1.10	0.89	0.77, 1.02	
18.1–29.0 years	29,752	293,781	949	3.2	0.96	0.88, 1.05	0.83	0.76, 0.90	0.76	0.68, 0.85	
29.1–39.0 years	14,692	145,269	418	2.9	0.85	0.76, 0.95	0.79	0.70, 0.88	0.73	0.65, 0.84	
>39.0 years	11,063	106,733	308	2.9	0.68	0.60, 0.77	0.72	0.63, 0.81	0.68	0.59, 0.77	<0.001

Table continues

Table 2. Continued

Alcohol Consumption Category and Age at Alcohol Initiation	No. of Persons	No. of Person-Years	No. of Cases	No. of Cases per 1,000 Person-Years	Model 1[a]		Model 2[b]		Model 3[c]		*P* for Trend[d]
					HR	95% CI	HR	95% CI	HR	95% CI	
Women (n = 271,932)											
Abstainer	171,449	1,704,180	6,780	4.0	1.00		1.00		1.00		
Occasional drinker	92,440	926,075	2,352	2.5	0.71	0.68, 0.74	0.89	0.84, 0.94	0.89	0.84, 0.94	
Ex-drinker	2,251	22,041	143	6.5	1.34	1.14, 1.59	1.02	0.86, 1.21	1.02	0.86, 1.21	
Current drinker											
<18.1 years	322	3,215	18	5.6	1.26	0.80, 2.01	0.95	0.59, 1.51	0.97	0.58, 1.64	
18.1–29.0 years	1,297	13,103	44	3.4	0.89	0.66, 1.20	0.76	0.56, 1.02	0.78	0.54, 1.12	
29.1–39.0 years	1,705	17,327	47	2.7	0.78	0.59, 1.05	0.68	0.51, 0.91	0.69	0.49, 0.98	
>39.0 years	2,468	24,342	93	3.8	0.75	0.61, 0.93	0.72	0.59, 0.89	0.74	0.57, 0.95	<0.001

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Model 1 adjusted for age.

[b] Model 2 adjusted for age (in years); education (no formal schooling, primary school, middle school, high school, or college/university or higher); household income (<2,500, 2,500–4,999, 5,000–9,999, 10,000–19,999, 20,000–34,999, or ≥35,000 Chinese yuan/year); marital status (married, widowed, divorced/separated, or never married); smoking status (nonsmoker, ex-smoker, current smoker of 1–9 cigarettes/day, current smoker of 10–19 cigarettes/day, or current smoker of >19 cigarettes/day); physical activity (in metabolic equivalent of task-hours/day); intake of red meat, fresh fruits and vegetables, and whole grains (monthly frequency); body mass index (weight (kg)/height $(m)^2$); family history of type 2 diabetes (presence or absence); and menopausal status (for women).

[c] Model 3 was based on model 2 and further adjusted for ethanol consumption (in g/day).

[d] Restricted to abstainers, occasional drinkers, and current drinkers.

Table 3. Risk of Type 2 Diabetes Mellitus According to Alcohol Consumption Status and (Among Current Drinkers) Duration of Alcohol Consumption, China Kadoorie Biobank, 2004–2008

Alcohol Consumption Category and Duration of Alcohol Consumption	No. of Persons	No. of Person-Years	No. of Cases	No. of Cases per 1,000 Person-Years	Model 1[a]		Model 2[b]		Model 3[c]		*P* for Trend[d]
					HR	95% CI	HR	95% CI	HR	95% CI	
Total (n = 461,013)											
Abstainer	208,906	2,059,035	8,141	4.0		1.00		1.00		1.00	
Occasional drinker	165,209	1,641,614	4,194	2.6	0.71	0.68, 0.73	0.89	0.85, 0.93	0.89	0.85, 0.93	
Ex-drinker	16,730	157,873	775	4.9	1.10	1.02, 1.18	0.99	0.92, 1.08	0.99	0.92, 1.08	
Current drinker											
<10.1 years	13,200	132,008	292	2.2	0.56	0.50, 0.63	0.66	0.59, 0.75	0.65	0.57, 0.74	
10.1–20.0 years	18,130	182,657	483	2.6	0.66	0.61, 0.73	0.67	0.61, 0.75	0.66	0.58, 0.74	
20.1–30.0 years	20,177	200,380	653	3.3	0.82	0.76, 0.89	0.74	0.67, 0.81	0.72	0.64, 0.80	
>30.0 years	18,661	175,553	795	4.5	1.16	1.08, 1.25	0.93	0.85, 1.02	0.90	0.81, 1.01	<0.001
Men (n = 189,081)											
Abstainer	37,457	354,855	1,361	3.8		1.00		1.00		1.00	
Occasional drinker	72,769	715,538	1842	2.6	0.76	0.70, 0.81	0.87	0.81, 0.93	0.87	0.81, 0.93	
Ex-drinker	14,479	135,831	632	4.7	1.18	1.08, 1.30	0.99	0.90, 1.09	0.99	0.90, 1.09	
Current drinker											
<10.1 years	10,729	107,269	224	2.1	0.59	0.51, 0.68	0.61	0.53, 0.71	0.59	0.50, 0.69	
10.1–20.0 years	16,733	168,531	431	2.6	0.64	0.57, 0.72	0.62	0.55, 0.70	0.59	0.52, 0.68	
20.1–30.0 years	19,104	189,519	616	3.3	0.77	0.70, 0.85	0.73	0.65, 0.80	0.69	0.61, 0.78	
>30.0 years	17,810	167,290	750	4.5	1.01	0.92, 1.11	0.98	0.89, 1.08	0.94	0.83, 1.05	<0.001
Women (n = 271,932)											
Abstainer	171,449	1,704,180	6,780	4.0		1.00		1.00		1.00	
Occasional drinker	92,440	926,075	2,352	2.5	0.71	0.68, 0.74	0.89	0.84, 0.94	0.89	0.84, 0.94	
Ex-drinker	2,251	22,041	143	6.5	1.34	1.14, 1.59	1.02	0.86, 1.21	1.02	0.86, 1.21	
Current drinker											
<10.1 years	2,471	24,738	68	2.8	0.71	0.56, 0.90	0.78	0.61, 0.99	0.81	0.61, 1.07	
10.1–20.0 years	1,397	14,125	52	3.7	0.86	0.65, 1.13	0.86	0.85, 1.14	0.92	0.66, 1.29	
20.1–30.0 years	1,073	10,861	37	3.4	0.70	0.50, 0.97	0.60	0.44, 0.84	0.65	0.44, 0.95	
>30.0 years	851	8,263	45	5.4	1.11	0.82, 1.49	0.83	0.61, 1.11	0.89	0.61, 1.27	<0.001

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Model 1 adjusted for age.

[b] Model 2 adjusted for age (in years); education (no formal schooling, primary school, middle school, high school, or college/university or higher); household income (<2,500, 2,500–4,999, 5,000–9,999, 10,000–19,999, 20,000–34,999, or ≥35,000 Chinese yuan/year); marital status (married, widowed, divorced/separated, or never married); smoking status (nonsmoker, ex-smoker, current smoker of 1–9 cigarettes/day, current smoker of 10–19 cigarettes/day, or current smoker of >19 cigarettes/day); physical activity (in metabolic equivalent of task-hours/day); intake of red meat, fresh fruits and vegetables, and whole grains (monthly frequency); body mass index (weight (kg)/height (m)^2); family history of type 2 diabetes (presence or absence); and menopausal status (for women).

[c] Model 3 was based on model 2 and further adjusted for ethanol consumption (in g/day).

[d] Restricted to abstainers, occasional drinkers, and current drinkers.

compelling epidemiologic studies have assessed the relationship between AAI and subsequent development of alcohol dependence (9, 10, 17–22). Grant et al. (18) found that people who started drinking alcohol earlier were more likely to develop alcohol dependence in the future, but the risk of alcohol dependence might decrease if AAI was delayed. It has also been found that there is a robust association between AAI and excessive alcohol consumption that is highly associated with the risk of alcohol dependence, after adjustment for a wide range of baseline risk factors, drinking duration, and family history of diabetes (11, 13, 23). In the present study, although we did not collect information on alcohol dependence, we found that AAI and drinking duration played important roles in the development of alcohol-

Table 4. Risk of Type 2 Diabetes Mellitus Among Current Alcohol Drinkers According to Age at Initiation of Alcohol Consumption and Duration of Alcohol Consumption, China Kadoorie Biobank, 2004–2008

Variable	Model 1[a]		Model 2[b]		Model 3[c]	
	HR	95% CI	HR	95% CI	HR	95% CI
Total (n = 70,168)						
Age at alcohol initiation, years						
<18.1	1.19	1.05, 1.34	1.18	1.05, 1.34	1.18	1.04, 1.33
18.1–29.0	1.00	Reference	1.00	Reference	1.00	Reference
29.1–39.0	0.94	0.84, 1.05	0.94	0.84, 1.05	0.95	0.85, 1.06
>39.0	0.90	0.79, 1.02	0.90	0.79, 1.02	0.91	0.80, 1.03
P for trend		<0.001		<0.001		<0.001
Drinking duration, years						
<10.1	1.00	Reference	1.00	Reference	1.00	Reference
10.1–20.0	1.27	1.10, 1.47	1.09	0.94, 1.26	1.08	0.93, 1.25
20.1–30.0	1.38	1.20, 1.59	1.08	0.93, 1.25	1.06	0.92, 1.23
>30.0	1.62	1.40, 1.87	1.22	1.05, 1.43	1.20	1.03, 1.40
P for trend		<0.001		0.01		0.03
Men (n = 64,376)						
Age at alcohol initiation, years						
<18.1	1.25	1.11, 1.42	1.18	1.05, 1.34	1.17	1.04, 1.33
18.1–29.0	1.00	Reference	1.00	Reference	1.00	Reference
29.1–39.0	0.88	0.78, 0.99	0.95	0.85, 1.07	0.96	0.85, 1.08
>39.0	0.70	0.61, 0.80	0.87	0.76, 1.00	0.88	0.77, 1.01
P for trend		<0.001		<0.001		0.001
Drinking duration, years						
<10.1	1.00	Reference	1.00	Reference	1.00	Reference
10.1–20.0	1.29	1.01, 1.52	1.08	0.92, 1.27	1.07	0.90, 1.26
20.1–30.0	1.45	1.24, 1.70	1.12	0.95, 1.31	1.09	0.93, 1.28
>30.0	1.72	1.46, 2.02	1.26	1.06, 1.49	1.22	1.03, 1.45
P for trend		<0.001		0.01		0.02
Women (n = 5,792)						
Age at alcohol initiation, years						
<18.1	1.42	0.82, 2.46	1.34	0.76, 2.37	1.34	0.76, 2.37
18.1–29.0	1.00	Reference	1.00	Reference	1.00	Reference
29.1–39.0	0.88	0.58, 1.34	0.96	0.63, 1.46	0.95	0.62, 1.45
>39.0	0.87	0.60, 1.25	1.21	0.81, 1.80	1.19	0.80, 1.78
P for trend		0.09		0.76		0.83

Table continues

Table 4. Continued

Variable	Model 1[a]		Model 2[b]		Model 3[c]	
	HR	95% CI	HR	95% CI	HR	95% CI
Drinking duration, years						
<10.1	1.00	Reference	1.00	Reference	1.00	Reference
10.1–20.0	1.35	0.94, 1.93	0.99	0.68, 1.45	1.06	0.72, 1.54
20.1–30.0	1.06	0.71, 1.59	0.65	0.42, 1.01	0.65	0.42, 1.01
>30.0	1.44	0.98, 2.15	0.90	0.59, 1.39	0.97	0.63, 1.50
P for trend	0.14		0.30		0.34	

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Model 1 adjusted for age.

[b] Model 2 adjusted for age (in years); education (no formal schooling, primary school, middle school, high school, or college/university or higher); household income (<2,500, 2,500–4,999, 5,000–9,999, 10,000–19,999, 20,000–34,999, or ≥35,000 Chinese yuan/year); marital status (married, widowed, divorced/separated, or never married); smoking status (nonsmoker, ex-smoker, current smoker of 1–9 cigarettes/day, current smoker of 10–19 cigarettes/day, or current smoker of > 19 cigarettes/day); physical activity (in metabolic equivalent of task-hours/day); intake of red meat, fresh fruits and vegetables, and whole grains (monthly frequency); body mass index (weight (kg)/height $(m)^2$); family history of type 2 diabetes (presence or absence); and menopausal status (for women).

[c] Model 3 was based on model 2 and further adjusted for ethanol consumption (in g/day).

related problems, especially in finding it hard to stop drinking. Moreover, in our analysis, daily alcohol consumption in participants with AAI <18.1 years was nearly 20 g higher than that in participants with AAI >39.0 years. Previous studies found a similar association of AAI and drinking duration with ethanol consumption (10, 17, 18, 20).

Previous studies found that moderate alcohol consumption was associated with decreased risk of type 2 diabetes. In the EPIC-InterAct Study (based on the European Prospective Investigation Into Cancer and Nutrition (EPIC) cohort), Huang et al. (24) found that moderate alcohol consumption was related to a lower risk of diabetes in women but not in men. Similarly, Rasouli et al. (25) reported that modest alcohol consumption was associated with lower diabetes risk in middle-aged and elderly Chinese men. Among Chinese in Taiwan, Lai et al. (26) observed that participants with social alcohol consumption had a reduced risk of incident diabetes compared with abstainers. In our study, participants with a late AAI or a short drinking duration, who were more likely to drink moderately, had lower hazard ratios for type 2 diabetes than abstainers. Although some research implied that the association between AAI or drinking duration and type 2 diabetes might be due to level of pure ethanol consumption, the model we used adjusted for daily ethanol consumption, so we did our utmost to control for the impact of ethanol consumption. Additional studies to explore the biological pathway should be encouraged.

In previous studies, it was reported that excessive alcohol consumption, which might be caused by early AAI or a long drinking duration, led to type 2 diabetes (5, 26–28). Research identified excessive alcohol consumption as the one of key risk behaviors for type 2 diabetes in Americans, especially women (28). Recently, a Mendelian randomization analysis showed that excessive alcohol consumption was more likely to be causally associated with increased diabetes risk and worsened related traits among Chinese men (3). However, we did not observe an association between early AAI or long drinking duration with increased type 2 diabetes risk in comparison with abstention. In our study, the reference group was abstainers, defined as persons who had never consumed alcohol during the previous 12 months at baseline and not drunk weekly in the past. But it was hard to distinguish "real" abstainers from persons who had stopped drinking but consumed alcohol occasionally in their younger years. In addition, some abstainers might be likely to not consume alcohol because of poor health. Thus, the risk of type 2 diabetes may have been increased at baseline among abstainers.

In addition, the association of AAI and drinking duration with type 2 diabetes was attenuated after adjustment for daily alcohol consumption in persons with different patterns of alcohol drinking. It was likely that the association of AAI and drinking duration with type 2 diabetes was partly due to amount of ethanol consumption in our study. In addition, we did not observe any interaction association for different patterns of alcohol drinking. The result implied that AAI <18.1 years would diminish the positive effect of moderate alcohol consumption, regardless of pattern of alcohol drinking.

Moreover, previous research found that current smoking, high BMI, and hypertension were important risk factors for type 2 diabetes (5, 29, 30). Although we did not find any interaction association in our study, current drinkers with an early AAI or a long drinking duration should be encouraged to reduce their BMI, control high blood pressure, and give up smoking in order to decrease their risk of type 2 diabetes.

An association of AAI and drinking duration with type 2 diabetes is biologically plausible. Moderate drinking has been found to be associated with a lower plasma level of fetuin-A, while fetuin-A and fasting insulin level explain

Figure 1. Risk of incident type 2 diabetes mellitus among current alcohol drinkers according to age at initiation of alcohol consumption, China Kadoorie Biobank, 2004–2008. A) All participants; B) men; C) women. The solid lines show multivariable-adjusted hazard ratios, and the dashed lines indicate 95% confidence intervals derived from a restricted cubic spline regression. Hazard ratios and 95% confidence intervals are shown on the natural log scale. Participants with exposures between the first and 99th percentiles were included. Age (in days) was the underlying time axis. The models adjusted for age; education; marital status; household income; tobacco smoking; alcohol consumption; physical activity; intakes of red meat, fresh fruits and vegetables, and whole grains; body mass index; family history of diabetes; and menopausal status (for women).

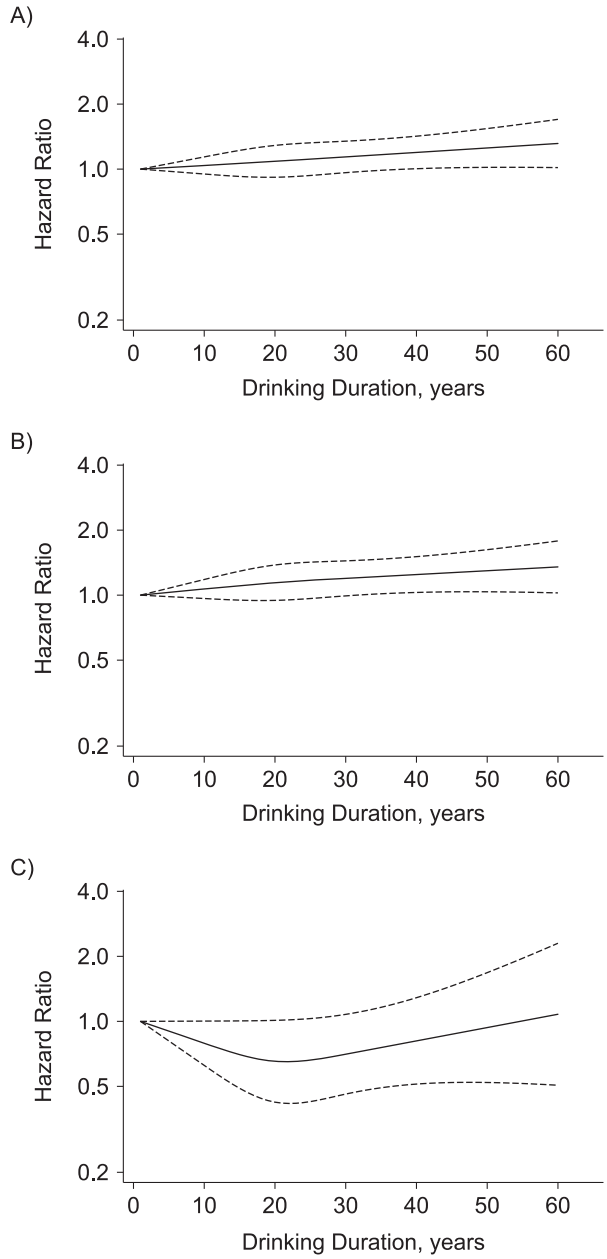

Figure 2. Risk of incident type 2 diabetes mellitus among current alcohol drinkers according to duration of alcohol consumption, China Kadoorie Biobank, 2004–2008. A) All participants; B) men; C) women. The solid lines show multivariable-adjusted hazard ratios, and the dashed lines indicate 95% confidence intervals derived from a restricted cubic spline regression. Hazard ratios and 95% confidence intervals are shown on the natural log scale. Participants with exposures between the first and 99th percentiles were included. Age (in days) was the underlying time axis. The models adjusted for age; education; marital status; household income; tobacco smoking; alcohol consumption; physical activity; intakes of red meat, fresh fruits and vegetables, and whole grains; body mass index; family history of diabetes; and menopausal status (for women).

a significant proportion of the association between alcohol consumption and type 2 diabetes (24). However, an animal study showed that chronic alcohol consumption could induce heart deformation, a slower heart rate, and damaged or incomplete blood vessels (31). At the same time, alcohol consumption may increase blood pressure, which is one of the main risk factors for type 2 diabetes (29). Moreover, alcohol consumption is associated with insulin sensitivity. In a recent meta-analysis, Schrieks et al. (32) estimated that light-to-moderate alcohol consumption did not influence insulin sensitivity. In a South Korean study, Lee et al. (4) found that heavy alcohol consumption could reduce insulin sensitivity and damage pancreatic β-cell function.

To the best of our knowledge, our study is the largest prospective study by far to have estimated the association of AAI and drinking duration, independently of amount of ethanol consumption and frequency of drinking, with the risk of incident type 2 diabetes that could be prevented through delaying AAI. For the first time, our study provided evidence for a joint harmful association of AAI, drinking duration, ethanol consumption, and drinking frequency with the risk of incident type 2 diabetes in a nationally representative general Chinese population. The prospective study design, the geographically widespread study population (across both urban and rural China), and the reasonable control for potentially confounding factors make our results more credible. We also excluded participants with major chronic diseases at baseline and distinguished former drinking from abstention in order to avoid reverse causality bias.

Some limitations need to be mentioned. First, our measures of AAI and drinking duration relied on quantitative self-report data and were not validated by actual measurement. Psychological factors may lead participants to report AAI falsely. However, it is a challenge for most epidemiologic researchers to obtain a valid and reliable estimate of AAI. Second, data on AAI and drinking duration were only collected in weekly drinkers. We could not exclude persons who started drinking early but occasionally. This could have led to increased risk of type 2 diabetes at baseline among abstainers. Third, information on other factors related to drinking pattern was also self-reported and was collected only once, at baseline. In actuality, factors related to drinking patterns would change over time. Our study could not disentangle the causal effects of different aspects of alcohol consumption patterns on type 2 diabetes risk owing to the lack of longitudinal data. Fourth, we could not observe alcohol dependence directly in our study, so we estimated the association of AAI and drinking duration with symptoms related to alcohol dependence—a measurement which was indirect. Fifth, alcohol consumption may be correlated with a preference for eating certain foods or drinking other beverages which are highly associated with type 2 diabetes, but we did not collect information on diet or adjust for those factors in our analyses. It is possible that there was residual confounding in our study. Sixth, despite the large sample size, few women were current drinkers or smokers in the CKB cohort, which caused wide confidence intervals for the association estimates and inconclusive results for women. The number of cases may have been too low to obtain reliable estimates for the joint association. In addition, identification of type 2 diabetes cases in the CKB cohort relied on the Chinese health insurance system; some cases of asymptomatic disease might have been undiagnosed.

In conclusion, we found a decreased risk of type 2 diabetes associated with late AAI and short drinking duration in a large prospective cohort study of Chinese adults, but early AAI and long drinking duration did not decrease the risk of type 2 diabetes. People should be advised to postpone AAI and reduce drinking duration to decrease the risk of type 2 diabetes. Future studies should strive to elucidate whether AAI and drinking duration have the potential to increase the risk of type 2 diabetes through chronic alcohol consumption or other biological mechanisms.

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Author affiliations: Department of Epidemiology and Biostatistics, School of Public Health, Peking University, Beijing, China (Haoxin Li, Jun Lv, Canqing Yu, Junning Fan, Tao Huang, Liming Li); Peking University Health Science Center, Beijing, China (Haoxin Li, Jun Lv, Canqing Yu, Junning Fan, Tao Huang, Liming Li); Chinese Academy of Medical Sciences, Beijing, China (Yu Guo, Zheng Bian); MRC Population Health Research Unit at the University of Oxford, Oxford, United Kingdom (Ling Yang, Yiping Chen, Huaidong Du); Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, Medical Sciences Division, University of Oxford, Oxford, United Kingdom (Ling Yang, Yiping Chen, Huaidong Du, Zhengming Chen); China National Center for Food Safety Risk Assessment, Beijing, China (Junshi Chen); NCDs Prevention and Control Department, Liuyang Center for Disease Control, Liuyang, China (Huajun Long); Prevention and Control Department, Shinan Center for Disease Control, Shinan, China (Zengzhi Zhang); Key Laboratory of Molecular Cardiovascular Sciences (Peking University), Ministry of Education, Beijing, China (Jun Lv); and Peking University Institute of Environmental Medicine, Peking University, Beijing, China (Jun Lv).

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