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在线全文

模拟饮酒干预与肝脂肪变性：一项大型队列的纵向研究*

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【摘要】 目的 基于一项大型队列的纵向研究数据，模拟评估饮酒干预（饮酒量和种类的改变）对肝脂肪变的影响。**方法** 基于英国生物银行（UK Biobank, UKB），纳入同时接受了基线及重复调查的12 687人。使用脂肪肝指数（fatty liver index, FLI）作为结局指标。参与者根据其饮酒量被分为不饮酒者、中度饮酒者和重度饮酒者。定义了以下干预措施：从基线到重复调查，酒精消费水平不变（如持续不饮酒、持续中度饮酒）；以及饮酒水平发生改变（如不饮酒到中度饮酒）。饮酒种类的干预类似于酒精量的干预。应用parametric g-formula模拟反事实场景下饮酒干预对FLI的影响。**结果** 在UKB人群中，无论基线饮酒水平如何，相比于饮酒量恒定，饮酒量增加与更高的FLI水平有关。与其他饮酒种类相比，饮酒种类转变为红酒与较低的FLI水平有关。**结论** 无论目前饮酒水平如何，饮酒量增加会增加肝脂肪变性的风险，如果戒酒具有挑战性，红酒可能是比其他类型更好的选择，本研究可为未来的实践指南和卫生政策提供信息支持。

【关键词】 饮酒量 饮酒种类 肝脏脂肪变性 目标试验 模拟干预

Hypothetical Alcohol Consumption Interventions and Hepatic Steatosis: A Longitudinal Study in a Large Cohort

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【Abstract】 Objective Non-alcoholic fatty liver disease (NAFLD) and alcohol-associated fatty liver disease (ALD) are the most common chronic liver diseases. Hepatic steatosis is an early histological subtype of both NAFLD and ALD. Excessive alcohol consumption is widely known to lead to hepatic steatosis and subsequent liver damage. However, reported findings concerning the association between moderate alcohol consumption and hepatic steatosis remain inconsistent. Notably, alcohol consumption as a modifiable lifestyle behavior is likely to change over time, but most previous studies covered alcohol intake only once at baseline. These inconsistent findings from existing studies do not inform decision-making concerning policies and clinical guidelines, which are of greater interest to health policymakers and clinician-scientists. Additionally, recommendations on the types of alcoholic beverages are not available. Usually, assessing the effects of two or more hypothetical alcohol consumption interventions on hepatic steatosis provides answers to questions concerning the population risk of hepatic steatosis if everyone changes from heavy drinking to abstinence, or if everyone keeps on drinking moderately, or if everyone of the drinking population switches from red wine to beer? Thus, we simulated a target trial to estimate the effects of several hypothetical interventions, including changes in the amount of alcohol consumption or the types of alcoholic beverages consumed, on hepatic steatosis using longitudinal data, to inform decisions about alcohol-related policymaking and clinical care. **Methods** This longitudinal study included 12 687 participants from the UK Biobank (UKB), all of whom participated in both baseline and repeat surveys. We excluded participants with missing data related to components of alcohol consumption and fatty liver index (FLI) in the baseline and the repeat surveys, as well as those who had reported liver diseases or cancer at the baseline survey. We used FLI as an outcome indicator and divided the participants into non-, moderate, and heavy drinkers. The surrogate marker FLI has been endorsed by many international organizations' guidelines, such as the European Association for the Study of the Liver. The calculation of FLI was based on laboratory and anthropometric data, including triglyceride, gamma-glutamyl transferase, body mass index, and waist circumference. Participants responded to questions about the types of alcoholic beverages, which were defined in 5 categories, including red wine, white wine/fortified wine/champagne, beer or cider, spirits, and mixed liqueurs, along with the average weekly or monthly amounts of alcohol consumed. Alcohol consumption was defined as pure alcohol consumed per week and was calculated according to the amount of alcoholic beverages consumed per week and the average ethanol content by volume in each alcoholic beverage. Participants were categorized as non-drinkers, moderate drinkers, and heavy drinkers according to the amount of their alcohol consumption. Moderate drinking was defined as consuming no more than 210 g of alcohol per week for men and 140 g of alcohol per week for women. We defined the following hypothetical interventions for the amount of alcohol consumed:

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sustaining a certain level of alcohol consumption from baseline to the repeat survey (e.g., none to none, moderate to moderate, heavy to heavy) and changing from one alcohol consumption level to another (e.g., none to moderate, moderate to heavy). The hypothetical interventions for the types of alcoholic beverages were defined in a similar way to those for the amount of alcohol consumed (e.g., red wine to red wine, red wine to beer/cider). We applied the parametric g-formula to estimate the effect of each hypothetical alcohol consumption intervention on the FLI. To implement the parametric g-formula, we first modeled the probability of time-varying confounders and FLI conditional on covariates. We then used these conditional probabilities to estimate the FLI value if the alcohol consumption level of each participant was under a specific hypothetical intervention. The confidence interval was obtained by 200 bootstrap samples. **Results** For the alcohol consumption from baseline to the repeat surveys, 6.65% of the participants were sustained non-drinkers, 63.68% were sustained moderate drinkers, and 14.74% were sustained heavy drinkers, while 8.39% changed from heavy drinking to moderate drinking. Regarding the types of alcoholic beverages from baseline to the repeat surveys, 27.06% of the drinkers sustained their intake of red wine. Whatever the baseline alcohol consumption level, the hypothetical interventions for increasing alcohol consumption from the baseline alcohol consumption were associated with a higher FLI than that of the sustained baseline alcohol consumption level. When comparing sustained non-drinking with the hypothetical intervention of changing from non-drinking to moderate drinking, the mean ratio of FLI was 1.027 (95% confidence interval [CI]: 0.997-1.057). When comparing sustained non-drinking with the hypothetical intervention of changing from non-drinking to heavy drinking, the mean ratio of FLI was 1.075 (95% CI: 1.042-1.108). When comparing sustained heavy drinking with the hypothetical intervention of changing from heavy drinking to moderate drinking, the mean ratio of FLI was 0.953 (95% CI: 0.938-0.968). The hypothetical intervention of changing to red wine in the UKB was associated with lower FLI levels, compared with sustained consumption of other types of alcoholic beverages. For example, when comparing sustaining spirits with the hypothetical intervention of changing from spirits to red wine, the mean ratio of FLI was 0.981 (95% CI: 0.948-1.014). **Conclusions** Regardless of the current level of alcohol consumption, interventions that increase alcohol consumption could raise the risk of hepatic steatosis in Western populations. The findings of this study could inform the formulation of future practice guidelines and health policies. If quitting drinking is challenging, red wine may be a better option than other types of alcoholic beverages in Western populations.

【Key words】 Alcohol consumption Alcoholic beverage type Hepatic steatosis Target trial Hypothetical interventions

非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)和酒精相关的脂肪性肝病(alcohol-associated fatty liver disease, ALD)是两种最常见的慢性肝病[1-4]。据估计,全球NAFLD患病率在过去十年中显著增加,现已超过30%[5]。同时,ALD全球发病率近年来也有所上升[4, 6]。肝脂肪变性是NAFLD和ALD最常见的早期组织学亚型,可发展为肝炎、肝硬化、肝癌,甚至造成肝相关死亡[7-8]。因此,迫切需要对肝脂肪变进行有效防控。

饮酒是导致肝脂肪变的重要危险因素[9-10]。过度饮酒是引发肝脂肪变和其他肝损伤的主要病因[11],然而中度饮酒和肝脂肪变性的关联尚无一致结论[12-14],难以为饮酒相关政策和措施的制定提供依据。饮酒习惯可能随时间变化,但大部分研究仅考虑了单一时点的饮酒行为。研究饮酒行为变化干预对肝脂肪变的影响可回答以下问题:如果从过量饮酒变为戒酒,那么人群中肝脏脂肪变性风险会是多少?如果保持中度饮酒会怎样?如果转变饮酒种类(如从红酒转为啤酒)呢?由于饮酒相关随机临床试验受到医学伦理、可行性、依从性、人群选择和研究持续时间的限制,上述问题通常需要基于纵向观察研究来近似或模拟目标试验(Target trial)[15-16]。

因此,本研究基于英国生物银行(UK Biobank, UKB)的纵向数据模拟了一项目标试验,在反事实场景下评估几种饮酒干预(饮酒量和种类的变化)对肝脏脂肪变性的影响,旨在为饮酒相关政策和措施提供信息支持。我们使用脂肪肝指数(fatty liver index, FLI)作为结果指标,FLI在既往研究中已被证实是反映肝脂肪变进展的准确指标[17],与肝脂肪变等长期慢性结局相比,FLI可以更敏感且迅速地捕捉酒精消费变化的影响[17-18]。

1 资料与方法

1.1 研究对象

UKB[19-20]是一项前瞻性队列研究,纳入了50万余名39~74岁的参与者,基线调查数据在2006–2010年间收集,20 343名参与者于2012年8月–2013年6月间参加了重复调查。参与者在基线和重复调查时接受了系列评估,包括电子问卷调查、人体测量、综合医疗检查和生化指标检测。所有参与者在数据收集前都签署了知情同意。UKB获得North-West Multi-centre Research Ethics Committee

批准。本研究纳入了同时参与基线及重复调查的参与者（n=20 343），排除了在两次调查中缺少饮酒和FLI相关数据的参与者（n=6 638），排除了在基线调查中报告患有肝病或癌症的参与者（n=1 018）。最后，12 687名参与者被纳入统计分析。

1.2　饮酒评估

UKB收集了参与者饮酒种类（红酒、白酒或香槟、啤酒或苹果酒、烈酒或利口酒、强化酒等）及每周或每月的平均饮酒量信息。与既往研究类似，参与者的酒精摄入量根据每种酒精饮料的平均酒精含量和每周消耗量计算[21]。本研究将参与者分为不饮酒者、中度饮酒者和重度饮酒者。根据欧洲肝脏研究协会（European Association for the Study of the Liver, EASL）[22]和美国肝脏研究协会（American Association for the Study of the Liver, AASLD）[23]的建议，中度饮酒被定义为男性每周饮酒不超过210 g，女性每周饮酒不超过140 g，超过上述推荐的酒精量被定义为重度饮酒。与既往研究类似[24]，饮酒种类定义为占每周消耗总酒精量的50%以上的酒精饮料类型，最终将饮酒种类分为5类，即红酒、干白/强化酒/香槟、啤酒/苹果酒、烈酒以及混合酒。

本研究中饮酒干预包括饮酒量和饮酒种类。饮酒量干预包括从基线到重复调查保持恒定的酒精量，以及从基线饮酒水平改变为另一水平。类似地，饮酒种类干预包括从基线到重复调查维持恒定的饮酒类型，以及从基线饮酒种类改变为另一种类。

1.3　脂肪肝指数评估

本研究使用的结局指标FLI已被许多国际组织指南认可（如EASL和APASL指南）[22, 25-28]。FLI的计算均基于实验室生化检测及人体测量数据，包括三酰甘油（TG, mmol/L）、γ-谷氨酰转移酶（GGT, U/L）、体质量指数（body mass index, BMI, kg/m^2）和腰围（WC, cm）。FLI的计算公式为[28]：

$$\mathrm{FLI}=\frac{e^{0.953\times log(\mathrm{TG}/0.0113)+0.139\times \mathrm{BMI}+0.718\times log(\mathrm{GGT})+0.053\times \mathrm{WC}-15.745}}{1+e^{0.953\times log(\mathrm{TG}/0.0113)+0.139\times \mathrm{BMI}+0.718\times log(\mathrm{GGT})+0.053\times \mathrm{WC}-15.745}}\times 100$$

1.4　协变量

为了更好地指导潜在混杂因素的选择，我们首先根据文献[29]构建了有向无环图（Evidence Synthesis for Constructing Directed Acyclic Graphs, ESC-DAGs）。然后，基于DAGs和后门标准确定潜在的混杂集。在纵向研究中，我们将混杂分为非时变混杂和时变混杂[30]。我们考虑了以下非时变混杂：性别、种族、教育、社会经济地位以及家族史。时变混杂包括年龄、女性月经状况、饮食评分、吸烟状况、高血压状况、糖尿病状况、体力活动水平（METs-h/d）、失眠状况、抑郁状况、焦虑状况。

1.5　统计学方法

参与者的基线和重复调查特征被描述为平均值（标准差，SD）或中位数（四分位数间距）以及频数（百分比）。此外，我们还对饮酒行为变化进行了描述。

Parametric g-formula是因果推断框架下对标准化法在时变暴露和时变混杂情形的拓展，可以处理受过去暴露影响的混杂对估计值造成的偏倚，在反事实框架下估计干预的效果，这种方法已广泛用于各种临床场景[30-32]。因此，本研究应用parametric g-formula来估计每种模拟场景下的饮酒干预对FLI的影响。饮酒干预措施已在“饮酒评估”一节进行了描述。为了实现参数parametric g-formula，我们首先建立时变混杂因素的条件概率模型；然后，在特定的饮酒行为干预下，使用这些条件概率来估计FLI值。进而，将特定饮酒行为干预下的FLI值与参考组进行比较，并计算FLI的平均差异（mean difference, MD）和平均比率（mean ratio, MR）。为了更直观地比较模拟干预的影响，我们选择饮酒量或饮酒种类恒定组（与基线相比）作为参考组。置信区间由200个bootstrap样本获得。对于协变量中的缺失数据，我们使用链式方程法进行多重插补（5次）。此外，本研究计算E值来评估可能的未测量混杂因素的影响，较大的E值意味着需要大量未测量混杂因素来解释掉效应估计值[33]。除了计算E值，我们还通过固定效应模型（fixed effect model, FEM）评估了饮酒量变化和FLI之间的关系，该模型可以控制未测量非时变混杂因素对效应估计值造成的偏倚[34]。我们使用R 4.1.1版本进行所有分析。

2　结果

2.1　参与者特征

本研究12 687名参与者的平均年龄为57.13岁（SD 7.36）；46.7%的参与者为女性（表1）。基线和重复调查的平均FLI水平分别为44.84（SD 29.23）和46.27（SD 28.66）。对于饮酒量，6.65%的参与者保持不饮酒，63.68%的参与者保持中度饮酒，14.74%的参与者保持大量饮酒，8.39%的参与者从大量饮酒变为中度饮酒（表2）。在基线及重复调查均饮酒人群中（11 499人），27.06%的饮酒者持续摄入红酒，13.48%的饮酒者持续摄入干白/强化酒/香槟，19.13%的饮酒者持续摄入啤酒/苹果酒，2.43%的饮酒者持续摄入烈酒，4.08%的饮酒者从混合饮酒类型转变为红酒（表3）。

2.2　不同饮酒量及饮酒种类干预下的FLI水平

本研究使用parametric g-formula模拟特定的饮酒量与饮酒种类干预下的FLI水平。结果（图1）显示，无论

表 1 UKB参与者的基线及重复调查特征 (*n*=12 687)

Table 1 The baseline and repeat survey characteristics of the study participants in the UKB (*n*=12 687)

Characteristic	Baseline survey	Repeat survey
Age/yr., mean (SD)	57.13 (7.36)	61.35 (7.35)
Female/case (%)	5 926 (46.7)	
White race/case (%)	12 438 (98.0)	
Low education level/case (%)	1 031 (8.2)	
Socioeconomic status (median [IQR])	−2.81 (−4.03, −0.93)	
Menopausal status in female/case (%)		
Pre-menopause	1 253 (21.1)	597 (10.1)
Post-menopause	3 765 (63.5)	4 423 (74.6)
Not sure	904 (15.3)	902 (15.2)
Family history/case (%)	9 534 (75.1)	
Self-reported hypertension/case (%)	2 834 (22.3)	3 300 (26.0)
Self-reported diabetes/case (%)	471 (3.7)	651 (5.1)
Current smoking/case (%)	822 (6.5)	575 (4.5)
Dietary score (median [IQR])	4.00 (3.00, 5.00)	4.00 (3.00, 5.00)
Total physical activity/(MET h/d), median [IQR]	4.13 (1.91, 7.96)	4.24 (2.03, 7.87)
Insomnia symptoms/case (%)	9 352 (73.7)	9 526 (75.1)
Depressive symptoms/case (%)	402 (3.3)	380 (3.1)
Anxiety symptoms/case (%)	359 (2.9)	291 (2.3)
BMI/(kg/m^2), mean (SD)	26.74 (4.28)	26.79 (4.34)
FLI (mean [SD])	44.84 (29.23)	46.27 (28.66)

FLI: fatty liver index, BMI: body mass index. The data are expressed as mean (standard deviation), median (interquartile range), or percentage. Low education level is defined as none of advanced (A/AS) levels, ordinary level (O-level), general certificate of secondary education, and the other equivalent or higher levels. Socioeconomic status is defined on the basis of the Townsend deprivation index. Family history refers to self-reported history of hypertension, stroke, or CVD from at least one first-degree relative (biological parents and siblings) in the baseline survey. The dietary score is based on the consumption of 7 dietary components ranging from 0 to 7[35].

表 2 UKB参与者基线及重复调查的饮酒量特征 (*n*=12 687)

Table 2 Characteristics of alcohol consumption in UKB baseline and repeated surveys (*n*=12 687)

Alcohol consumption	Baseline survey	Repeat survey
Capacity for alcohol/(g/week), mean (SD)	126.43 (119.15)	109.52 (108.12)
Level of drink/case (%)		
None	963 (7.6)	1 069 (8.4)
Moderate	8 768 (69.1)	9 256 (73.0)
Heavy	2 956 (23.3)	2 362 (18.6)
Changes in the level of alcohol consumption/case (%)		
None to none	844 (6.65)	
None to moderate	114 (0.90)	
None to heavy	5 (0.04)	
Modest to none	202 (1.59)	
Moderate to moderate	8 079 (63.68)	
Moderateto heavy	487 (3.84)	
Heavy to none	23 (0.18)	
Heavy to moderate	1 063 (8.39)	
Heavy to heavy	1 870 (14.74)	

Moderate drinking is defined as ⩽210 g/week for men and ⩽140 g/week for women in the UKB. Levels exceeding those mentioned above are defined as heavy drinking.

表 3　UKB饮酒人群基线及重复调查饮酒种类特征 (*n*=11 499)

Table 3　Characteristics of the types of alcoholic beverages among the drinkers in the UKB baseline and repeated surveys (*n*=11 499)

Alcoholic beverages type	Baseline survey	Repeat survey
Type/case (%)		
Red wine	4 205 (36.6)	4 158 (36.2)
Other wines	2 188 (19.0)	2 261 (19.7)
Beer/cider	2 793 (24.3)	2 817 (24.5)
Spirits	482 (4.2)	535 (4.7)
Mixed	1 831 (15.9)	1 728 (15.0)
Changes in the alcoholic beverages type among drinkers from baseline to repeat survey/case (%)		
Red wine to red wine	3 112 (27.06)	
Red wine to other wines	363 (3.16)	
Red wine to beer/cider	197 (1.71)	
Red wine to spirits	79 (0.69)	
Red wine to mixed	454 (3.95)	
Other wines to red wine	304 (2.64)	
Other wines to other wines	1 550 (13.48)	
Other wines to beer/cider	90 (0.78)	
Other wines to spirits	58 (0.50)	
Other wines to mixed	186 (1.62)	
Beer/cider to red wine	213 (1.85)	
Beer/cider to other wines	90 (0.78)	
Beer/cider to beer/cider	2 200 (19.13)	
Beer/cider to spirits	48 (0.42)	
Beer/cider to mixed	242 (2.10)	
Spirits to red wine	60 (0.52)	
Spirits to other wines	48 (0.42)	
Spirits to beer/cider	51 (0.44)	
Spirits to spirits	279 (2.43)	
Spirits to mixed	44 (0.38)	
Mixed to red wine	469 (4.08)	
Mixed to other wines	210 (1.83)	
Mixed to beer/cider	279 (2.43)	
Mixed to spirits	71 (0.62)	
Mixed to mixed	802 (6.97)	

In the UKB, other wines refer to white wine/fortified wine/champagne in our study. We showed the changes in the alcoholic beverages among drinkers in both baseline and repeated surveys.

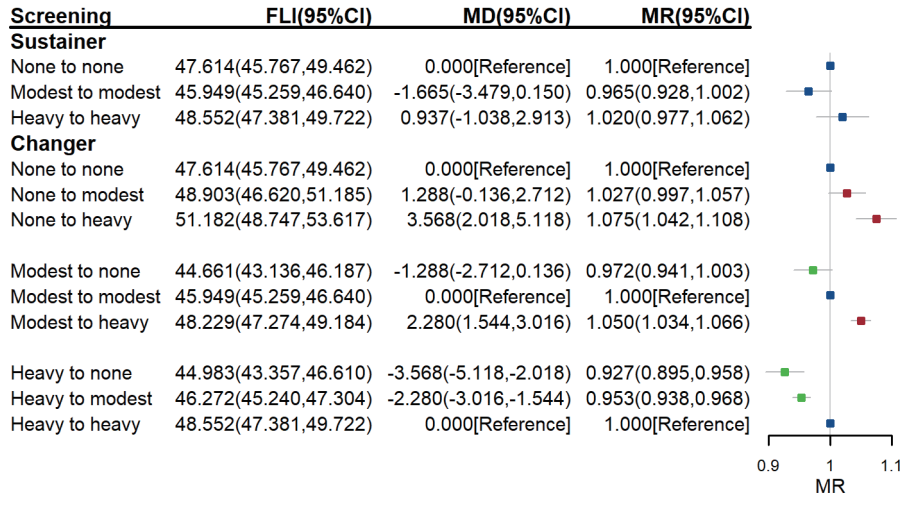

图 1 在UKB中模拟的不同饮酒量干预下FLI的平均差异和平均比率

Fig 1 The mean differences and mean ratio of FLI under the different hypothetical interventions for alcohol consumption in the UKB

FLI: fatty liver index; MD: mean difference; MR: mean ratio. The blue box represents the hypothetical interventions of sustaining alcohol consumption, the green box represents the hypothetical interventions of reducing alcohol consumption, and the red box represents the hypothetical interventions of increasing alcohol consumption.

基线饮酒水平如何，与保持基线饮酒量相比，增加酒精摄入与较高的FLI水平相关，减少酒精摄入与较低的FLI有关。例如，将持续不饮酒与从不饮酒改为重度饮酒的干预措施相比，FLI的平均比率为1.075（95%置信区间：1.042，1.108）；将持续中度饮酒与从中度饮酒变为不饮酒的措施相比，FLI的平均比率为0.972（95%置信区间：0.941，1.003）；将持续大量饮酒与从大量饮酒改为中度饮酒的干预相比，FLI的平均比率为0.953（95%置信区间：0.938，0.968）。图2为调整饮酒量后，模拟的几种饮酒类型干预下的估计结果。尽管估计结果的置信区间很宽，但结果提示，与保持其他饮酒种类相比，饮酒种类改变为红酒与较低的FLI水平相关。例如，将持续饮用烈酒与持续饮用红酒比较，FLI的平均比率为0.981（95%置信区间：0.948，1.014）。

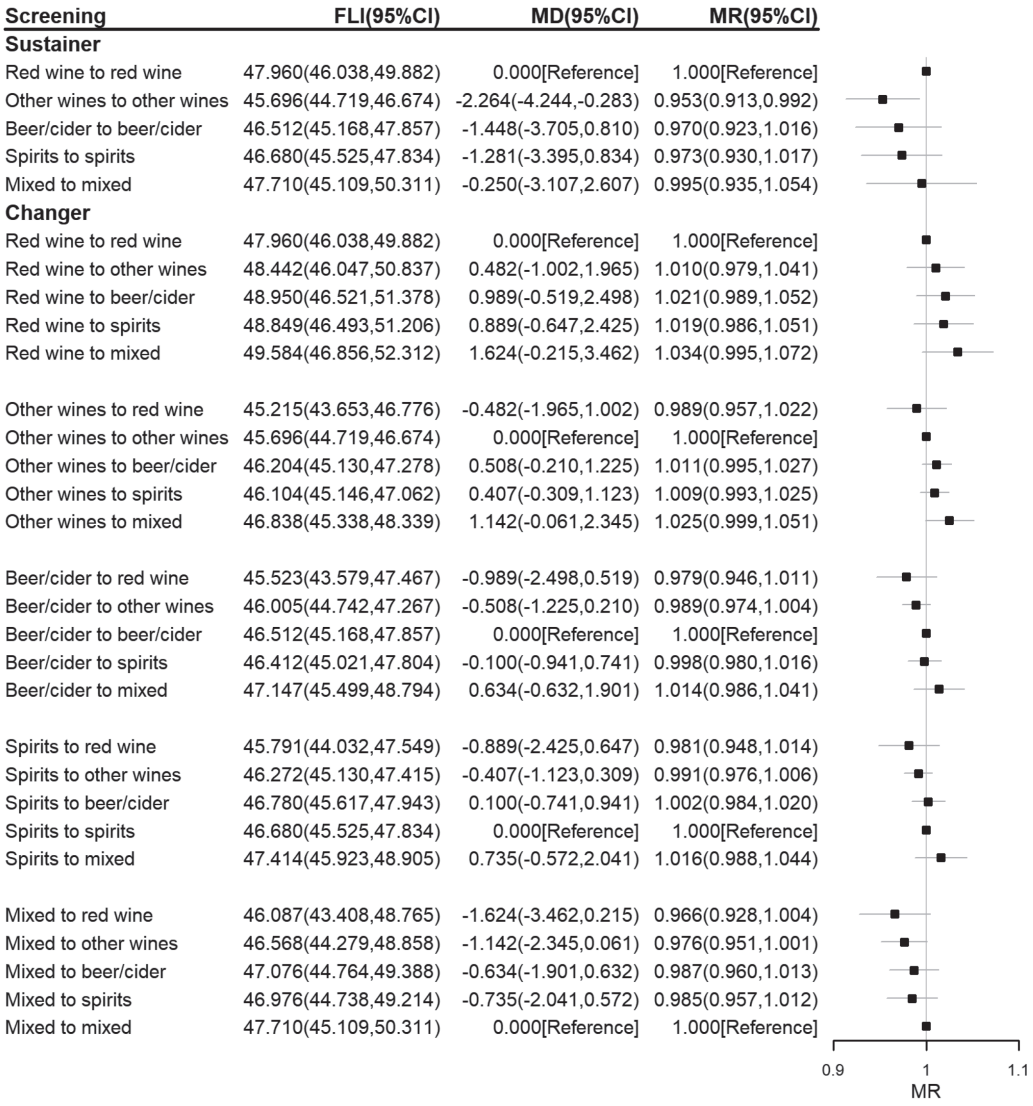

图 2 在UKB中模拟的不同饮酒种类下FLI的平均差异和平均比率

Fig 2 The mean differences and mean ratios of FLI under the different hypothetical interventions for alcoholic beverage types in the UKB

FLI: fatty liver index; MD: mean difference; MR: mean ratio.

研究结果显示，所有模拟饮酒量干预和FLI关联的最小*E*值为5.9，所有假设饮酒种类干预和FLI关联的最小*E*值为1.4，意味着在校正了所有可能的混杂后，未测量混杂至少需要是暴露和结果关联的1.4倍，才可能会造成偏倚。*E*值提示我们的结果较为稳健，不大可能受混杂因素的影响。在FEM分析中，考虑到饮酒种类的变化样本量很小，我们只关注酒精量变化和FLI之间的关联。FEM分析结果显示，与持续不饮酒相比，持续中度饮酒和增加饮酒与较高水平的FLI相关（表4）。

3 讨论

3.1 减少饮酒量可降低肝脂肪变性的风险

受随机临床试验可实行性的限制，既往关于饮酒和肝脂肪变性之间关系的研究主要是观察性研究，且未提

表 4　基于固定效应模型估计的饮酒量变化和FLI间的关联

Table 4　FEM analysis of the association between changes in alcohol consumption and changes in FLI in the UKB

Alcohol consumption	Point estimate	95% CI
Sustained non-drinking	Reference	–
Sustained modest drinking	0.72	−0.65, 2.10
Sustained heavy drinking	1.94	0.39, 3.49
Increased alcohol consumption	2.98	1.03, 4.94
Decreased alcohol consumption	−1.00	−2.65, 0.65

CI: confidence interval.

供一致研究结论[13, 36]。现有横断面研究、队列研究和荟萃分析发现，中度饮酒与肝脂肪变性和继发性肝病的风险降低相关[13, 37-38]。相反，一些研究发现，即使很少量的酒精摄入也与肝损伤有关[12, 36, 39-40]。目前大多数既往的观察性研究只关注基线时一次的饮酒，这有悖于饮酒行为可能会随着时间的推移而改变的事实。最近一项关于酒精消费量变化的研究表明，酒精量增加与肝癌风险增加有关，这与本研究结果方向一致，但该研究没有考虑复杂的时变混杂结构[41]。本研究中，parametric g-formula可以处理时变混杂因素，并模拟的饮酒量变化的影响，这可以被视为对随机试验的模拟，有助于为临床指导和指南提供信息[30, 42]。

本研究表明，无论基线饮酒水平如何，增加饮酒量是肝脂肪变性的高危因素。酒精对肝脏脂肪变性的影响可能是由于乙醇毒素，它可以破坏肝脏脂质稳态，包括表达、底物供应、氧化和分泌等过程[9]。在实践指南或政策层面，正如我们对大量饮酒的预期，大量饮酒会增加肝脂肪变性的风险，这与肝脏协会（The Asian Pacific Association for the Study of the Liver [43]、EASL[22]和AASLD[8]）的现行的临床指南一致。然而，这些指南均未明确指出中度饮酒对于普通人群中的脂肪肝疾病是否安全[44]。我们的结果表明，与持续不饮酒相比，增加中度饮酒会增加肝脂肪变性的风险，而与持续中度饮酒相比，戒酒会降低肝脂肪变性的风险，可为针对广大普通人群的指南提供信息。

3.2　对于难以完全戒酒的人，红酒可能是更好的选择

一项临床试验表明，一个月的中度啤酒消费不会增加西班牙成年人的肝酶值[45]。两项前瞻性队列研究表明，与啤酒和白酒相比，红酒可能与较低的肝硬化风险相关[24, 46]。本研究表明，相比于持续摄入其他类型的饮酒种类，红酒与较低的肝脂肪变性风险相关。红酒对肝脏的损害较小，这可能与富含酚类化合物（即白藜芦醇、酚酸和类黄酮）[47]有关，这些化合物已被证明具有抗炎、抗氧化和调节肝脏脂质代谢和抗炎的作用。目前现行的指南中，并没有对饮酒种类的推荐[44]。本研究结果提示，如果戒酒很难实现，喝红酒可能是更好的选择，这有助于为未来的实践指南和健康政策建议提供信息。

3.3　本研究的优势与局限性

据我们所知，这项研究首次尝试评估饮酒行为改变的假设干预对肝脂肪变性风险的影响。我们研究的优势包括使用经过充分研究论证的纵向队列数据集，其通过标准化数据采集方法和多重测量获得了高质量数据；基于DAG对潜在混杂因素进行充分调整；使用parametric g-formula来处理复杂的混杂结构。在难以开展临床试验的场景下，我们模拟了一项目标试验，可能具有重要的临床和公共卫生意义。但本研究也存在以下几方面的局限性：首先，我们使用FLI来指示肝脏脂肪变性，而不是直接通过MRI等测量肝脏脂肪变性。MRI等在这大规模人群研究中很难实现，我们使用准确且经过验证的连续生物标志物可以比长期逐渐发展的肝脏脂肪变性更敏感且迅速地捕捉酒精使用变化的影响。第二，饮酒量的计算来自于自报问卷，这可能会造成饮酒量的低估。第三，虽然我们已经仔细控制了混杂，仍可能存在其他未测量混杂。然而，*E*值和FEM分析提示研究结果很少受到未测量混杂的影响。第四，在不同的模拟干预下，sustainer与参考组的基线饮酒水平不同，changer与参考组相同的基线饮酒水平，相比于sustainer，changer的结果更具可比性。因此，在比较sustainer的效应时需谨慎。第五，本研究基于UKB人群的基线及重复调查数据分析显示出具有统计学意义的结果，但统计学意义并不代表临床意义，在实际指导临床时需注意。第六，由于本研究使用了完成基线和重复测量的小部分参与者的数据，本研究结论在推广至整体人群时需注意。

4　结论

我们的研究表明，无论目前饮酒水平如何，增加饮酒量的摄入都会增加肝脂肪变性的风险，而减少饮酒可以降低肝脂肪变性的风险，这有助于为未来的实践指南和卫生政策提供信息。如果戒酒有挑战性，红酒可能是减缓肝脂肪变性的更好选择。

*　　*　　*

作者贡献声明　张宁负责论文构思、数据审编、正式分析、调查研究、研究方法、可视化、初稿写作和审读与编辑写作，张圆负责数据审编和软件，魏君负责数据审编和验证，向毅负责调查研究和审读与编辑写作，胡逸凡负责审读与编辑写作，肖雄负责论文构思、经费获取、研究项目管理、提供资源和监督指导。所有作者已经同意将文章提交给本刊，且对将要发表的版本进行最终定稿，并同意对工作的所有方面负责。

Author Contribution ZHANG Ning is responsible for conceptualization, data curation, formal analysis, investigation, methodology, visualization, writing--original draft, and writing--review and editing. ZHANG Yuan is responsible for data curation and software. WEI Jun is responsible for data curation and validation. XIANG Yi is responsible for investigation and writing--review and editing. HU Yifan is responsible for writing--review and editing. XIAO Xiong is responsible for conceptualization, funding acquisition, project administration, resources, and supervision. All authors consented to the submission of the article to the Journal. All authors approved the final version to be published and agreed to take responsibility for all aspects of the work.

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参 考 文 献

[1] POWELL E E, WONG V W, RINELLA M. Non-alcoholic fatty liver disease. Lancet, 2021, 397(10290): 2212–2224. doi: 10.1016/S0140-6736(20)32511-3.

[2] YOUNOSSI Z M. Non-alcoholic fatty liver disease--a global public health perspective. J Hepatol, 2019, 70(3): 531–544. doi: 10.1016/j.jhep.2018.10.033.

[3] ASRANI S K, MELLINGER J, ARAB J P, *et al*. Reducing the global burden of alcohol-associated liver disease: a blueprint for action. Hepatology, 2021, 73(5): 2039–2050. doi: 10.1002/hep.31583.

[4] DEVARBHAVI H, ASRANI S K, ARAB J P, *et al*. Global burden of liver disease: 2023 update. J Hepatol, 2023, 79(2): 516-537. doi: 10.1016/j.jhep.2023.03.017.

[5] RIAZI K, AZHARI H, CHARETTE J H, *et al*. The prevalence and incidence of NAFLD worldwide: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol, 2022, 7(9): 851–861. doi: 10.1016/S2468-1253(22)00165-0.

[6] WU X, FAN X, MIYATA T, *et al*. Recent advances in understanding of pathogenesis of alcohol-associated liver disease. Annu Rev Pathol, 2023, 18: 411–438. doi: 10.1146/annurev-pathmechdis-031521-030435.

[7] ABDELMALEK M F. Nonalcoholic fatty liver disease: another leap forward. Nat Rev Gastroenterol Hepatol, 2021, 18(2): 85–86. doi: 10.1038/s41575-020-00406-0.

[8] CRABB D W, IM G Y, SZABO G, *et al*. Diagnosis and treatment of alcohol-associated liver diseases: 2019 practice guidance From the American association for the study of liver diseases. Hepatology, 2020, 71(1): 306–333. doi: 10.1002/hep.30866.

[9] YOU M, ARTEEL G E. Effect of ethanol on lipid metabolism. J Hepatol, 2019, 70(2): 237–248. doi: 10.1016/j.jhep.2018.10.037.

[10] YOUNOSSI Z, HENRY L. Contribution of alcoholic and nonalcoholic fatty liver disease to the burden of liver-related morbidity and mortality. Gastroenterology, 2016, 150(8): 1778–1785. doi: 10.1053/j.gastro.2016.03.005.

[11] SINGAL A K, BATALLER R, AHN J, *et al*. ACG clinical guideline: alcoholic liver disease. Am J Gastroenterol, 2018, 113(2): 175–194. doi: 10.1038/ajg.2017.469.

[12] CHOI J H, SOHN W, CHO Y K. The effect of moderate alcohol drinking in nonalcoholic fatty liver disease. Clin Mol Hepatol, 2020, 26(4): 662–669. doi: 10.3350/cmh.2020.0163.

[13] SOOKOIAN S, CASTAÑO G O, PIROLA C J. Modest alcohol consumption decreases the risk of non-alcoholic fatty liver disease: a meta-analysis of 43 175 individuals. Gut, 2014, 63(3): 530–532. doi: 10.1136/gutjnl-2013-305718.

[14] AJMERA V H, TERRAULT N A, HARRISON S A. Is moderate alcohol use in nonalcoholic fatty liver disease good or bad? A critical review. Hepatology, 2017, 65(6): 2090–2099. doi: 10.1002/hep.29055.

[15] DREYER N A, TUNIS S R, BERGER M, *et al*. Why observational studies should be among the tools used in comparative effectiveness research. Health Aff (Millwood), 2010, 29(10): 1818–1825. doi: 10.1377/hlthaff.2010.0666.

[16] HERNáN M A, ROBINS J M. Using big data to emulate a target trial when a randomized trial is not available. Am J Epidemiol, 2016, 183(8): 758–764. doi: 10.1093/aje/kwv254.

[17] HAN A L. Validation of fatty liver index as a marker for metabolic dysfunction-associated fatty liver disease. Diabetol Metab Syndr, 2022, 14(1): 44. doi: 10.1186/s13098-022-00811-2.

[18] ARONSON J K, FERNER R E. Biomarkers--a general review. Curr Protoc Pharmacol, 2017, 76: 9.23.1-9.23.17. doi: 10.1002/cpph.19.

[19] MANTHEY J, SHIELD K D, RYLETT M, *et al*. Global alcohol exposure between 1990 and 2017 and forecasts until 2030: a modelling study. Lancet, 2019, 393(10190): 2493–2502. doi: 10.1016/S0140-6736(18)32744-2.

[20] CONROY M, SELLORS J, EFFINGHAM M, *et al*. The advantages of UK Biobank's open-access strategy for health research. J Intern Med, 2019, 286(4): 389–397. doi: 10.1111/joim.12955.

[21] INNES H, CROOKS C J, ASPINALL E, *et al*. Characterizing the risk interplay between alcohol intake and body mass index on cirrhosis morbidity. Hepatology, 2022, 75(2): 369–378. doi: 10.1002/hep.32123.

[22] European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol, 2016, 64(6): 1388-1402. doi: 10.1016/j.jhep.2015.11.004.

[23] O'SHEA R S, DASARATHY S, MCCULLOUGH A J. Alcoholic liver disease. Hepatology, 2010, 51(1): 307–328. doi: 10.1002/hep.23258.

[24] JANI B D, MCQUEENIE R, NICHOLL B I, *et al*. Association between patterns of alcohol consumption (beverage type, frequency and consumption with food) and risk of adverse health outcomes: a prospective cohort study. BMC Med, 2021, 19(1): 8. doi: 10.1186/s12916-020-01878-2.

[25] ESLAM M, SARIN S K, WONG V W, *et al*. The Asian Pacific Association for the study of the liver clinical practice guidelines for the diagnosis and management of metabolic associated fatty liver disease. Hepatol Int, 2020, 14(6): 889–919. doi: 10.1007/s12072-020-10094-2.

［26］ SIAFI E, ANDRIKOU I, THOMOPOULOS C, *et al*. Fatty liver index and cardiovascular outcomes in never-treated hypertensive patients: a prospective cohort. Hypertens Res, 2023, 46(1): 119–127. doi: 10.1038/s41440-022-01015-x.

［27］ CALORI G, LATTUADA G, RAGOGNA F, *et al*. Fatty liver index and mortality: the Cremona study in the 15th year of follow-up. Hepatology, 2011, 54(1): 145–152. doi: 10.1002/hep.24356.

［28］ BEDOGNI G, BELLENTANI S, MIGLIOLI L, *et al*. The fatty liver index: a simple and accurate predictor of hepatic steatosis in the general population. BMC Gastroenterol, 2006, 6: 33. doi: 10.1186/1471-230X-6-33.

［29］ FERGUSON K D, MCCANN M, KATIKIREDDI S V, *et al*. Evidence synthesis for constructing directed acyclic graphs (ESC-DAGs): a novel and systematic method for building directed acyclic graphs. Int J Epidemiol, 2020, 49(1): 322–329. doi: 10.1093/ije/dyz150.

［30］ MANSOURNIA M A, ETMINAN M, DANAEI G, *et al*. Handling time varying confounding in observational research. BMJ, 2017, 359: j4587. doi: 10.1136/bmj.j4587.

［31］ NAIMI A I, COLE S R, KENNEDY E H. An introduction to g methods. Int J Epidemiol, 2017, 46(2): 756–762.

［32］ DOOSTI-IRANI A, MANSOURNIA M A, COLLINS G. Use of G-methods for handling time-varying confounding in observational research. Lancet Glob Health, 2019, 7(1): e35. doi: 10.1016/S2214-109X(18)30471-6.

［33］ VANDERWEELE T J, DING P. Sensitivity analysis in observational research: introducing the E-value. Ann Intern Med, 2017, 167(4): 268–274. doi: 10.7326/M16-2607.

［34］ ROHRER J M, MURAYAMA K. These are not the effects you are looking for: causality and the within-/between-persons distinction in longitudinal data analysis. Adv Method Pract Psychol Sci, 2023, 6(1): 25152459221140842.

［35］ ZHANG Y, YANG H, LI S, *et al*. Consumption of coffee and tea and risk of developing stroke, dementia, and poststroke dementia: a cohort study in the UK Biobank. PLoS Med, 2021, 18(11): e1003830. doi: 10.1371/journal.pmed.1003830.

［36］ ROERECKE M, VAFAEI A, HASAN O S M, *et al*. Alcohol consumption and risk of liver cirrhosis: a systematic review and meta-analysis. Am J Gastroenterol, 2019, 114(10): 1574–1586. doi: 10.14309/ajg.0000000000000340.

［37］ MORIYA A, IWASAKI Y, OHGUCHI S, *et al*. Alcohol consumption appears to protect against non-alcoholic fatty liver disease. Aliment Pharmacol Ther, 2011, 33(3): 378–388. doi: 10.1111/j.1365-2036.2010.04520.x.

［38］ DUNN W, SANYAL A J, BRUNT E M, *et al*. Modest alcohol consumption is associated with decreased prevalence of steatohepatitis in patients with non-alcoholic fatty liver disease (NAFLD). J Hepatol, 2012, 57(2): 384–391. doi: 10.1016/j.jhep.2012.03.024.

［39］ IM P K, MILLWOOD I Y, KARTSONAKI C, *et al*. Alcohol drinking and risks of liver cancer and non-neoplastic chronic liver diseases in China: a 10-year prospective study of 0.5 million adults. BMC Med, 2021, 19(1): 216. doi: 10.1186/s12916-021-02079-1.

［40］ BLOMDAHL J, NASR P, EKSTEDT M, *et al*. Moderate alcohol consumption is associated with advanced fibrosis in non-alcoholic fatty liver disease and shows a synergistic effect with type 2 diabetes mellitus. Metabolism, 2021, 115: 154439. doi: 10.1016/j.metabol.2020.154439.

［41］ YOO J E, HAN K, SHIN D W, *et al*. Association between changes in alcohol consumption and cancer risk. JAMA Netw Open, 2022, 5(8): e2228544. doi: 10.1001/jamanetworkopen.2022.28544.

［42］ ROJAS-SAUNERO L P, HILAL S, MURRAY E J, *et al*. Hypothetical blood-pressure-lowering interventions and risk of stroke and dementia. Eur J Epidemiol, 2021, 36(1): 69–79. doi: 10.1007/s10654-020-00694-5.

［43］ FARRELL G C, CHITTURI S, LAU G K, *et al*. Guidelines for the assessment and management of non-alcoholic fatty liver disease in the Asia-Pacific region: executive summary. J Gastroenterol Hepatol, 2007, 22(6): 775–777. doi: 10.1111/j.1440-1746.2007.05002.x.

［44］ FURTWAENGLER N A, De VISSER R O. Lack of international consensus in low-risk drinking guidelines. Drug Alcohol Rev, 2013, 32(1): 11–18. doi: 10.1111/j.1465-3362.2012.00475.x.

［45］ ROMEO J, GONZÁLEZ-GROSS M, WÄRNBERG J, *et al*. Effects of moderate beer consumption on blood lipid profile in healthy Spanish adults. Nutr Metab Cardiovasc Dis, 2008, 18(5): 365–372. doi: 10.1016/j.numecd.2007.03.007.

［46］ ASKGAARD G, GRØNBÆK M, KJÆR M S, *et al*. Alcohol drinking pattern and risk of alcoholic liver cirrhosis: a prospective cohort study. J Hepatol, 2015, 62(5): 1061–1067. doi: 10.1016/j.jhep.2014.12.005.

［47］ ZHOU Y, HUA J, HUANG Z. Effects of beer, wine, and baijiu consumption on non-alcoholic fatty liver disease: Potential implications of the flavor compounds in the alcoholic beverages. Front Nutr, 2022, 9: 1022977. doi: 10.3389/fnut.2022.1022977.

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