Association of thirty-year alcohol consumption typologies and fatty liver: findings from a large population cohort study

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Abstract

Objective: To evaluate the longitudinal relationship between repeated measures of alcohol consumption and risk of developing fatty liver.

Patients and Methods – This study includes 5,407 men and women from a British population based cohort, the Whitehall II study of civil servants, who self-reported alcohol consumption by questionnaire over approximately 30 years (1985-1989 through to 2012-2013). Drinking typologies during midlife were linked to measures of fatty liver (the fatty liver index, FLI) when participants were in older age (age range 60-84 years) and adjusted for age, socio-economic position, ethnicity, and smoking.

Results - Those who consistently drank heavily had two-fold higher odds of increased FLI compared to stable low-risk moderate drinkers after adjustment for covariates (men: OR=2.04, 95%CI=1.53-2.74; women: OR=2.24, 95%CI=1.08-4.55). Former drinkers also had an increased FLI compared to low-risk drinkers (men: OR=2.09, 95%CI=1.55-2.85; women: OR=1.68, 95%CI=1.08-2.67). There were non-significant differences in FLI between non-drinkers and stable low-risk drinkers. Among women, there was no increased risk for current heavy drinkers in cross sectional analyses.

Conclusion - Drinking habits among adults during midlife affect the development of fatty liver and sustained heavy drinking is associated with an increased FLI compared to stable low-risk drinkers. After the exclusion of former drinkers, there was no difference between non-drinkers and low-risk drinkers, which does not support a protective effect on fatty liver from low-risk drinking. Cross-sectional analyses among women did not find an increased risk of heavy drinking compared to low-risk drinkers, thus highlighting the need to take a longitudinal approach.

Keywords: fatty liver; alcohol; longitudinal; cohort

Abbreviations: UK (United Kingdom), BMI (body mass index), FLD (fatty liver disease), FLI (fatty liver index), SEP (socio-economic position), SD (standard deviation), OR (odds ratio), CI (confidence interval)

1. INTRODUCTION

Liver disease mortality rates in UK have increased four-fold since 1970 and liver disease is the third most common cause of premature death in the UK (Williams et al., 2014). It has long been known that chronic heavy drinking is major risk factor for liver cirrhosis and liver cancer; approximately 20-30% of lifelong heavy drinkers develop cirrhosis (Williams et al., 2014).

The relationship between alcohol consumption and fatty liver disease (FLD) is less clear. FLD is caused by the excessive accumulation of fat in liver cells and can progress to cirrhosis and hepatocellular carcinoma (Reddy and Rao, 2006). The findings from a recent meta-analysis of alcohol and risk of FLD suggest that light to moderate alcohol consumption is associated with a lower risk of FLD than non-drinking whilst heavy drinking is likely to be detrimental (Cao et al., 2016). However, most previous studies included in this meta-analysis were cross-sectional (15 out of 16 studies). Taking only a single measurement of alcohol consumption assumes that drinking is stable over the life course which is not necessarily true as data from descriptive studies indicate that people change their alcohol consumption habits over time (Britton et al., 2015; Kerr et al., 2002). (Greenfield and Kerr, 2011). Furthermore, cross-sectional studies are at risk of reverse causation whereby harm to health may have influenced drinking behaviour, i.e. an individual's current drinking habits may have been influenced by their health rather than vice versa. The meta-analysis of observational studies also did not distinguish between former drinkers and never drinkers (Bell and Britton, 2015a). Failure to include such dynamics can lead to incorrect inferences about the effects of alcohol on chronic disease risk (Arbeev et al., 2014).

The "fatty liver index" (FLI), a measure that incorporates anthropometry, liver enzymes and metabolic parameters, has been shown to correlate with hepatic steatosis and predict fatty liver disease (Bedogni et al., 2006). In this paper we sought to (1) describe long term drinker

typologies during mid-life, (2) link these drinker typologies to risk of fatty liver disease, as measured by FLI in older-age and (3) compare these longitudinal associations with cross-sectional findings in the same cohort (to contrast the associations in drinking typologies with associations among current drinker types).

2. METHODS

2.1 Participants and setting

Data were drawn from a population based cohort, the Whitehall II cohort of British civil servants.(Marmot and Brunner, 2005) The Whitehall II study is an on-going cohort study of men and women originally employed by the British civil service in London-based offices(Marmot and Brunner, 2005). A total of 10,308 persons (6,895 men and 3,413 women, aged 35 to 55 years) were recruited over the years 1985-1988. Since baseline, there has been a clinical examination every 4-5 years and a self-administered questionnaire every 2 to 3 years. Alcohol consumption was self-reported at six time points over nearly 30 years and the FLI was calculated when participants were in older-age (age range 60-84 years). Data used in the reported analyses come from phases 1 (1985-88), 3 (1991-1994), 5 (1997-1999), 7 (2002–2004), 9 (2007-2009) and 11 (2012-2013) of the study.

Of the 10,308 participants at baseline, 3,990 did not participate at phase 11 (died, withdrew or did not respond). The analyses are based on 5,407 participants with valid FLI and repeat alcohol data. We used modified Poisson regression (Zou, 2004) to compare baseline characteristics of those excluded and included in the analysis, and found those included were more likely to be of higher socio-economic position, low-risk drinkers and never smokers. The University College London Medical School Committee on the ethics of human research approved the Whitehall II study. Written informed consent was obtained at baseline and renewed at each contact. Whitehall II data, protocols, and other metadata are available to

bona fide researchers for research purposes (data sharing policy is available at http://www.ucl.ac.uk/whitehallII/data-sharing).

2.2 Measuring alcohol consumption

Alcohol measurements were available at six time points over a thirty year period up to the measurement of the FLI. Participants were asked to report the number of alcoholic drinks they had consumed in the last 7 days for beer/cider (pints), wine (glasses) and spirits (measures) separately. Drinks were converted into UK units of alcohol (where one unit is equivalent to 8g of ethanol). For phases 1 and 3 a conservative estimate was used of one UK unit for each measure of spirits and glass of wine, and two UK units for each pint of beer. From phase 5 onwards, an estimate of two units was used for each glass of wine, in recognition of increasing glass size and wine strength (Britton et al., 2016). These converted measurements were then summed to define the total weekly number of UK units consumed. Categories of alcohol consumption were then created based on UK guidelines for sensible drinking at the time of data collection (Department of Health, 1995), these were: "non-drinker", "former drinker", "low-risk drinker" (within guidelines (1-14 [8-112g] units per week for women, 1-21 [8-168g] units per week for men)), and "heavy drinker" (above guidelines (15+ units for women, 22+ units for men)). Typologies of alcohol consumption over the six measurement periods were then created as follows: (1) "stable non-drinker" (consistently reported non-drinking), (2) "stable low-risk drinker", (3) "stable heavy drinker", (4) "unstable low-risk drinker" (a low-risk drinker at the majority of phases but not consistently so), (5) "unstable heavy drinkers" and (6) "former drinkers" (previously reported alcohol consumption but did not drink at the time of the last data collection phase). When an individual reported low-risk or heavy drinking on an equal number of occasions, participants

were assigned to the unstable heavy drinking group. Participants were permitted one missing alcohol value during follow-up (O'Neill et al., 2018).

2.3 Calculating fatty liver

FLI was used as a proxy for fatty liver disease (Bedogni et al., 2006). At phase 11 (2012-2013), FLI was derived from measures of triglycerides, body mass index, waist circumference and γ-glutamyltransferase as follows:

$$FLI = (e^{0.953*\log_e(\text{triglycerides}) + 0.139*BMI + 0.718*\log_e(GGT) + 0.053*\text{waist circumference} - 15.745)} / (1+e^{0.953*\log_e(\text{triglycerides}) + 0.139*BMI + 0.718*\log_e(GGT) + 0.053*\text{waist circumference} - 15.745})* 100$$

A FLI greater than or equal to 60 was considered to be high as this indicates hepatic steatosis as detected by ultrasonography.

2.4 Covariates

Covariates included age, sex, ethnicity, smoking status and socio-economic position (SEP). Smoking status (never, ex, current smoker consuming 1-10 cigarettes per days, current smoker of 11+ cigarettes per day) and SEP (defined using last known employment grade as high, intermediate and low (Britton and Marmot, 2004)) were identified from self-reported questionnaires completed at the time of FLI measurement. Ethnicity was categorised as white or non-white.

2.5 Analysis

Logistic regression was used to assess typologies of alcohol use over 30 year period and risk of having a FLI ≥60. Adjustments were made for age, sex, SEP, smoking status and

ethnicity. All analyses were performed in R (v3.4.1; R Foundation for Statistical Computing, Vienna, Austria) in 2018. Comparisons were made with cross-sectional analyses, using current drinker type at phase 11 (non-drinker, former drinker, current low-risk drinker, current heavy drinker) as the exposure and phase 11 FLI ≥60 or not as the outcome). Analyses were carried out in the pooled sample and separately by sex.

There were some missing data so we performed multiple imputation (generating 100 datasets for both the longitudinal and cross-sectional analyses) and compared the results using imputation and not using imputation.

3. RESULTS

The most common alcohol typology for men was "unstable heavy" (31.1%) and "unstable low-risk" (30.0%) for women (Table 1). "Stable non-drinkers" were less common among men (3.2%) compared with women (10.2%). Higher proportions of current and ex-smokers were found among stable heavy drinkers. Women of high SEP were more likely to be heavy drinkers. The mean FLI was 47.0 (SD 27.0) for men and 36.2 (SD 29.0) for women.

The association between typologies of drinking during mid-life and FLI are shown in Figure 1. "Stable heavy" drinkers over the 30 year measurement period had higher odds of high FLI compared to "stable low-risk" drinkers (men: OR=2.04, 95%CI=1.53-2.74; women: OR=2.24, 95%CI=1.08-4.55), after adjustment for covariates. There were no significant differences between "stable non-drinkers" and "stable low-risk" drinkers (men: OR=1.21, 95%CI=0.73-1.96; women: OR=1.50, CI=0.86-2.63). Former drinkers had increased odds of high FLI compared to "stable low-risk" drinkers (men: OR=2.09, 95%CI=1.55-2.85; women: OR=1.68, 95%CI=1.08-2.67).

Cross-sectional analyses among women showed no difference in odds of elevated FLI between current heavy drinkers and low-risk drinkers (Figure 2). However, longitudinal analyses showed that stable heavy drinking women had higher odds of elevated FLI compared to stable low-risk drinkers (Figure 1). Among both men and women, former drinkers had increased odds of elevated FLI compared to current low-risk drinkers (men: OR=1.71, 95%CI=1.37-2.15; women: OR=1.62, 95%CI=1.18-2.22). Non-drinkers (excluding former drinkers) did not differ to current low-risk drinkers in their odds of having an elevated FLI. Analyses using imputed data generated very similar results to the non-imputed findings (data not shown).

4. **DISCUSSION**

We derived 30 year drinking typologies during midlife in a large British population based cohort study and linked these to an indicator of fatty liver disease in early old age. We found that former drinkers and those with sustained heavy drinking during midlife had greater FLI values than stable low-risk drinkers. We also observed that, on average, stable low-risk drinkers did not have reduced FLI values compared to stable non-drinkers. These findings converge to suggest that midlife drinking habits affect the development of fatty liver disease. The increased risk to health among former drinkers is found in multiple studies, most likely due to concurrent ill-health rather than the effect of stopping drinking (the so-called 'sick-quitter phenomenon') (Shaper et al., 1988). We have previously shown that former drinkers in this study are a diverse group (Sabia et al., 2018) and this should not be taken as evidence that stopping drinking is bad for health; a more nuanced message may be required (Bell, 2018).Our finding that stable low-risk drinking is not associated with reduced risk of fatty liver challenges the conclusion from a recent meta-analysis (Cao et al., 2016) (in which cross sectional data were used almost exclusively and former drinkers were not separated from

never drinkers) that reported low-risk drinking is associated with a lower risk of fatty liver disease. However, our findings are in agreement with a Mendelian randomization study that found no evidence of beneficial effect of moderate consumption on non-alcoholic fatty liver disease severity. (Sookoian et al., 2016)

We found that, among women, the risks associated with heavy drinking in mid-life were only appreciable when considering a longitudinal drinking typology and not in cross-sectional analyses. This further emphasises the necessity of taking a life course approach when assessing the association between alcohol consumption and health outcomes (Bell and Britton, 2015b; O'Neill et al., 2017). There is a serious risk of misclassification if only one measure of alcohol is considered. Alcohol consumption is not a stable phenomenon over the life course [5], as shown in this study by the large proportion of participants that did not have stable drinking typologies over the thirty years. Our longitudinal work suggests that clinicians should consider collecting brief drinking histories as well as information on current intake.(Greenfield et al., 2014; Bell and Britton, 2015c)

A major strength of this study is our ability to use repeated prospectively collected measures of alcohol consumption on the same individuals over three decades up to the assessment of FLI. The derived typologies have policy relevance as they were defined using UK government guidelines at the time (Department of Health, 1995). Treating FLI as a surrogate endpoint allowed for us to investigate how drinking during this period might set the stage for the development of liver disease – before it is necessarily symptomatic.

4.1 Limitations

Alcohol consumption was self-reported in this study and therefore at risk of misreporting (Bellis et al., 2015; Boniface et al., 2013). Furthermore, we were only able to capture snap shots of drinking over the past week and have assumed that these are a general representation

of levels consumed over that period, other methods that could be used to circumvent this include collecting brief drinking histories (Greenfield et al., 2014).

The study sample consists of individuals who have remained in the cohort study for three decades and therefore there is a risk of selective attrition (Britton and Bell, 2017; Hernán et al., 2004). We found those remaining in the study and attending clinical research facilities to be a healthier subsample than those who dropped out or who did not participate fully. Furthermore, occupational-based studies do not capture the extremes of drinking and therefore may be underpowered to look at the effects of very heavy drinking. The proportion of participants in this study that drink in excess of alcohol guidelines is considerably lower than in the general population (Health and Social Care Information Centre, 2013). In addition, we were unable to assess the effects of binge drinking, as these data were not adequately captured. It is possible that that the results from our sample may underestimate the risks associated with consuming alcohol if a lower proportion of the participants are binge drinkers compared to the general population. However, aetiological associations, such as those reported here, from occupational cohorts are reliable and relevant to wider populations (Batty et al., 2014). Although we included several covariates in the analysis, as with most observational studies, we cannot rule out that possibility of residual confounding. As a minimum we were able to adjust for smoking which is critical as heavy drinkers tend to smoke more than non-drinkers (Ferrence and Kozlowski, 1995). Other important behavioural confounders may include diet and physical activity, however our findings are concordant with the only Mendelian Randomisation study on this topic (Sookoian et al., 2016).

4.2 Conclusions

These findings indicate that the drinking habits adopted by adults during midlife affect the development of fatty liver, and that sustained heavy drinking is associated with an increased risk of poor liver health compared to stable low-risk drinking. For women, this finding was

not seen when only using cross-sectional analyses, thus highlighting the importance of taking a longitudinal approach. Furthermore, there was no evidence of a favourable liver function among stable low-risk drinkers compared to non-drinkers.

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Author Contributions: AB and SB conceived the research question. DON carried out the analysis. AB completed the first draft of the manuscript. SB, DO and GM provided additional intellectual content and technical assistance. All authors saw and agreed on the final submitted manuscript. None of the authors has any conflict of interest to declare.

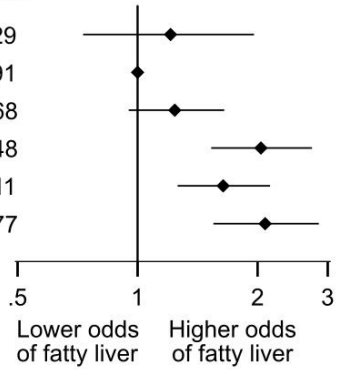
Table 1. Characteristics of participants by 30 year alcohol typologies in Whitehall II

		Stable non-drinker	Stable low-risk	Stable heavy	Unstable low-risk	Unstable heavy	Former drinker	Unknown	Overall
MEN		% (N)/Mean (SD)	% (N)/Mean (SD)	% (N)/Mean (SD)	% (N)/Mean (SD)	% (N)/Mean (SD)	% (N)/Mean (SD)	% (N)/Mean (SD)	% (N)/Mean (SD)
TOTAL		3.2 (124)	10.5 (411)	15.8 (621)	25.4 (995)	31.1 (1220)	12.4 (487)	1.7 (67)	100 (3925)
FLI		39.4 (28.2)	40.3 (25.3)	52.9 (27.2)	44.1 (25.9)	48.3 (26.8)	49.5 (27.8)	51.0 (28.2)	47.0 (27.0)
Age		69.8 (6)	69.6 (5.8)	69 (5.4)	69.6 (5.9)	69.3 (5.7)	69.4 (5.7)	67 (4.1)	69.4 (5.7)
Ethnicity	White	69.4 (86)	93.9 (386)	98.6 (612)	94 (935)	96.8 (1181)	90.1 (439)	95.5 (64)	94.3 (3703)
	Non-white	30.6 (38)	5.8 (24)	1.3 (8)	5.9 (59)	3.1 (38)	9.9 (48)	4.5 (3)	5.6 (218)
Smoking	Non-smoker	58.1 (72)	53.3 (219)	27.1 (168)	47.3 (471)	38.3 (467)	42.5 (207)	10.4 (7)	41 (1611)
	Ex-smoker	32.3 (40)	39.9 (164)	65.2 (405)	46.2 (460)	55.6 (678)	45.6 (222)	58.2 (39)	51.2 (2008)
	Current 0-10	1.6 (2)	0.7 (3)	1.4 (9)	1 (10)	1.6 (20)	1 (5)	1.5 (1)	1.3 (50)
	Current 11+	1.6 (2)	1.5 (6)	2.9 (18)	1.3 (13)	1.1 (14)	1.8 (9)	3 (2)	1.6 (64)
SEP	Low	10.5 (13)	2.9 (12)	0.8 (5)	4.2 (42)	1.7 (21)	7.6 (37)	7.5 (5)	3.4 (135)
	Medium	54 (67)	41.4 (170)	31.6 (196)	40.9 (407)	33.1 (404)	51.3 (250)	40.3 (27)	38.8 (1521)
	High	35.5 (44)	55.7 (229)	67.6 (420)	54.9 (546)	65.2 (795)	41.1 (200)	52.2 (35)	57.8 (2269)
WOMEN									
TOTAL		10.2 (151)	12.3 (183)	3.7 (55)	30.0 (444)	18.7 (277)	23.8 (352)	1.3 (20)	100 (1482)
FLI		41.9 (31.7)	31.3 (25.6)	45.9 (31.7)	35.3 (28.3)	29.8 (27.5)	40.8 (29.6)	39.4 (27.7)	36.2 (29.0)
Age		70.9 (6.2)	69.4 (6)	67.6 (5.4)	69.3 (6)	68.4 (5.4)	70.9 (5.8)	67.3 (5.4)	69.6 (5.9)
Ethnicity	White	58.3 (88)	94 (172)	100 (55)	89.9 (399)	98.6 (273)	83.5 (294)	95 (19)	87.7 (1300)
	Non-white	41.1 (62)	6 (11)	0 (0)	9.9 (44)	1.4 (4)	16.5 (58)	5 (1)	12.1 (180)
Smoking	Non-smoker	63.6 (96)	62.3 (114)	38.2 (21)	51.8 (230)	36.8 (102)	52 (183)	25 (5)	50.7 (751)
	Ex-smoker	17.9 (27)	30.1 (55)	47.3 (26)	40.5 (180)	54.9 (152)	33.5 (118)	45 (9)	38.3 (567)
	Current 0-10	3.3 (5)	1.1 (2)	1.8 (1)	1.1 (5)	2.9 (8)	1.1 (4)	0 (0)	1.7 (25)
	Current 11+	2 (3)	1.1 (2)	0 (0)	1.4 (6)	2.9 (8)	3.1 (11)	0 (0)	2 (30)
SEP	Low	45 (68)	15.3 (28)	0 (0)	24.1 (107)	7.6 (21)	35.8 (126)	40 (8)	24.2 (358)
	Medium	45 (68)	55.2 (101)	36.4 (20)	50 (222)	44.4 (123)	50.6 (178)	35 (7)	48.5 (719)
	High	9.9 (15)	29.5 (54)	63.6 (35)	25.9 (115)	48 (133)	13.6 (48)	25 (5)	27.3 (405)

Figure 1. 30 year typologies of alcohol consumption and odds of high FLI (reference group: stable low-risk drinkers). Adjusted for age, ethnicity, socio-economic position and smoking status

Men

Category	N	Events	OR (95% CI)
Stable non-drinker	116	29	1.21 (0.73, 1.96)
Stable low-risk drinker	391	91	1.00 (ref.)
Unstable low-risk drinker	953	268	1.24 (0.95, 1.65)
Stable heavy drinker	599	248	2.04 (1.53, 2.74)
Unstable heavy drinker	1178	411	1.64 (1.26, 2.15)
Former drinker	443	177	2.09 (1.55, 2.85)



Women

Category	N	Events	OR (95% CI)
Stable non-drinker	130	37	1.50 (0.86, 2.63)
Stable low-risk drinker	173	34	1.00 (ref.)
Unstable low-risk drinker	420	94	1.11 (0.72, 1.75)
Stable heavy drinker	48	17	2.24 (1.08, 4.55)
Unstable heavy drinker	270	44	0.75 (0.45, 1.25)
Former drinker	316	98	1.68 (1.08, 2.67)

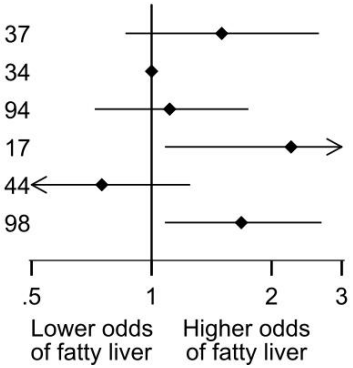
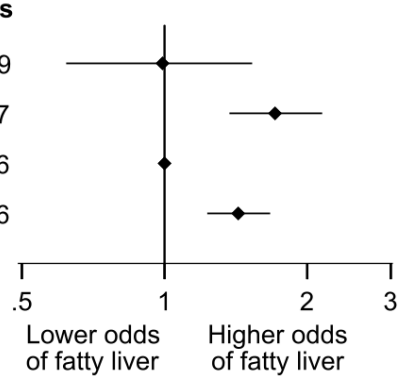


Figure 2. Cross-sectional associations of alcohol intake and odds of high FLI (reference group: low-risk drinkers) Adjusted for age, ethnicity, socio-economic position and smoking status

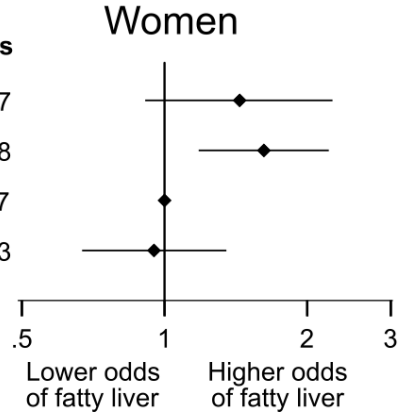
Men

Category	N	Events	OR (95% CI)
Non-drinker	116	29	0.99 (0.62, 1.53)
Former drinker	443	177	1.71 (1.37, 2.15)
Low-risk drinker	1501	416	1.00 (ref.)
Heavy drinker	1631	606	1.43 (1.23, 1.67)



Women

Category	N	Events	OR (95% CI)
Non-drinker	130	37	1.44 (0.91, 2.26)
Former drinker	316	98	1.62 (1.18, 2.22)
Low-risk drinker	606	127	1.00 (ref.)
Heavy drinker	308	63	0.95 (0.67, 1.35)



References

Arbeev, K.G., Akushevich, I., Kulminski, A.M., Ukraintseva, S., Yashin, A.I., 2014. Joint analyses of longitudinal and time-to-event data in research on aging: Implications for predicting health and survival. Front. Public Health 2. https://doi.org/10.3389/fpubh.2014.00228

Batty, G.D., Shipley, M., Tabák, A., Singh-Manoux, A., Brunner, E., Britton, A., Kivimäki, M., 2014. Generalizability of occupational cohort study findings. Epidemiology 25, 932–933. https://doi.org/10.1097/EDE.0000000000000184

Bedogni, G., Bellentani, S., Miglioli, L., Masutti, F., Passalacqua, M., Castiglione, A., Tiribelli, C., 2006. The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. BMC Gastroenterol. 6, 1.

Bell, S., 2018. Alcohol Consumption, Hypertension, and Cardiovascular Health Across the Life Course: There Is No Such Thing as a One-Size-Fits-All Approach. JAHA—Journal Am. Heart Assoc. 7.

Bell, S., Britton, A., 2015a. Protective effects of moderate alcohol consumption on fatty liver: A spurious association? J. Hepatol. https://doi.org/10.1016/j.jhep.2014.12.037

Bell, S., Britton, A., 2015b. The role of alcohol consumption in regulating circulating levels of adiponectin: A prospective cohort study. J. Clin. Endocrinol. Metab. 100, 2763–2768. https://doi.org/10.1210/jc.2015-1845

Bell, S., Britton, A., 2015c. Reliability of a retrospective decade-based life-course alcohol consumption questionnaire administered in later life. Addiction 110, 1563–1573.

Bellis, M.A., Hughes, K., Jones, L., Morleo, M., Nicholls, J., McCoy, E., Webster, J., Sumnall, H., 2015. Holidays, celebrations, and commiserations: Measuring drinking during feasting and fasting to improve national and individual estimates of alcohol consumption. BMC Med. 13, 113.

Boniface, S., Kneale, J., Shelton, N., 2013. Actual and Perceived Units of Alcohol in a Self-Defined “Usual Glass” of Alcoholic Drinks in England. Alcohol. Clin. Exp. Res. 37, 978–983.

Britton, A., Bell, S., 2017. The protective effects of moderate drinking: lies, damned lies, and... selection biases. Addiction 112, 218–219.

Britton, A., Ben-Shlomo, Y., Benzeval, M., Kuh, D., Bell, S., 2015. Life course trajectories of alcohol consumption in the United Kingdom using longitudinal data from nine cohort studies. BMC Med. 13, 47. https://doi.org/10.1186/s12916-015-0273-z

Britton, A., Marmot, M., 2004. Different measures of alcohol consumption and risk of coronary heart disease and all-cause mortality: 11-year follow-up of the Whitehall II Cohort Study. Addiction 99, 109–116. https://doi.org/10.1111/j.1360-0443.2004.00530.x

Britton, A., O’Neill, D., Bell, S., 2016. Underestimating the Alcohol Content of a Glass of Wine: The Implications for Estimates of Mortality Risk. Alcohol Alcohol. https://doi.org/10.1093/alcalc/agw027

Cao, G., Yi, T., Liu, Q., Wang, M., Tang, S., 2016. Alcohol consumption and risk of fatty liver disease: a meta-analysis. PeerJ 4, e2633.

Department of Health, L. (United K., 1995. Sensible drinking: Report of an inter-departmental working group. Department of Health London.

Ferrence, R., Kozlowski, L.T., 1995. Moderate drinking and health: being confunded by confouders. Addiction 90, 485–488.

Greenfield, T.K., Kerr, W.C., 2011. Commentary on Liang & Chikritzhs (2011): Quantifying the impacts of health problems on drinking and subsequent morbidity and mortality – life-course measures are essential. Addiction 106, 82–83. https://doi.org/10.1111/j.1360-0443.2010.03298.x

Greenfield, T.K., Nayak, M.B., Bond, J., Kerr, W.C., Ye, Y., 2014. Test–Retest Reliability and Validity of Life-Course Alcohol Consumption Measures: The 2005 National Alcohol Survey Follow-Up. Alcohol. Clin. Exp. Res. n/a-n/a. https://doi.org/10.1111/acer.12480

Health and Social Care Information Centre, 2013. Statistics on Alcohol: England, 2013. Health and Social Care Information Centre.

Hernán, M.A., Hernández-Díaz, S., Robins, J.M., 2004. A Structural Approach to Selection Bias. Epidemiology 15, 615–625. https://doi.org/10.1097/01.ede.0000135174.63482.43

Kerr, W.C., Fillmore, K.M., Bostrom, A., 2002. Stability of alcohol consumption over time: evidence from three longitudinal surveys from the United States. J. Stud. Alcohol Drugs 63, 325.

Marmot, M., Brunner, E., 2005. Cohort Profile: The Whitehall II study. Int. J. Epidemiol. 34, 251–256. https://doi.org/10.1093/ije/dyh372

O'Neill, D., Britton, A., Brunner, E.J., Bell, S., 2017. Twenty-Five-Year Alcohol Consumption Trajectories and Their Association With Arterial Aging: A Prospective Cohort Study. J. Am. Heart Assoc. 6. https://doi.org/10.1161/JAHA.116.005288

O'Neill, D., Britton, A., Hannak, M., Goldberg, M., Kuh, D., Bell, S., 2018. Association of longitudinal alcohol consumption trajectories with coronary heart disease: a meta-analysis of six cohort studies using individual participant data. BMC Med. 22, 1123–1126.

Reddy, J.K., Rao, M.S., 2006. Lipid metabolism and liver inflammation. II. Fatty liver disease and fatty acid oxidation. Am. J. Physiol.-Gastrointest. Liver Physiol. 290, G852–G858.

Sabia, S., Fayosse, A., Dumurgier, J., Dugravot, A., Akbaraly, T., Britton, A., Kivimaki, M., Singh-Manoux, A., 2018. Alcohol consumption and risk of dementia: 23 year follow-up of Whitehall II cohort study. BMJ 362.

Shaper, A.G., Wannamethee, G., Walker, M., 1988. Alcohol and mortality in British men: explaining the U-shaped curve. The Lancet 332, 1267–1273.

Sookoian, S., Flichman, D., Castano, G., Pirola, C., 2016. Mendelian randomisation suggests no beneficial effect of moderate alcohol consumption on the severity of nonalcoholic fatty liver disease. Aliment. Pharmacol. Ther. 44, 1224–1234.

Williams, R., Aspinall, R., Bellis, M., Camps-Walsh, G., Cramp, M., Dhawan, A., Ferguson, J., Forton, D., Foster, G., Gilmore, I., 2014. Addressing liver disease in the UK: a blueprint for attaining excellence in health care and reducing premature mortality from lifestyle issues of excess consumption of alcohol, obesity, and viral hepatitis. The Lancet 384, 1953–1997.

Zou, G., 2004. A Modified Poisson Regression Approach to Prospective Studies with Binary Data. Am. J. Epidemiol. 159, 702–706. https://doi.org/10.1093/aje/kwh090