1 **Trajectories of alcohol consumption up to 30 years before and after the diagnosis of**

2 **cardiovascular diseases: a longitudinal case-control study of 12502 participants**

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ABSTRACT

Background: To examine the longitudinal trajectories of alcohol consumption prior to and following the diagnosis of cardiovascular diseases (CVD).

Methods: We conducted a case-control study of 2501 incident cases of angina, myocardial infarction or stroke and 10001 matched controls without the condition. Repeated measures of alcohol were centred on the date of diagnosis, spanning up to 30 years before and after CVD onset. Mean trajectories of weekly consumption were estimated using growth curve models.

Results: For trajectories prior to diagnosis, mean volume of alcohol consumed among male cases increased over time, peaking at around eight years before diagnosis at 95 (95% CI 60-130) g/week and declining afterwards. Trajectories following diagnosis showed mean consumption in male cases dropped from 87 (95% CI 54-120) g/week to 74 (95% CI 45-102) g/week after the date of diagnosis and then slightly rose to 78 (95% CI 40-116) g/week at the subsequent 3.5 years, before gradually declining to 31 (95% CI 2-61) g/week at 30 years after diagnosis. Mean consumption among female cases remained stable prior to diagnosis (at about 30 g/week), fell marginally to 25 (95% CI 20-30) g/week after the date of diagnosis, and kept decreasing afterwards. Similar trajectories were obtained in cases and controls.

Conclusions: This is the first attempt to show how CVD patients change their drinking volume over such a wide time span. Future research needs to establish insight into drinking behaviour in other ways (such as frequency, context) and address the impact of changes in drinking on CVD patients.

Keywords: cardiovascular diseases, case-control study, drinking trajectories, longitudinal

What is already known on this subject

- Much of the evidence linking alcohol to the onset and prognosis of cardiovascular diseases (CVD) arises from observational studies that measured exposure to alcohol only once at baseline.

- Drinking behaviour varies over the life course. The onset of disease may lead individuals to re-evaluate their lifestyles and change their drinking accordingly.

- Analysis of drinking trajectories with repeat alcohol measures is therefore needed to reveal longitudinal stability of consumption in CVD patients. Such trajectory studies are scarce in the literature and mostly of short duration.

What this study adds

- This is the first study to show amongst CVD patients specifically how weekly alcohol consumption changes over a prolonged period of up to 30 years before and after the diagnosis.

- For male CVD patients, mean consumption of alcohol increased over time, peaked at eight years before diagnosis at 95 grams per week, and declined afterwards. A flatter trajectory was seen in female patients, which remained stable at around 30 grams per week and started to decline after diagnosis.

- Little difference in trajectories of mean consumption was apparent between those diagnosed with CVD and those without the condition.

- Future research needs to examine the drinking behaviour in other ways, such as frequency and context of consumption (for example, with meal or role in wider dietary guidance), as well as address the impact of changes in drinking on CVD patients to better inform lifestyle advice and healthcare policy.

INTRODUCTON

As a result of both demographic change and enhancements in screening, diagnostics and treatment, the number of individuals living with cardiovascular diseases (CVD) is increasing in most global regions. In the UK, it is estimated that there are around 4 million men and 3.6 million women living with CVD.[1] However, current guidelines for common health behaviours such as alcohol consumption are inconsistent regarding their suggested limits of alcohol intake in those managing their CVD [2][3] and mainly rely on evidence from observational studies assessing alcohol at a single point in time (typically at baseline, either before [4-6] or after being diagnosed with CVD [7-10]). In doing so, these studies assume that levels of alcohol consumption remain stable over time, but there are reasons to doubt this. Drinking behaviour varies across the life course.[11][12] There is also possibility that the onset of disease may lead individuals to re-evaluate their lifestyles and foster positive behaviour changes to enjoy better health outcomes. Analysis of drinking trajectories with repeat alcohol measures is therefore needed to examine longitudinal stability of consumption among CVD patients, particularly possible changes in consumption in relation to the diagnosis. Such information can be used to inform ongoing investigation into how drinking behaviour is associated with the onset and long-term prognosis of CVD.

Few studies have assessed drinking trajectories over time among CVD patients. Levantesi *et al.* found that most patients reduced their wine consumption during the first six months after myocardial infarction (MI).[13] With no drinking data prior to MI, the authors did not examine the impact of MI diagnosis itself on alcohol use. Pai *et al.* reported a high correlation between levels of consumption assessed immediately before and after MI.[14] However, their analysis included men only. Notably, change in consumption was based on only two time-point assessments of alcohol and, therefore, the authors were unable to estimate the shape of trajectories or distinguish true change from measurement error.[15]

Estimations of longitudinal drinking trajectories have also been drawn from studies linking alcohol to broader categories of life events which include newly occurring CVD.[16-18] However, these analyses were characterised by heterogeneous results as well as different methodological limitations such as (i) reliance on crudely categorised measures of alcohol intake, (ii) short durations of observation and (iii) utilisation of a small number of measurement occasions, which in combination limited insights into trajectories of alcohol consumption from pre- to post-CVD diagnosis over an extended time frame.

In this study, we examined the extent to which alcohol consumption changed over a prolonged period of up to 30 years before and after the onset of CVD with repeated alcohol measures from two

1   large UK cohorts. By using a case-control study design, we also sampled controls from the same

2   source population that gave rise to the CVD cases but without the condition. Given that the study

3   aimed to offer perspectives on a changing behaviour (rather than defining its health risk), this

4   control group served as a background reference, which helped to illustrate potential fluctuations in

5   alcohol intake as individuals age over the life course rather than being a comparator about how

6   drinking trajectories might be related to the occurrence of CVD.

7   **METHODS**

8   **Study design and population**

9   We conducted a 'nested' case-control study within two ongoing UK cohorts: the Whitehall II study,

10   comprising 10308 British civil servants aged 35-55 years at enrolment during 1985-88,[19] and the

11   European Prospective Investigation of Cancer-Norfolk (EPIC-Norfolk), comprising 25639 residents in

12   Norfolk aged 39-79 years at enrolment in 1993.[20] Both cohorts were regularly linked to electronic

13   health records and participants with a previous diagnosis of coronary heart disease (CHD; angina or

14   MI) or stroke prior to the enrolment date were excluded from the analysis. We defined cases as

15   participants who developed incident CHD or stroke during follow-up (until 31 March 2019 in

16   Whitehall II and 31 March 2016 in EPIC-Norfolk) and had at least one alcohol measure both before

17   and after the date of diagnosis. Cases were ascertained from linked hospital admissions data (using

18   the International Classification of Diseases, version 9 [ICD-9] codes 410-414, ICD-10 codes I20-I25, or

19   procedures K40-K49, K50, K75, U19 for CHD; ICD-9 codes 430-438 or ICD-10 codes I60-I69 for

20   stroke), as well as based on 12-lead resting electrocardiogram recording (for CHD only) or self-

21   reported diagnosis that had been verified against information from the participants' general

22   practitioners or by manual retrieval of medical records.[21 22] We randomly selected up to four

23   controls for each case from those who were free of CHD and stroke during follow-up and provided at

24   least one alcohol measure both before and after the time of diagnosis of the case. Cases and

25   controls were individually matched by cohort, sex, and age at baseline (±1 year).

26   **Alcohol consumption**

27   Data on alcohol consumption were extracted from eight phases of the Whitehall II study and three

28   phases of the EPIC-Norfolk study. At each phase, participants were asked to report the number of

29   alcoholic drinks ('measures' of spirits, 'glasses' of wine and 'pints' of beer/cider) they had consumed

30   in the week prior to interview. Drinks were converted into grams of ethanol by assuming 8g per

31   'measure' of spirits or 'glass' of wine and 16g per 'pint' of beer/cider.[23] These converted

32   measurements were then added up to define the total volume of weekly alcohol consumption in

33   grams. The date of interview was compared with the date of diagnosis (for controls the date of

1 diagnosis of their matched case) to determine whether an alcohol measure reflected the drinking

2 level before or after the onset of disease.

Covariates

Covariates were drawn from each phase along with alcohol assessment and included age, sex, ethnicity (white, non-white) and marital status (married/cohabiting, other). Socioeconomic position was measured using occupational information and categorised as high, intermediate or low, representing income and status at work. Additional data on health behaviours were obtained on smoking (current, former, never), physical activity (active, inactive) and dietary behaviour (frequency of fruit and vegetables consumed in a week). We also collected information on body mass index (BMI; kg/m^2), self-reported history of hypertension or use of anti-hypertensive drugs and self-rated health (excellent/good, fair, poor).

Statistical analysis

Time (in years) was centred on the date of diagnosis for cases and for controls the date of diagnosis of their matched case, which were each coded as year zero. Volume of alcohol consumed as a function of time prior to or following diagnosis was estimated using multilevel growth curve models in which observations were nested within individuals within cohorts. The models were fit with a random intercept and random slope on time at the individual level, and a random intercept at the cohort level. This allowed each individual to have their own drinking trajectory and accounted for the clustered nature of the data. The fixed effects of the models thus described the population mean trajectories.

Models were fit separately for case and control and for male and female. To examine how drinking may change following the onset of CVD, we also constructed separate models according to whether alcohol measures were reported before or after the documented date of diagnosis. We then incrementally adjusted the analyses for sociodemographic factors, health behaviours and health status. All of the covariates were allowed to vary over time, except for sex and ethnicity.

We used fractional polynomial terms (power= -2, -1, -0.5, 0, 0.5, 1, 2 and 3) to best describe the shape of the trajectory. Model fit was assessed using the Bayesian information criterion (BIC), with fit statistics for each model reported in online supplemental appendix S1. An improvement in fit was defined as any reduction in the BIC ≥10.[24] Robust standard errors were calculated for the best fitting model.

Missing covariate data were handled with multiple imputation by chained equations.[25 26] Alcohol consumption and time to diagnosis were included in the imputation model but not imputed.

Imputations were done separately by cohort and 50 imputations were run within each cohort. We

carried out sensitivity analysis comparing imputed data (primary analysis) to complete case data.

Results derived using complete case methods were broadly concordant with those obtained using

multiple imputation (see online supplemental appendices S2 and S3). We also examined the drinking

trajectories within subgroups defined by age at the time of diagnosis and further used age (in years)

as the time scale in a series of post hoc analyses. All analyses were performed using Stata 15.1.

RESULTS

Sample characteristics

Of the 35947 participants enrolled at baseline, there were 9178 incident CVD cases during a median

follow up of 21.2 (interquartile range [IQR] 19.8-31.3) years. Among these, 2501 cases had ≥1

alcohol measure both before and after the time of diagnosis, providing 12285 observations (Figure

1). Eligible cases were predominantly male (71.6%) and had a mean age of 65.39 (standard deviation

9.33) years at diagnosis.

Table 1 shows the characteristics of the cases and their matched controls (control: n=10001,

observations=50357) at the most recent phase prior to the diagnosis. Median time from this phase

to diagnosis was 2.6 (IQR 1.3-3.9) years among Whitehall participants and 4.0 (IQR 2.3-6.7) years

among EPIC-Norfolk participants. On average, cases showed a worse cardiovascular risk profile than

controls, with a greater proportion of the participants currently smoking, being physically inactive

and having higher BMI. Cases were also more likely to have hypertension and rate their health as

poor. In terms of alcohol consumption, cases in the EPIC-Norfolk study reported slightly lower levels

of drinking than matched controls, whereas drinking levels were similar for the two groups in the

Whitehall II study.

Table 1. Sample characteristics at the most recent phase before diagnosis

| | Whitehall II | | | | | EPIC-Norfolk | | | | |
	Case (n=1349)		Control (n=5396)		P-value[a]	Case (n=1152)		Control (n=4605)		P-value[a]
Age (years)[b]	62.05	(9.04)	61.87	(8.98)	0.509	69.30	(8.07)	69.13	(8.06)	0.522
Male	1027	(76.13)	4108	(76.13)	1.000	764	(66.32)	3053	(66.30)	0.989
Alcohol consumption in last week (grams)[c]	56	(8, 128)	56	(16, 128)	0.446	28	(10, 80)	36	(12, 92)	0.031
Ethnicity										
White	1161	(86.06)	5054	(93.66)	<0.001	1146	(99.48)	4582	(99.50)	0.169
Non-white	186	(13.79)	328	(6.08)		1	(0.09)	15	(0.33)	
Missing	2	(0.15)	14	(0.26)		5	(0.43)	8	(0.17)	
Marriage										
Married/cohabiting	1054	(78.13)	4191	(77.67)	0.748	943	(81.86)	3918	(85.08)	0.003
Other	295	(21.87)	1201	(22.26)		205	(17.80)	656	(14.25)	
Missing	0	(0.00)	4	(0.07)		4	(0.35)	31	(0.67)	

	n	(%)	n	(%)	p-value	n	(%)	n	(%)	p-value
Socioeconomic position										
High	538	(39.88)	2546	(47.18)	<0.001	524	(45.49)	2254	(48.95)	0.128
Intermediate	604	(44.77)	2191	(40.60)		446	(38.72)	1659	(36.03)	
Low	207	(15.34)	659	(12.21)		161	(13.98)	636	(13.81)	
Missing	0	(0.00)	0	(0.00)		21	(1.82)	56	(1.22)	
Smoking										
Never smoker	574	(42.55)	2691	(49.87)	<0.001	413	(35.85)	2052	(44.56)	<0.001
Ex-smoker	578	(42.85)	2217	(41.09)		616	(53.47)	2198	(47.73)	
Current smoker	197	(14.60)	484	(8.97)		114	(9.90)	329	(7.14)	
Missing	0	(0.00)	4	(0.07)		9	(0.78)	26	(0.56)	
Physical activity										
Active	1222	(90.59)	4988	(92.44)	0.024	746	(64.76)	3393	(73.68)	<0.001
Inactive	124	(9.19)	397	(7.36)		406	(35.24)	1212	(26.32)	
Missing	3	(0.22)	11	(0.20)		0	(0.00)	0	(0.00)	
Fruit and vegetable consumption										
≥ Daily	915	(67.83)	3833	(71.03)	0.021	1122	(97.40)	4472	(97.11)	0.908
< Daily	434	(32.17)	1563	(28.97)		4	(0.35)	17	(0.37)	
Missing	0	(0.00)	0	(0.00)		26	(2.26)	116	(2.52)	
BMI (kg/m²) [b]	26.83	(4.08)	25.88	(3.93)	<0.001	27.35	(3.74)	26.41	(3.51)	<0.001
Missing	0	(0.00)	1	(0.02)		1	(0.09)	6	(0.13)	
Hypertension										
No	931	(69.01)	4319	(80.04)	<0.001	582	(50.52)	3566	(77.44)	<0.001
Yes	415	(30.76)	1056	(19.57)		570	(49.48)	1039	(22.56)	
Missing	3	(0.22)	21	(0.39)		0	(0.00)	0	(0.00)	
Self-rated health										
Excellent/good	983	(72.87)	4611	(85.45)	<0.001	813	(70.57)	4072	(88.43)	<0.001
Fair	300	(22.24)	680	(12.60)		289	(25.09)	496	(10.77)	
Poor	66	(4.89)	102	(1.89)		36	(3.13)	21	(0.46)	
Missing	0	(0.00)	3	(0.06)		14	(1.22)	16	(0.35)	

Covariates were drawn from the phase just before the date of diagnosis for cases and for controls the date of diagnosis of their matched case.

Values are numbers (percentages) unless otherwise specified.

BMI=Body mass index.

[a] To examine within-cohort differences between case and control groups, one-way ANOVA was used on continuous data and the chi-squared test on categorical data;

[b] Mean (standard deviation);

[c] Median (interquartile range).

1

2 **Trajectories of alcohol consumption prior to diagnosis**

3 Drinking trajectories prior to diagnosis were estimated based on 5367 observations among 1791

4 male cases and 1868 observations among 710 female cases. For trajectories among matched

5 controls, there were 7161 men and 2840 women, providing 37395 and 12962 observations,

6 respectively.

7 Overall, among male cases, mean consumption increased over time, peaking at around eight years

8 before diagnosis at 95 (95% confidence interval [CI] 60-130) g/week and declining afterwards. At 30

9 years prior to diagnosis, the mean weekly volume of alcohol consumed among male cases was

10 higher than among controls; however, by the time of diagnosis, the consumption was estimated to

11 be roughly equivalent between the two groups, at around 90 g/week (Figure 2).

Mean consumption among female cases remained stable over time, at about 30 g/week. We noted little difference in the average volume of alcohol consumption between female cases and controls at 30 years prior to diagnosis, whereas controls had a weekly consumption about 10 g higher than cases by the time of diagnosis (Figure 2).

The crude models were incrementally adjusted to assess the effect of a broad range of sociodemographic, lifestyle and health-related factors on disparities in alcohol consumption between cases and controls. Results are reported in Table 2 and displayed in Figure 3. Up to the time of diagnosis, variation in alcohol volume grew substantially among female cases. Differences in consumption at the time of diagnosis were greater between male cases and controls following adjustments but attenuated between female cases and controls.

Trajectories of alcohol consumption following diagnosis

Drinking trajectories following diagnosis were estimated using the same set of cases as in the pre-diagnosis analysis above. A total of 3722 observations from male cases and 1328 observations from female cases contributed to the post-diagnosis estimation.

As shown in Figure 2, the mean volume of alcohol consumption among male cases dropped from 87 (95% CI 54-120) g/week to 74 (95% CI 45-102) g/week after the date of diagnosis, and then slightly rose to 78 (95% CI 40-116) g/week at the subsequent 3.5 years, before gradually declining to 31 (95% CI 2-61) g/week at 30 years after diagnosis. By contrast, a continuous steeper decrease in consumption was found for their matched controls. These results, however, should be interpreted with caution as the CIs continued to be wide and greatly overlapped.

Among female cases, mean consumption fell marginally to 25 (95% CI 20-30) g/week after the date of their diagnosis. Consumption kept decreasing in both female cases and controls during the 30 years following diagnosis, with a steeper rate of decrease in the latter.

Similar regression coefficients and drinking trajectories were obtained from adjusted models, except that we observed a markedly attenuated drop in the average volume of alcohol consumption after the date of diagnosis among male cases and a greater variation in alcohol consumed among female cases (Table 2 and Figure 3).

Post hoc analyses

Drinking trajectories prior to and following diagnosis within different age groups (35-49, 50-59, 60-69, ≥70 years at the time of diagnosis) are presented in online supplemental appendices S4 and S5. Among females, age groups 35-49 and 50-59 years were combined due to the small number of cases in the former (n=31). For both sexes, trajectories from adjusted analyses (with adjustment for the

1   same covariates listed in Table 2 Model 4) had highly overlapping CIs, indicating little difference in

2   mean weekly consumption of alcohol between cases and controls in any specific age group. Similar

3   trajectories of mean consumption were also found between cases and controls when using age as

4   the time scale (see online supplemental appendix S6).

Table 2. Regression coefficients for the fixed effects of the best-fitting multilevel growth curve models using imputed data

Best-fitting models [a]		Obs	n	Model 1			Model 2			Model 3			Model 4		
				Coefficient	Robust SE	P-value	Coefficient	Robust SE	P-value	Coefficient	Robust SE	P-value	Coefficient	Robust SE	P-value
Male															
Case, pre-onset	Time ^{2}	5367	1791	14.02	0.68	<0.001	13.15	1.19	<0.001	13.68	1.14	<0.001	10.31	0.52	<0.001
	Time ^{2}			-10.77	0.59	<0.001	-10.35	0.92	<0.001	-10.69	0.85	<0.001	-8.83	0.12	<0.001
	Intercept			68.09	16.68	<0.001	113.90	1.89	<0.001	88.99	5.01	<0.001	23.21	29.99	0.439
Case, post-onset	Time $^{-2}$	3722	1791	-2436.96	919.61	0.008	-2837.56	1164.62	0.015	-2808.99	1214.59	0.021	-2635.08	1092.75	0.016
	Time $^{-2}$			3386.79	1042.04	0.001	4088.46	1386.48	0.003	4030.64	1435.09	0.005	3873.59	1335.15	0.004
	Intercept			-70.03	11.21	<0.001	38.80	10.75	<0.001	20.13	8.55	0.019	-35.36	40.10	0.378
Control	Time ^{1}	37395	7161	44.32	7.17	<0.001	43.81	7.45	<0.001	44.08	7.40	<0.001	35.17	4.70	<0.001
	Time ^{2}			-9.07	0.75	<0.001	-9.16	0.85	<0.001	-9.17	0.83	<0.001	-8.00	0.61	<0.001
	Intercept			39.70	1.28	<0.001	141.43	0.91	<0.001	128.35	4.76	<0.001	60.39	15.74	<0.001
Female															
Case, pre-onset	Time ^{3}	1868	710	-0.02	0.04	0.553	-0.06	0.02	0.021	-0.02	0.02	0.134	-0.01	0.02	0.785
	Intercept			30.01	0.54	<0.001	52.13	4.65	<0.001	42.88	11.41	<0.001	54.15	7.84	<0.001
Case, post-onset	Time ^{3}	1328	710	-0.10	0.03	<0.001	-0.12	0.03	<0.001	-0.11	0.03	<0.001	-0.12	0.03	<0.001
	Intercept			27.72	3.24	<0.001	66.70	20.69	0.001	61.86	21.54	0.004	60.92	16.83	<0.001
Control	Time ^{1}	12962	2840	15.00	6.51	0.021	13.72	5.84	0.019	13.27	5.82	0.023	11.77	4.24	0.005
	Time ^{2}			-3.41	0.82	<0.001	-3.29	0.79	<0.001	-3.18	0.80	<0.001	-2.93	0.66	<0.001
	Intercept			24.31	6.41	<0.001	71.88	12.75	<0.001	66.30	14.76	<0.001	62.58	10.93	<0.001

[a] To describe the shape of each trajectory, a group of first- and second-degree fractional polynomials with powers from a predefined set (-2, -1, -0.5, 0, 0.5, 1, 2, 3) was used to derive a power transformation of the 'Time' variable. The superscript numbers following 'Time' in the table above refer to power terms that provide the best fit.
Obs=observations, SE=standard errors.
Model 1: unadjusted;
Model 2: as Model 1, plus adjustment for age at diagnosis, sex, ethnicity, marital status and socioeconomic position;
Model 3: as Model 2, plus adjustment for smoking, physical activity, frequency of fruit and vegetables consumed in a week;
Model 4: as Model 3, plus adjustment for prevalent hypertension (self-reported doctor diagnosed hypertension or use of antihypertensive drugs), body mass index, self-rated health.

DISCUSSION

This is the first study to describe the mean trajectory of weekly alcohol consumption spanning up to 30 years before and after CVD diagnosis. Overall, little difference was found in the mean volume of alcohol consumed among those diagnosed with CVD and those without the condition. For patients of both sexes, there was a small reduction in alcohol consumption in the years straddling the diagnosis. Altogether, the findings from this study provide novel insights into how engagement in a known determinant of health changes before and after the onset of disease. These insights can inform future inquiry into how drinking behaviour in an at-risk population is related to initial/subsequent disease onset as well as mortality.

The drinking trajectories observed among controls in this study are broadly in agreement with studies on lifetime drinking patterns among general population samples which report that alcohol consumption peaks at early adulthood and decreases as people age, with lower overall consumption in women than men.[11] We extended these findings by looking at CVD patients and found consumption trajectories that were roughly similar to the consumption patterns observed in their matched controls; similarities between cases and controls regarding drinking trajectories were seen within different age groups, suggesting that changes in consumption over time may be largely attributable to the effect of age. This is an important observation which has not typically been reflected in current evidence base for alcohol drinking among CVD patients. Studies linking alcohol to long-term prognosis of CVD have predominantly used just one measure of exposure, mostly at baseline, and thus overlook the changes in drinking during follow up (which may be several decades for some health outcomes) and are at risk of misclassification bias, with longer intervals increasing the likelihood of misclassification.[27] For the few studies with serial measures of alcohol, levels of consumption were commonly categorized according to each individual's average intake during follow up.[14 28] Such aggregation can still mask the pattern of changes in consumption within individuals over time and its possible impact on subsequent health risks.

We observed wide CIs for estimates of population mean trajectories, which are likely to be attributable to a high variability in trajectories across individual CVD patients. Addressing heterogeneity in drinking pattern over time has been the research focus of alcohol epidemiology in recent years.[29] Many efforts have been made to differentiate between long-term trajectories of alcohol intake among the general population in terms of drinker typologies (for instance, persistent moderate drinker, mostly heavy drinker, increasing drinker, etc.)[30 31] and link these typologies to health outcomes such as incidence of type 2 diabetes (T2DM)[32] and CHD.[33] However, such a trajectory approach has yet to be used to examine the health consequences of alcohol among CVD patients. Future research needs to investigate the benefits/harms of well-classified drinking patterns

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1 in secondary prevention of CVD to better inform lifestyle choices and health education in regard to

2 these.

3 Over the years surrounding diagnosis, we observed a drop in the mean volume of alcohol consumed

4 among CVD patients, although the overlapping CIs limits interpretation of this finding. A similar

5 pattern of results has been reported for a new diagnosis of T2DM[34] and other medical conditions

6 including cancer.[16][18] Mechanisms underlying the reductions in drinking following CVD onset could

7 not be identified with information from the source cohorts. Likely reasons for the reductions include

8 ill health (and related reduction in ability to socialise or enjoy alcohol consumption), health

9 precaution, pharmacological contraindication or adherence to medical advice. Patients included in

10 the present study were diagnosed across a broad span of time (spanning 1986 to 2016) where

11 different drinking advice and CVD management were applied. In the UK, low risk drinking guidelines

12 were first released in 1987 with recommendations of no more than 21 units (1 unit equals 8g of pure

13 ethanol) per week for men and 14 units per week for women.[35] The recommended limits were

14 transited to daily (≤ 3-4 units per day for men and 2-3 units per day for women) in 1995,[36] before

15 reverting to weekly (≤ 14 units per week for both men and women) in the latest drinking guidelines

16 published in 2016.[37] For secondary prevention of CVD, it has been recommended that advice on

17 alcohol consumption should be given in line with the above-mentioned national recommendations.[3]

18 [38] Unfortunately, we were not able to ascertain what advice the CVD participants in each cohort

19 were told in real clinical practice where drinking decisions need to be made appropriate to the

20 circumstances of each individual.

21 A key strength of this study is our ability to use repeated measures of weekly alcohol intake on the

22 same individuals over prolonged follow-up, covering a period of up to 30 years before and after CVD

23 diagnosis. This enabled us to examine longer-term drinking trajectories both pre- and post-CVD

24 onset at higher resolution (continuous rather than categorized alcohol data) by using an innovative

25 analytical strategy that mapped and centred alcohol data on the date of diagnosis. We were able to

26 fit drinking trajectories pre- or post-CVD with separate models, allowing more accurate

27 representations of longitudinal changes in drinking levels across both periods. Our study also

28 benefited from its prospective case-control design (being able to provide a larger reference sample),

29 reliable ascertainment of CVD cases and wide coverage of the adult life span (with data collected

30 from ages 35 to 92 years).

31 The present study is limited in several respects. First, as with other longitudinal cohort studies, our

32 findings were prone to selection attrition. Heavier drinkers might be more likely to drop out and be

33 under-represented in our datasets, which could have biased downwards the mean estimates. Also,

34 the present analyses included only patients who were able to provide information on alcohol use

1 after their CVD onset and thereby were restricted to survivors. We found incident fatal cases

2 (male=517, female=212) were older on average, more likely to report poor self-rated health, past or

3 current smoking, physical inactivity and to have hypertension than non-fatal cases at baseline. For

4 both sexes, mean consumption among fatal cases was higher than non-fatal cases (and their

5 matched controls) at 30 years prior to diagnosis and kept decreasing in the period leading up to

6 diagnosis (see online supplemental appendix S7), highlighting the possibility of reverse causation in

7 the association between alcohol and cardiovascular health. Secondly, the measurement of alcohol

8 was based on self-reports; although it is subject to estimation error and the strength of some alcohol

9 beverages is likely to have increased over time,[39] research has shown that drinking data collected

10 through this method remains valid and reliable.[40 41] Thirdly, analyses of drinking trajectories in the

11 present study was dependent on drinking volume only. Sufficient data on other characteristics of

12 alcohol consumption, such as drinking frequency and context, may provide a more detailed

13 illustration of how drinking behaviour changes over time. Furthermore, many major life events, such

14 as retirement,[42] could affect alcohol drinking and were not included in our analyses; however, a

15 comprehensive discussion of possible predictors of changes in alcohol consumption is beyond the

16 scope of this paper. Data presented in this study were collected from two UK cohorts: one being a

17 'white collar' occupational cohort (the Whitehall II study) and the other a population-based cohort.

18 Clearly, there were some cohort differences, most likely due to demographic characteristics such as

19 socioeconomic position. Apart from adjustments for these characteristics, the inclusion of cohort-

20 level random effects in the modelling took into account data clustering and thereby improved the

21 validity of the results obtained. Although we attempted to account for concurrent changes in many

22 other lifestyle and health-related factors, residual confounding owing to unmeasured factors might

23 still be possible.

24 In conclusion, this is the first study to show amongst CVD patients specifically how weekly alcohol

25 intake changes across a wide span of the life course, covering a period of up to 30 years before and

26 after the diagnosis. Trajectories of patients' mean consumption may well reflect age-related

27 patterns in alcohol use, given the absence of notable differences when compared to trajectories

28 among those without the condition. Our findings provide a basis of evidence that can inform future

29 inquiry into how drinking behaviour in an at-risk population is related to initial/subsequent disease

30 onset as well as mortality. Future research needs to examine the drinking behaviour in other ways,

31 such as the frequency and context of consumption (for example, with meal or role in wider dietary

32 guidance), as well as address the impact of changes in drinking behaviour on CVD patients to better

33 inform lifestyle advice and healthcare policy.

34

15

16 **Patient consent for publication:** Not required.

17 **Competing interests:** None declared.

18

19 **Ethics approval:** All data used in this study were secondary data that had previously been

20 anonymised by the individual cohort studies. No additional ethical approval was necessary for this

21 secondary data analysis. Ethical approval for the EPIC-Norfolk study was received from the Norwich

22 District Health Authority Ethics Committee. The Whitehall II study received approval from the

23 University College London Medical School Committee on the Ethics of Human Research. All

24 participants gave written informed consent.

25

26 **Data availability statement:** Data from the EPIC-Norfolk study (https://www.epic-norfolk.org.uk/)

27 and the Whitehall II study (https://www.ucl.ac.uk/epidemiology-health-

28 care/research/epidemiology-and-public-health/research/whitehall-ii) are available to researchers

29 upon application.

REFERENCES

1. British Heart Foundation. BHF Statistics Factsheet-UK. 2021. Available: https://www.bhf.org.uk/what-we-do/our-research/heart-statistics (accessed 21 March 2021).

2. Smith SC, Jr., Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation endorsed by the World Heart Federation and the Preventive Cardiovascular Nurses Association. *J Am Coll Cardiol*. 2011;58(23):2432-46.

3. The National Institute for Health and Care Excellence. Cardiovascular disease: risk assessment and reduction, including lipid modification. 2014. Available: https://www.nice.org.uk/guidance/cg181/resources/cardiovascular-disease-risk-assessment-and-reduction-including-lipid-modification-pdf-35109807660997 (accessed 21 March 2021).

4. Janszky I, Ljung R, Ahnve S, et al. Alcohol and long-term prognosis after a first acute myocardial infarction: the SHEEP study. *Eur Heart J.* 2008;29:45-53.

5. Mukamal KJ, Maclure M, Muller JE, et al. Prior Alcohol Consumption and Mortality Following Acute Myocardial Infarction. *JAMA*. 2001;285:1965-70.

6. Rosenbloom JI, Mukamal KJ, Frost LE, et al. Alcohol consumption patterns, beverage type, and long-term mortality among women survivors of acute myocardial infarction. *Am J Cardiol.* 2012;109(2):147-52.

7. Jackson VA, Sesso HD, Buring JE, et al. Alcohol Consumption and Mortality in Men With Preexisting Cerebrovascular Disease. *Arch Intern Med*. 2003;163:1189-93.

8. Masunaga N, Kimura A, Miyataka M, et al. Effects of Alcohol Consumption on Cardiovascular Events in Male Patients With Healed Myocardial Infarction. *Circ J.* 2006;70:1263-8.

9. Shaper AG, Wannamethee SG. Alcohol intake and mortality in middle aged men with diagnosed coronary heart disease. *Heart*. 2000;83:394-9.

10. Valmadrid CT, Klein R, Moss SE, et al. Alcohol Intake and the Risk of Coronary Heart Disease Mortality in Persons With Older-Onset Diabetes Mellitus. *JAMA*. 1999;282:239-46.

11. Britton A, Ben-Shlomo Y, Benzeval M, et al. Life course trajectories of alcohol consumption in the United Kingdom using longitudinal data from nine cohort studies. *BMC Med*. 2015;13:47.

12. Johnson FW, Gruenewald PJ, Treno AJ, et al. Drinking over the life course within gender and ethnic groups: a hyperparametric analysis. *J Stud Alcohol*. 1998;59(5):568-80.

13. Levantesi G, Marfisi R, Mozaffarian D, et al. Wine consumption and risk of cardiovascular events after myocardial infarction: results from the GISSI-Prevenzione trial. *Int J Cardiol.* 2013;163(3):282-7.

14. Pai JK, Mukamal KJ, Rimm EB. Long-term alcohol consumption in relation to all-cause and cardiovascular mortality among survivors of myocardial infarction: the Health Professionals Follow-up Study. *Eur Heart J.* 2012;33(13):1598-605.

15. Singer JD, Willett JB. A Framework for Investiagting Change over Time. In: Applied Longitudinal Data Analysis: Modeling Change and Event Occurrence. Oxford University Press, New York;2003.

16. Molander RC, Yonker JA, Krahn DD. Age-related changes in drinking patterns from mid- to older age: results from the Wisconsin longitudinal study. *Alcohol Clin Exp Res*. 2010;34(7):1182-92.

17. Gavens L, Goyder E, Hock ES, et al. Alcohol consumption after health deterioration in older adults: a mixed-methods study. *Public Health*. 2016;139:79-87.

18. Perreira KM, Sloan FA. Life events and alcohol consumption among mature adults: a longitudinal analysis. *J Stud Alcohol*. 2001;62(4):501-8.

19. Marmot MG, Smith GD, Stansfeld S, et al. Health inequalities among British civil servants: the Whitehall II study. *Lancet*. 1991;337(8754):1387-93.

20. Day N, Oakes S, Luben R, et al. EPIC-Norfolk: study design and characteristics of the cohort. European Prospective Investigation of Cancer. *Br J Cancer*. 1999;80 Suppl 1:95-103.

21. Kivimäki M, Batty GD, Singh-Manoux A, et al. Validity of cardiovascular disease event ascertainment using linkage to UK hospital records. *Epidemiology (Cambridge, Mass).* 2017;28(5):735.

22. Wijndaele K, Brage S, Besson H, et al. Television viewing and incident cardiovascular disease: prospective associations and mediation analysis in the EPIC Norfolk Study. *PloS one.* 2011;6(5):e20058.

23. Kalinowski A, Humphreys K. Governmental standard drink definitions and low-risk alcohol consumption guidelines in 37 countries. *Addiction*. 2016;111(7):1293-8.

24. Raftery AE. Bayesian model selection in social research. Sociol Methodol. 1995:111-63.

25. Royston P, White IR. Multiple imputation by chained equations (MICE): implementation in Stata. *J Stat Softw*. 2011;45(4):1-20.

26. Huque MH, Carlin JB, Simpson JA, et al. A comparison of multiple imputation methods for missing data in longitudinal studies. *BMC Med Res Methodol*. 2018;18(1):168.

27. Kuh D, Ben-Shlomo Y, Lynch J, et al. Life course epidemiology. *J Epidemiol Community Health*. 2003;57(10):778-83.

28. de Lorgeril M, Salen P, Martin JL, et al. Wine drinking and risks of cardiovascular complications after recent acute myocardial infarction. *Circulation*. 2002;106(12):1465-9.

29. Naimi TS, Stockwell T, Zhao J, et al. Selection biases in observational studies affect associations between 'moderate' alcohol consumption and mortality. *Addiction*. 2017;112(2):207-14.

30. Casswell S, Pledger M, Pratap S. Trajectories of drinking from 18 to 26 years: identification and prediction. *Addiction*. 2002;97(11):1427-37.

31. Muthen B, Muthen LK. Integrating person-centered and variable-centered analyses: growth mixture modeling with latent trajectory classes. *Alcohol Clin Exp Res.* 2000;24(6):882-91.

32. Joosten MM, Chiuve SE, Mukamal KJ, et al. Changes in alcohol consumption and subsequent risk of type 2 diabetes in men. *Diabetes*. 2011;60(1):74-9.

33. O'Neill D, Britton A, Hannah MK, et al. Association of longitudinal alcohol consumption trajectories with coronary heart disease: a meta-analysis of six cohort studies using individual participant data. *BMC Med.* 2018;16(1):124.

34. Knott CS, Britton A, Bell S. Trajectories of alcohol consumption prior to the diagnosis of type 2 diabetes: a longitudinal case-cohort study. *Int J Epidemiol*. 2018;47(3):953-65.

35. The Royal College of Physicans. A Great and Growing Evil: The Medical Consequences of Alcohol Abuse. Tavistock, London;1987.

36. British Medical Association (BMA). Alcohol: guidelines on sensible drinking. BMA, London;1995.

37. UK Chief Medical Officers' Low Risk Drinking Guidelines. 2016. Available: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/545937/UK_CMOs__report.pdf (accessed 21 March 2021).

38. Cooper A, O'Flynn N, Guideline Development Group. Risk assessment and lipid modification for primary and secondary prevention of cardiovascular disease: summary of NICE guidance. *BMJ*. 2008;336(7655):1246-8.

39. Britton A, O'Neill D, Bell S. Underestimating the Alcohol Content of a Glass of Wine: The Implications for Estimates of Mortality Risk. *Alcohol Alcohol*. 2016;51(5):609-14.

40. Batty GD, Shipley M, Tabak A, et al. Generalizability of occupational cohort study findings. *Epidemiology*. 2014;25(6):932-3.

41. Bell S, Britton A. Reliability of a retrospective decade-based life-course alcohol consumption questionnaire administered in later life. *Addiction*. 2015;110(10):1563-73.

42. Zins M, Gueguen A, Kivimaki M, et al. Effect of retirement on alcohol consumption: longitudinal evidence from the French Gazel cohort study. *PLoS One.* 2011;6(10):e26531.

Figure legends

Figure 1. Flow chart of the study.

1   Figure 2. Trajectories of the mean volume of weekly alcohol consumption prior to and following the

2   diagnosis of cardiovascular diseases, stratified by sex and case/control group (crude models using

3   imputed data). CI, confidence interval.

4

5   Figure 3. Trajectories of the mean volume of weekly alcohol consumption prior to and following the

6   diagnosis of cardiovascular diseases, stratified by sex and case/control group (maximally adjusted

7   models using imputed data). Figures are reported according to mean and referent held values (i.e.,

8   65 years old at diagnosis, white, married, high socioeconomic position, never-smoking, physically

9   active, eating fruits/vegetable daily, self-rated health as excellent, reporting no history of

10   hypertension, with body mass index of 26 kg/m^2). CI, confidence interval.