Full Length Report

Drinking pattern during midlife and risk of developing depression during 28 years of follow-up: a prospective cohort study

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Abstract (180 words):

Background: The long-term impact of alcohol intake in midlife on developing depression is not clear. We aimed to investigate drinking pattern during midlife as a risk factor for developing depression during 28 years of follow-up.

Methods: We used data from a well characterised prospective cohort study (the Whitehall II study) of 7,583 men and women (70% male) aged 35 to 55 years, and free from depression in 1985-1988, followed up regularly until 2013. Drinking pattern was defined in terms of usual and maximum amounts consumed within a single drinking session, total weekly volume of alcohol consumed and drinking frequency. Depression was assessed using the General Health Questionnaire Depression Subscale at multiple follow-up occasions (up to eight times in total). Associations between different drinking pattern components during midlife and depression were estimated using flexible parametric survival models.

Results: After adjustment for confounding factors only abstaining from alcohol during midlife was associated with an increased risk of developing depression during long-term observation. However, this association became non-significant after adjusting for baseline self-reported health.

Conclusions: In this community dwelling population, drinking pattern during midlife was not associated with an increased risk of developing depression.

Keywords: alcohol; depression; epidemiology; drinking pattern; longitudinal; mental health

1. Introduction

There are concerns about the long-term ill health effects of the drinking habits of middle aged adults (Royal College of Psychiatrists, 2011). Drinking patterns during midlife are relatively stable (Johnstone et al., 1996; Platt et al., 2010) and therefore make this group an important population to study. Drinking habits present at this stage in the life course are likely to persist into old age and therefore reflect long-term exposure enabling one to better quantify the association between particular patterns of alcohol consumption and risk of ill health. It is important that multiple drinking components (such as usual and maximum amount consumed, as well as drinking frequency and abstinence) are examined as distinct drinking dimensions are differentially related to disease burden (Graff-Iversen et al., 2013; Rehm et al., 2006). Depression is a major public health issue and is projected to increase in the future (Mathers and Loncar, 2006). Several studies have examined the relationship between drinking pattern and depression (Hartka et al., 1991; Peele and Brodsky, 2000) producing conflicting findings. For example, some investigators have shown that episodic heavy drinking is associated with an increased risk of depression (Choi and DiNitto, 2011; Paljärvi et al., 2009; Wang and Patten, 2002) while others find no association (Haynes et al., 2005). Similarly, some have shown that compared to abstinence, those who drink in moderation have a lower risk of depression (Gea et al., 2013, 2012), but others have observed that abstainers have a reduced risk of developing depression compared to moderate drinkers (Haynes et al., 2005). Those considered hazardous drinkers on the basis of overall volume of alcohol consumed have typically been shown to be more likely to become depressed (Gea et al., 2013; Tait et al., 2012) than moderate drinkers but this effect is not universally observed (Gea et al., 2012). However, a major limitation of the current evidence base is the relatively short follow-up schedules used to determine depression (typically around 12-18 months) in addition to only using one follow-up occasion to determine depression status. It is important to quantify the

long-term risk of health behaviours, as it may be that some exposure-outcome relationships take time to develop. On the other hand, it could also be the case that an exposure is only linked with an outcome in the short-term. Understanding how the relationship between an exposure and outcome sit in time is of importance to tailoring effective interventions/treatment plans as well as generally improving our understanding of the aetiology of disease.

The purpose of this paper is to examine the association between drinking habits in midlife and depression during long-term follow-up.

2. Material and Methods

2.1 Participants

Participants were British civil servants aged 35-55 years at baseline (1985-88) from the Whitehall II prospective cohort study (Marmot and Brunner, 2005) who have been followed up regularly since (most recently in 2012-13) - resulting in a follow-up period lasting up to 28.3 years. In total there were eight follow-up occasions that included depression measures, these were at study phases 2 (1989-90), 3 (1991-94), 5 (1997-99), 6 (2001), 7 (2002-04), 8 (2006), 9 (2007-09) and 11 (2012-13). The original sample consisted of 10,308 men and women but for the purposes of this study those who were depressed at baseline (n=1,370) and those with no information on depression status at baseline (n=100) where excluded from analysis as the interest was in new incident cases of depression arising during follow-up. Those who were not depressed at baseline but did not return to the study at any subsequent follow-up occasion were also excluded (n=700), as were those with missing values for any of the drinking variables and covariates (n=660) leaving a combined final sample of 7,478 individuals (median follow-up 22.7 years). The University College London Medical School Committee on the ethics of human research approved the Whitehall II study. 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. Please refer to the Whitehall II data sharing policy at http://www.ucl.ac.uk/whitehallII/data-sharing.

2.2 Depression measure and drinking habit exposures

2.2.1 Depression measure

Depression was dichotomised into case (scores ≥ 4) or no-case using the depression subscale of the 30-item General Health Questionnaire (GHQ-30) (Stansfeld et al., 1995) and then used as an outcome variable. The GHQ-30 was administered 9 times in total (8 times post-baseline) during observation. During follow-up, once a participant was identified as a depression case, their record was censored to prevent reoccurring cases of depression influencing the final estimates obtained (non-depressed participants who were lost to attrition were also censored).

2.2.2 Drinking session variables

At baseline participants were asked about the usual (fixed responses of: none, 1-2, 3-4 and 5 or more) and maximum (open response) number of drinks they consumed in a single drinking session. For these questions beer was asked about separately from wine and spirits, which were combined. From these questions it was possible to generate indicators of episodic heavy drinking. Participants were grouped according to their self-reported usual and maximum number of drinks consumed in a single drinking session, as described below. No specific reference to a timeframe for usual or maximum drinking sessions was indicated in the baseline questionnaire.

The number of UK alcohol units (1 UK unit = 8g ethanol) consumed was calculated by converting the number of drinks participants reported consuming using a conservative

estimate of one UK unit of alcohol for each measure of spirits and glass of wine and two UK units for each pint of beer.

2.2.2.1 Hazardous usual drinking sessions
Questions relating to usual drinking sessions enforced fixed responses, we chose the response categories which most closely related to current UK daily drinking guidelines (Department of Health, 1995) – using a threshold of 5 or more UK units (40g) to define hazardous drinkers. Those who reported consuming between 1-4 UK units of wine/spirits or beer in a usual session were categorised as moderate drinkers (i.e. non-hazardous drinkers) while those reporting consuming no alcohol were classified as abstainers (see below for further information on how alcohol abstention was defined). Non-beverage specific usual drinking session variables were generated by coding anyone who was classified as a hazardous drinker for the separate beer or wine/spirit variables described above as hazardous drinkers.

2.2.2.2 Episodic heavy drinking in maximum drinking sessions
The questions concerning maximum drinking sessions allowed for open responses. We took a threshold of 8/6 or more UK units (64/48g) in a single sitting for men/women to define episodic heavy drinking (alternatively referred to as binge drinking, defined as consuming twice the recommended daily limits(Department of Health, 1995)). As in the case of the usual drinking session variable, a non-beverage specific maximum drinking session variable was created by coding anyone identified as an episodic heavy drinker for either beer or wine/spirits as episodic heavy drinkers. Those who reported not consuming alcohol were defined as abstainers (see below).

2.2.2.3 Abstention
In both drinking session variables outlined above, three items were used to determine abstainer status in the drinking session variables; having responded positively to having not consumed alcohol in the previous year, reporting consuming no drinks in a usual or

maximum drinking session as well as indicating no alcohol consumption in the week prior to participation.

2.2.3 Hazardous weekly drinking

An indicator for those exceeding UK weekly drinking guidelines of 21 or less UK units (168g) for men and 14 or less UK units (112g) for women (Batty et al., 2009; Department of Health, 1995) was derived from participants reported past weekly consumption (using the same drink conversions outlined above) at baseline. Those who had not consumed alcohol in the previous week were classified as abstainers and those who consumed within recommended limits were categorised as moderate drinkers).

2.2.4 Drinking frequency

Participants were asked to provide information on their typical drinking frequency at baseline with options of not in the past 12 months, special occasions only, monthly, weekly, daily or more than once daily (the latter two categories were combined).

2.2.5 Covariates

Demographic covariates included age, socioeconomic position (measured by civil service employment grade; high, intermediate and low) and marital status (married/cohabiting , or other).

Other health behaviours also adjusted for include smoking status (never, ex- and current) and physical activity (lowest sex-specific quartile of combined hours of moderate and vigorous physical activity defined as "physically inactive"). Diet quality was classified as poor or good on the basis of type of milk and bread usually consumed and daily intake of fruit and vegetables. For each component a score of zero or one was assigned for indicators of poor

diet (whole milk, white bread, fruit and vegetable intake less than daily) – poor diet was
defined a summed score ≥ 2.

Participants were asked to self-rate their health at baseline, this was dichotomised into good
(very good/good) and poor (average, poor and very poor).

2.3 Statistical analyses
To examine the relationship between drinking pattern in midlife and depression during up to
28 years of follow-up survival analysis was used. Flexible parametric survival models were
used to estimate Hazard Ratios (HR) and their associated 95% Confidence Intervals (CI) of
depression by drinking category status at baseline for usual and maximum drinking sessions,
hazardous weekly consumption and drinking frequency. We used three internal spline knots
(d.f. = 4). Drinking category by gender interactions were tested – none were significant so
analyses were fitted within the pooled cohort with adjustment for sex(Altman and Matthews,
1996; Matthews and Altman, 1996).

We estimated two models for each exposure: model one was adjusted for age and sex only,
and model two which was adjusted for all covariates described above. We present separate
models for each exposure, not adjusted for each other, as including multiple alcohol
components in the same model would likely represent overadjustment (Schisterman et al.,
2009). Estimates were similar after adjustment for confounders, therefore only the hazard
ratios and 95% CIs from the multivariable adjusted models are presented. To aid
interpretation we present predicted HRs in graphical form, however all estimated coefficients
are available in *Online data supplement 1*.

As health status possibly lies on the causal pathway between alcohol intake and depression
we did not adjust estimates for self-rated health as standard, however, we provide a

sensitivity analysis of the impact of doing so as an online appendix (*Online data supplement 2*).

Our reference categories were as follows: (1) non-episodic heavy drinkers in maximum drinking session models, (2) non-hazardous drinkers in usual drinking session models, (3) moderate drinkers in hazardous weekly drinking models, and (4) weekly drinkers in drinking frequency models.

All analyses were conducted using Stata v13(StataCorp, 2013) (in 2014) using the stpm2 command (Lambert and Royston, 2009). An alpha level of 0.05 was considered statistically significant for all analyses.

3. Results

3.1 Descriptive information
Table 1 shows the descriptive statistics of the analytic sample. The mean age of participants was just over 44 years, almost 71% of the sample were men, a large proportion of the sample were of high to intermediate socioeconomic position, and over three-quarters of the sample were married or cohabiting. Around half of participants had never smoked while fewer than 17% were current smokers. Approximately 25% of participants went on to experience a depressive episode during follow-up.

In terms of the main exposures of interest, 15% of the sample drank hazardously in a usual drinking session at baseline while 26% of participants met the criteria for episodic heavy drinking in a maximum drinking session. Around 15% of the sample drank above recommended weekly levels. Around 30% of the sample drank on a daily basis, a little over 40% drank on a weekly basis and around 12% drank monthly or on special occasions. Approximately 4% of participants were classified as abstainers based on single drinking

session variables and frequency of consumption in the previous year, whereas 16% of the sample were categorised as abstainers when using past week consumption alone.

3.2 Regression estimates

3.2.1.1 <u>Maximum drinking session</u>
Presented in Figure 1 are the time-varying hazard ratios for abstainers and episodic heavy drinkers in a maximum drinking session compared to those drinking within limits. In the period immediately following baseline neither those who exceeded drinking thresholds in a maximum drinking session or abstainers had a significantly increased risk of developing depression when compared to moderate drinkers. However, after around five years post-baseline abstainers had an approximately two-fold increased risk of developing depression which persisted until the end of follow-up.

3.2.1.2 <u>Usual drinking session</u>
Presented in Figure 2 are the hazard ratios concerning usual drinking session status. Similar to the maximum drinking session model, abstainers did not have an increased risk of depression in comparison to moderate drinkers in immediately following baseline but after 5 years post baseline they had a significantly higher risk of developing depression. At no point during follow-up did those who exceeded daily drinking limits at baseline have a significantly increased risk of developing depression compared to moderate consumers.

3.2.1.3 <u>Past week drinking volume</u>
Those who exceeded weekly drinking limits in the week preceding baseline did not have a significantly increased risk of depression compared to those who drank within guidelines (Figure 3). Those who abstained from alcohol in the week before participating had an increased risk of developing depression for a small period of follow-up, spanning from around 8 to 13 years in comparison to those whose alcohol intake fell within recommended weekly limits.

3.2.1.4 <u>Drinking frequency</u>

Monthly and special occasion drinkers did not significantly differ in their risk of developing depression when compared to those who drank on a weekly basis (Figure 4). Drinking on a daily basis was associated with an increased risk of depression for period of approximately 8 years (9-17 years) during follow whilst those who did not drink in the year before baseline had an increased risk of depression after five years of follow-up onwards (Figures 5).

3.2.1.5 <u>Sensitivity analysis</u>

The pattern of findings remained largely unchanged after additional adjustment for self-rated health at baseline (*Online supplement 2*), however, estimates for the effect of abstaining no longer met the threshold for statistical significance.

4. Discussion

4.1 Summary

In our analysis of drinking habits in midlife as risk factors for developing depression during up to 28 years of follow-up we found that only abstainers had an increased risk of developing depression when compared to moderate/within limit drinkers. Typically this increased risk did not manifest until after at least five years of observation and continued following from then. However, after adjustment for baseline health status this association was no longer statistically significant.

4.2 Interpretation

Our findings contradict the majority of other longitudinal studies that have explored drinking pattern as risk factors for depression(Hartka et al., 1991; Paljärvi et al., 2009; Wang and Patten, 2002). While there are differences in the consumption categories used in the present study and those of previous studies, typically prior studies have found that hazardous patterns of consumption were related to a greater overall risk of depression. However, our findings are consistent with the only other UK based study(Haynes et al., 2005) which found no

significant increase in the odds of having a common mental health disorder at follow-up based on drinking category at baseline. The work by Haynes and colleagues(2005) was limited to a single follow-up occasion 18 months after baseline while our analyses covered a period of approximately 28 years. Furthermore, our analyses are consistent with prior work examining the dominant temporal relationship between alcohol intake and mental health, which showed that alcohol consumption was not a significant predictor of changes in psychological distress (Bell et al., 2015; Bell and Britton, 2014).

Those who abstained from alcohol at baseline had a greater risk of developing depression; fitting in with existing work on the beneficial psychological effects of moderate alcohol consumption (Peele and Brodsky, 2000). The most curious finding was that this increased risk did not surface until after approximately 5 years of follow-up. It is possible that the negative effects of abstaining, for example having lower social support (Choi and DiNitto, 2011; Lucas et al., 2010; Peirce et al., 2000) or poorer health profiles (Brien et al., 2011), which have been found to be associated with an increased risk of depression (Kivimäki et al., 2012; Rodgers et al., 2000; Shinn et al., 2001; Stansfeld and Rasul, 2007), take time to manifest. This would mean that the immediate risk of depression for abstainers would not differ from that of moderate drinkers, but over time this would change. An alternate explanation resides in having grouped different types of abstainers (lifelong non-drinkers and former drinkers) together. This has been shown to distort (over estimate) the relationship between abstaining and other health outcomes (Fillmore et al., 2007; Kerr and Ye, 2010), including depression (Bell et al., 2014) (although this would not necessarily explain why the increased risk for abstention is not observed until after eight years of follow-up). Unfortunately, no information was available at baseline to correct for this. Future work will be needed to determine whether this increased risk is an artefact driven by the poor health and psychosocial characteristics of abstainers (Naimi et al., 2013) or a genuine beneficial effect of

moderate alcohol consumption. Our sensitivity analysis adjusting for baseline health status indicates that ill-health may partly explain this association. Until then our findings should not be used as a justification for taking up drinking, nor should they be used to excuse drinking in a hazardous manner (as there is consistent evidence that hazardous drinking is associated with an increased risk of many health outcomes (Rehm et al., 2006) and that the purported health benefits of moderate drinking are likely to have been exaggerated (Chikritzhs et al., 2015; Fekjær, 2013; Holmes et al., 2014)).

4.3 Specific strengths and limitations
Particular strengths include the large sample size, length of follow-up time (to our knowledge this is the longest existing period of follow-up used to explore the relationship between drinking pattern and depression, and one of the only studies to use more than a single follow-up phase to determine depression status), using a standardised psychiatric tool to determine depression status at nine occasions post-baseline occasion, as well as having examined multiple drinking components.

There are, however, also a number of limitations of our study. First, only information on drinking pattern at baseline was used to define drinking categories, meaning that changes in consumption over time were not directly incorporated in the models. There may be concerns that using a single exposure at baseline is perhaps more useful in predicting the immediate but not long-term risk of depression. However, by modelling the hazard function using splines this concern has somewhat been accounted for – one can see the immediate and long term risk following this after a possible initial latency period. Some studies suggest that drinking pattern from midlife onwards is relatively stable (Johnstone et al., 1996; Platt et al., 2010) but others show that there is some variation (Britton et al., 2010; Meng et al., 2014), particularly increases in alcohol abstention with older age (Britton et al., 2015). Quantifying the effect of changes in consumption, using a life course perspective, is clearly a priority area

for future studies (Britton et al., 2015). Our study also only focussed on drinking habits at midlife, not earlier or later in the life course, so our findings may not necessarily be generalizable to younger or older adults.

A second limitation is related to the measurement of alcohol consumption. Specifically, the questions used to define usual and maximum drinking sessions did not directly allow for participants to report drinking sessions during which they mix beer, wine and spirits in a single sitting. There are also general concerns that self-reported measures of alcohol consumption may be biased (Laatikainen et al., 2002). Combined, this means that the reference group of moderate/within-limit drinkers is likely to contain several participants who either exceeded the threshold for hazardous drinking in a single session but where not captured because they consumed a combination of beer and wine/spirits, or due to under-reporting of actual alcohol intake. The definition of abstaining was also not consistent across drinking exposures, with stricter definitions imposed for usual and maximum drinking session variables as well as drinking frequency than that used for past week alcohol intake. Furthermore, as outlined above, abstainers were not stratified by lifetime non-drinking. Other investigators have noted the drawbacks of using an aggregated group of abstainers as a category to be compared to other drinking groups (Fillmore et al., 2007; Kerr and Ye, 2010; Stockwell et al., 2012). Unfortunately, no information was available at baseline to correct for this.

A third limitation is that we used data from the Whitehall II cohort of British civil servants which is not a sample representative of the general population, particularly not blue-collar workers and those unemployed. However, aetiological findings from the Whitehall II study have been demonstrated to be concordant with those from the general population (Batty et al., 2014). Other issues pertaining to generalisability include that the Whitehall II sample is

comprised mainly of men. This is possibly an issue as women generally drink less than men and have higher rates of depression. Previous studies have shown that the association between alcohol consumption and depression may differ by gender (Choi and DiNitto, 2011). It is possible that we were underpowered to detect a moderating effect of gender, however, other studies have similarly found no differential effect for alcohol consumption and depression by sex (Gea et al., 2013, 2012; Paljärvi et al., 2009).

5. Conclusion
While the current concerns regarding the long-term ill health effects of the drinking habits of middle aged adults (Royal College of Psychiatrists, 2011) are warranted, we found no relationship between hazardous alcohol consumption in midlife and developing depression in a community dwelling population, comprising of mostly white, male, moderate drinkers – indicating that drinking habits during this period of the life course are unlikely to explain increasing trends in depression(Mathers and Loncar, 2006). However, we found that those who abstained from alcohol had a significantly increased risk of depression, but at this stage, we cannot discount that this effect may be driven by former drinkers who may have quit drinking for health and/or social reasons that would increase their risk of developing depression.

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Table captions

Table 1 - Descriptive information for the sample at baseline

Figure captions

Figure 1 - 28 year hazard ratios and 95% confidence intervals for depression by maximum drinking session status at baseline

Figure 2 - 28 year hazard ratios and 95% confidence intervals for depression by usual drinking session status at baseline

Figure 3 - 28 year hazard ratios and 95% confidence intervals for depression by weekly alcohol intake at baseline

Figure 4 - 28 year hazard ratios and 95% confidence intervals for depression in monthly and special occasion only drinkers at baseline

Figure 5 - 28 year hazard ratios and 95% confidence intervals for depression in daily drinkers and past year non-drinkers at baseline