Letter

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# Non-linear association between alcohol and incident frailty among community-dwelling older people: A dose-response meta-analysis

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**Summary** **A recent systematic review and meta-analysis study suggested that higher alcohol consumption is associated with lower risks for frailty. However the apparent protective effect may not be true because of some limitations. Therefore we further explored potential linear and non-linear associations using a two-stage dose-response meta-analysis. Restricted cubic splines were applied with three fixed knots at percentiles (10%, 50%, and 90%). A two-stage dose-response meta-analysis showed a significant non-linear association (*p* for non-linearity < 0.001); incident frailty risk decreased until around 15 g/day of alcohol consumption and increased thereafter. This suggests that while moderate alcohol consumption is associated with a lower risk of frailty, at higher consumption levels this apparent protect effect is lost. Given these findings, non-linear associations should be considered in future research on alcohol and frailty.**

***Keywords:*** Frailty, alcohol, dose-response meta-analysis, older people

Beneficial effects of light-to-moderate alcohol consumption against various diseases suggested by numerous population-based studies have been controversial and debated in the literature (*1*). There has been limited evidence regarding whether light-to-moderate alcohol consumption is also protective against frailty (*2*). Frailty is a state characterized by decreased physiological reserve resulting from age-related accumulated deficits across multiple systems, with increased risks of various negative health outcomes (*3*). Although a few prospective cohort studies have examined associations between alcohol and risk of frailty, the results are mixed and inconclusive (*4-6*). Our recent systematic review and meta-analysis study suggested that alcohol consumption is associated with lower risks for frailty (pooled odds ratio (OR) of incident frailty among the highest alcohol use categories compared with non-drinkers = 0.44, 95% confidence interval (CI) = 0.19-1.00, $p = 0.05$) (*2*). However, only data of the heaviest drinkers were used in the main meta-analysis and the association of intermediate alcohol use categories with incident frailty has not been investigated (*2*). Therefore, to further explore potential linear and non-linear associations between alcohol consumption and incident frailty risk, we conducted a two-stage dose-response meta-analysis using the data from the same longitudinal cohort studies.

The data used come from three prospective studies examining associations between quantity of alcohol consumption and incident frailty (*4-6*), identified in our previous systematic review and meta-analysis study, that provided data on frailty risk according to quantity of alcohol consumption (*2*). A value (in grams of alcohol per day) assigned to each alcohol consumption category was based on a mid-point of the upper and lower boundary values of the category. When the ranges of the alcohol consumption were different by gender in the same category, the assigned value was modified based on the gender proportion in the category. For the highest alcohol consumption category with only the lower boundary value, the boundary value multiplied by 1.2 was assigned (*7*). All three studies included had defined frailty according to the Fried phenotype (*8*). Crude relative risk (RR) and 95% CI of incident frailty for each alcohol consumption category compared with non-drinking category were calculated and used for the meta-

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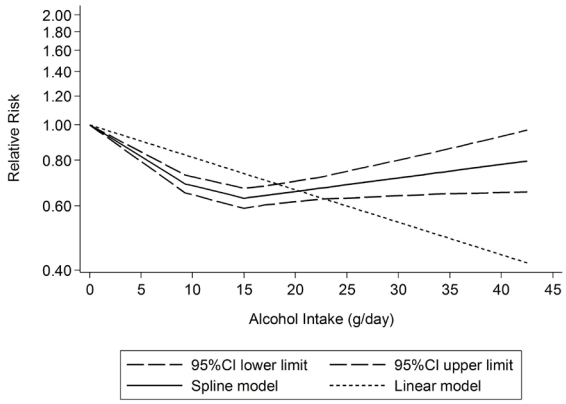


**Figure 1. Dose-response linear and non-linear relationships between alcohol consumption and incident frailty risk.** CI: confidence interval.

analyses.

Potential linear and non-linear dose-response associations between alcohol consumption and incident frailty were estimated using a two-stage dose-response meta-analysis (*9*). A random-effect model was used when heterogeneity was detected using the chi-square test, and a fixed-effect model was used otherwise. For the non-linear association, in the first stage, the restricted cubic spline method was applied with three fixed knots at percentiles (10%, 50%, and 90%) of the alcohol consumption distribution. In the second stage, the regression coefficients and the variance/covariance matrix were combined. Non-linearity was examined by the null hypothesis that the coefficient of the second spline is equal to zero. All statistical analyses were conducted using StataSE 14 (StataCorp LP, College Station, Texas, USA).

We included three studies examining incident frailty risks according to alcohol consumption among a total of 30,929 community-dwelling older people (age ≥ 60 years old) with 4,433 incident frailty cases (*4-6*). These studies categorized alcohol consumption into three or four categories with various cut-points (*4-6*).

For the linear association, a two-stage fixed-effect dose-response meta-analysis was conducted because of absence of significant heterogeneity ($p = 0.27$). There was a significant inverse linear association (pooled RR = 0.83 per 10 g/day increase in alcohol, 95% CI = 0.80-0.85, $p < 0.001$). However there was also a significant non-linear association between alcohol consumption and incident frailty risk ($p$ for non-linearity < 0.001). In the model, the incident frailty risk by alcohol consumption showed a U-shaped association. The frailty risk decreased until around 15 g/day of alcohol consumption and increased thereafter. Predicted linear and non-linear incident frailty risk estimates by alcohol consumption are depicted in Figure 1. The non-linear model had a better fit, based on Akaike's information criterion (AIC) and Bayesian information criterion (BIC); AIC and BIC of the linear model were 82.6 and 81.7, respectively, while AIC and BIC of the non-linear model were 21.5 and 21.4, respectively.

We found a significant non-linear dose-response association between alcohol consumption and incident frailty among community-dwelling older people. Our analysis showed a U-shaped association, with the lowest risk with drinking around 15 g of alcohol per day (equivalent to approximately 2 UK units of alcohol or approximately 1 standard drink in the US). The incident frailty risk slowly increased at consumption above 15 g/day, however remained below that of non-drinkers until the highest alcohol value in our dataset (40 g/day).

These results should be interpreted with caution because of some limitations. First, only three studies were included in the analysis. The small number of the included studies also limited us in undertaking flexible non-linear dose-response analysis with more knots. Second, the highest alcohol consumption category was approximately 40 g/day (*4*) and it was not possible to examine frailty risk above that limit. Alcohol consumption less than 40 g/day may be too low to cause any clinically meaningful worsening of frailty even in older people (*10*). Third, all RRs used in the dose-response meta-analyses were unadjusted since they were calculated based on data from the included studies. Therefore our findings may be confounded by important factors like age, gender, smoking and socioeconomic status.

More research on the associations between alcohol consumption and frailty is needed. Future research should consider using higher cut-points to categorize alcohol consumption than 40 g/day, and use such statistical methods to examine potential dose-response non-linear associations. It is also vital to that future studies control for potential confounders.

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