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Association between alcohol drinking behaviour and cognitive function: results from a nationwide longitudinal study of South Korea

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ABSTRACT

Objectives: This research intends to determine how drinking behaviour, such as episodic heavy drinking, is related to cognitive performance in middle-aged and old-aged people in South Korea.

Methods: A cohort data of 5157 adults, age 45 years or older, with normal cognitive function (the Korean version of the Mini-mental state examination (K-MMSE) ≥24) at baseline (2006), was derived from the Korean Longitudinal Study of Aging. Alcohol drinking behaviour was assessed using the CAGE (Cut down, Annoyed, Guilty, Eye-opener) questionnaire. The relationships between baseline drinking behaviour (in 2006) to the extent of cognitive decline (between 2006 and 2012) and development of cognitive impairment (in 2012) were assessed.

Results: Individuals with problematic drinking behaviour at baseline experienced a faster decline in cognitive function than those with non-problematic drinking (p<0.05) during 6 years of follow-up, especially among those with relatively low-normal K-MMSE score (24–26) at baseline (p<0.05). Problematic alcohol drinking behaviour was also significantly associated with onset of severe cognitive impairment (SCI) (K-MMSE score ≤17) among those with relatively low-normal K-MMSE score (adjusted OR (aOR)=3.76, 95% CI 1.46 to 9.67). In addition, abstinence, compared with non-problematic drinking, was related to higher risk for developing SCI among men (aOR=1.62, 95% CI 1.09 to 2.39).

Conclusions: Our results suggest that those with problematic alcohol drinking behaviour could be at an increased risk of cognitive impairment/decline. While further research will provide stronger evidence, intervention targeting alcohol abuse may play a role in prevention of cognitive impairment.

INTRODUCTION

Along with demographic transition, cognitive impairment is increasing globally. For example, as of 2010, approximately 36 million people worldwide have dementia, and the number is projected to nearly double every 20 years, to 66 million in 2030 and to 115 million in 2050. Given that a cure for dementia and cognitive impairment has been elusive, as well as the fact of recent rising burden of the disease, there is a crucial need to identify modifiable risk factors associated with cognitive impairment.

The protective effects of light-to-moderate alcohol consumption against cognitive impairment have been widely reported along with detrimental effects of heavy alcohol consumption. While most of the findings are from western countries including Western Europe and the USA, conflicting results have been reported in other regions, such as Eastern Europe and Asian countries; for instance, no significant association between heavy alcohol consumption and cognitive impairment was observed among Eastern European adults, or linear negative relationships between alcohol consumption and cognitive function were reported among South Korean adults. These discrepancies between different studies may be explained not only by heterogeneity in the population but also by differences in baseline cognitive performance, differences in follow-up period...
and reverse-causality, such as abstinence due to health problems.

Meanwhile, since existing literature focuses on mean alcohol intake, little is known about the relationship between drinking patterns, such as alcohol use disorders, to cognitive impairment.\(^7\) \(^9\) \(^{10}\) For example, a history of problematic alcohol drinking (PrAD) may not simply reflect current heavy mean alcohol consumption,\(^9\) and in itself may be indicative of alcohol-related brain damage, metabolic changes in the brain,\(^11\) and nutritional deficiency,\(^12\) which result in dementia and cognitive impairment in later life. Few studies, however, have investigated the causal relationship between the history of alcohol use disorders and the risk of cognitive impairment.\(^7\) \(^9\) \(^{10}\)

Alcohol consumption is not unusual in South Korea (hereafter Korea). In 2010, persons aged 15 years or older drank, on average, 12.3 L of pure alcohol per year in Korea, which is almost double the worldwide consumption of 6.2 L. The levels of alcohol consumption in Korea are particularly higher among men than women (21.0 vs 3.9 L), whereas they were at 12.5 vs 2.9 L in the world’s population. In addition, the prevalence of alcohol use disorders (including alcohol dependence and harmful use of alcohol) was 6.2% in Korea (10.3% for men and 2.2% for women), which was higher than worldwide prevalence of 4.1% (7.2% for men and 1.3% for women).\(^13\) While common social and business drinking may contribute to high alcohol consumption, traditional norms against female drinking may be related to the significant gender difference.\(^14\) Moreover, high alcohol consumption is attributable to more years of life lost in Korea.\(^13\)

In light of this context, this study intends to investigate whether/how drinking patterns such as non-problematic drinking and episodic heavy drinking play a role in the development of severe cognitive impairment (SCI), and the extent to which drinking patterns influence the decline in cognitive performance, by using a nationally representative longitudinal sample of Korean middle-aged and old-aged adults with normal cognitive function at baseline.

**METHODS**

**Study population**

Data was taken from the Korean Longitudinal Study of Aging (KLoSA), administered by the Korea Labor Institute. KLoSA is a nationally representative panel study of middle-aged and old-aged household-dwelling adults in Korea. Basing on area (urban/rural) and type of housing (apartment/ordinary housing), 1000 enumeration districts (EDs) were sampled. Approximately six households within each ED were randomly selected, which, in turn, resulted in a total of 6171 households and 10 254 individuals (aged 45 years or older) sampled at baseline (2006). The survey has been conducted every even-numbered year, starting from 2006, thereby currently providing publicly available data with a total of four waves (2006, 2008, 2010 and 2012). At each wave, data regarding health status, income, assets, employment and subjective expectation were collected. The follow-up rate per each wave was 86.6%, 80.3% and 76.2% for the 2008, 2010 and 2012 survey, respectively.\(^15\) Since anonymous KLoSA data, which is publicly available in the website (http://survey.keis.or.kr/), was used, institutional review board approval was waived for this study.

For the study, of 10 254 individuals, for whom cognitive function was assessed at baseline (2006), 7299 individuals with normal cognitive function (the Korean version of the Mini-mental state examination (K-MMSE) >23) were selected as baseline study population.\(^16\) Individuals numbering 1763 were excluded from the fourth wave (330 due to death, 1433 due to non-response). Of 5536 individuals, after excluding 379 individuals with at least one missing value for independent variables used in this study, a total of 5157 respondents were investigated as our analytic sample.

**Outcome measures**

This study measured cognitive function by using K-MMSE scores. The MMSE is a simple instrument developed to measure global cognitive performance and help screen for dementia. The MMSE questionnaire consists of 11 items in seven categories of cognitive functions including orientation for time, orientation for place, registration of three objects, attention and calculation, recall of three words, language and visual construction.\(^16\) \(^17\) The total score of the measure ranged from 0 to 30. The validity of the K-MMSE has been reported elsewhere.\(^17\) The measurement defines mild cognitive impairment (MCI) as scoring 23 point or less, and SCI as scoring 17 point or less.\(^16\) \(^17\) For this study, the onset of SCI (K-MMSE ≤17) and change in K-MMSE scores over a 6-year follow-up were employed as outcome measures.

**Drinking status**

Drinking behaviour was categorised into four groups: No alcohol drinking (NAD), past alcohol drinking (PaAD), non-problematic alcohol drinking (NPAD), and PrAD. We distinguished non-problematic drinking from PrAD based on the CAGE (acronym referring to four questions, see below) questionnaire, which is an assessment instrument widely used for identifying alcoholics.\(^16\) The questionnaire includes the following questions: ‘Have you ever felt you ought to Cut down on your drinking?’; ‘Have people Annoyed you by criticizing your drinking?’; ‘Have you ever felt bad or Guilty about your drinking?’; ‘Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover (Eye opener)?’ The respondent answering ‘yes’ for at least two of the CAGE questions was considered to have problematic drinking behaviour. The other drinkers answering ‘yes’ for one or none of the
questions were defined as having NPAD behaviour. In addition, NAD indicated that a respondent never had a drink; PaAD identified that a respondent used to drink, but has quit drinking. In all analyses, NPAD was used as the reference group.

Covariates

All covariates were collected from the 2006 survey. The sociodemographic variables include age groups (45–54; 55–64 and 65 years or older); gender (female or male), marital status (married or single); educational status (elementary school, middle school, high school, or college or more); equivalised household income quartile (the poorest, second, third or the wealthiest quartile); health insurance status (the National Health Insurance or Medicaid) and living places (rural or urban). Other health behaviours, such as smoking (ever or never smokers) and physical activity (at least once a week or no) were identified as dummy variables. In addition, health status was assessed using three dummy variables as follows: chronic disease (≥1 or none), activities of daily living (ADL) (≥1 or none) and depressive symptoms based on the Center for Epidemiological Studies Depression Scale 10 scale (≥4 or <4 symptoms). To address the issue of reverse causation, baseline MMSE was used as a covariate besides limiting study participants to those with normal cognitive function at baseline.

Statistical analysis

We estimated adjusted means of change in K-MMSE score and adjusted ORs (aORs) of the development of SCI by using linear regressions and logistic regressions, respectively. For each outcome, starting from model 1 adjusting age and gender, we sequentially added a set of covariates. Model 2 further adjusted for sociodemographic characteristics including marital status, educational levels, household income, health insurance status and living place, in addition to age and gender. Model 3 added health behaviours, such as exercise and smoking status, and chronic disease status in model 2. In model 4, baseline K-MMSE score, ADL and depression status were further adjusted based on model 3.

After investigating the overall association of drinking behaviour with each outcome, subgroup analyses were performed with respect to factors including baseline K-MMSE scores (24–26 as lower normal and 27–30 as higher normal), age (<65 years and ≥65 years), gender, education (<college and ≥college), income (<50th and ≥50th centiles), living area (urban and rural), smoking (ever and never smokers), physical activity, BMI (<25 and ≥25 kg/m²) and comorbidity (0 and 1+). We applied longitudinal sampling weight for the first (2006) and fourth (2012) waves, and adjusted for design effect to correct for SEs. For all analyses, Stata (V.12.0/SE) was used, and level of significance was set as 0.05 (two-sided).

RESULTS

Descriptive statistics

Table 1 presented the baseline characteristics of the study participants, Korean adults aged 45 years or older (N=5157). The proportion of current drinkers was greater in younger age groups; 48.5%, 40.7%, 33.3% for NPAD, and 4.3%, 4.3%, 2.8% for PrAD among those aged 45–54, 55–64 and ≥65 years, respectively. The majority of men were current drinkers (NPAD 63.2%, PrAD 7.3%), while these proportions were much smaller among women (NPAD 23.5%, PrAD 0.6%).

Association of drinking behaviour with change in cognitive performance

Figure 1 presents the association between drinking behaviour and change in cognitive function both for all individuals and stratified by K-MMSE scores at baseline. Among all participants (N=5157), baseline drinking behaviours were statistically significantly associated with a change in cognitive function over the follow-up period. When compared with NPAD, PrAD was associated with, on average, a 1.30 point (95% CI 0.08 to 2.52) greater decline in K-MMSE score over the follow-up period in the fully adjusted model.

The magnitude of the association was even greater among individuals with normal but relatively lower K-MMSE scores at baseline (β=−3.28, 95% CI −6.14 to −0.42), while the association was not statistically significant among those with relatively higher K-MMSE scores at baseline (β=−0.51, 95% CI −1.72 to −0.69).

Figure 2 presents the results from subgroup analyses for the association between drinking behaviour and change in cognitive function with respect to gender, age, income, education, BMI, smoking, physical activity, place of living and chronic disease status at baseline in our fully adjusted model. When compared to men with NPAD, men with PrAD at baseline experienced greater decline in K-MMSE score points (β=−1.54, 95% CI −2.83 to −0.25), while the association was not significant among females (β=−0.01, 95% CI −4.23 to 4.21). In addition, among individuals with at least one chronic disease at baseline, PrAD led to greater reduction in cognitive function when compared to NPAD (β=−3.57, 95% CI −6.14 to −1.00), while there was no significant evidence of association among those without chronic disease at baseline (β=0.21, 95% CI −0.73 to 1.15).

Association of drinking behaviour with SCI

Table 2 presents the association between drinking behaviour and SCI both among all individuals, and stratified by K-MMSE scores at baseline. Among all study participants (N=5157), there was no statistically significant evidence of association between types of alcohol drinking at baseline and development of SCI (K-MMSE ≤17) after the 6 year follow-up period.

However, among individuals with normal but relatively low cognitive function (24≤K-MMSE score≤26) at baseline (n=1564), there was statistically significant evidence
### Table 1 Baseline sociodemographic characteristics of Korean adults aged 45 years or older according to drinking behaviour

|                      | Overall       | No alcohol drinking | Past alcohol drinking | Non-problematic alcohol drinking | Problematic alcohol drinking | p Value |
|----------------------|---------------|---------------------|-----------------------|----------------------------------|-------------------------------|---------|
|                      | n wt%         | n wt%               | n wt%                 | n wt%                            | n wt%                         |         |
| All                  | 5157 2597 47.1| 296 50.0            | 2071 43.8             | 193 4.1                          |                              |         |
| Age (years)          |               |                     |                       |                                 |                              |         |
| 45–54                | 2128 55.7     | 1024 43.9           | 66 3.3                 | 953 48.5                         | 85 4.3                         | <0.001  |
| 55–64                | 1686 28.6     | 860 49.3            | 94 5.7                 | 661 40.7                         | 71 4.3                         |         |
| 65+                  | 1343 15.7     | 713 54.5            | 136 9.4                | 457 33.3                         | 37 2.8                         |         |
| Sex                  |               |                     |                       |                                 |                              |         |
| Male                 | 2528 51.2     | 583 21.3            | 258 8.2                | 1511 63.2                        | 176 7.3                        | <0.001  |
| Female               | 2629 48.8     | 2014 74.3           | 94 3.8                 | 560 23.5                         | 17 0.6                         |         |
| Marital status       |               |                     |                       |                                 |                              |         |
| Married              | 4515 88.4     | 2191 45.5           | 265 4.9                | 1876 45.2                        | 183 4.4                        | <0.001  |
| Unmarried            | 642 11.6      | 406 59.7            | 31 5.1                 | 195 33.3                         | 10 1.9                         |         |
| Education            |               |                     |                       |                                 |                              |         |
| Elementary school    | 410 5.8       | 261 63.9            | 30 6.8                 | 109 26.7                         | 10 2.6                         | <0.001  |
| Middle school        | 1334 21.9     | 752 55.1            | 84 5.9                 | 449 34.3                         | 49 4.7                         |         |
| High school          | 1014 19.8     | 521 48.2            | 64 5.9                 | 385 41.7                         | 44 4.3                         |         |
| College+             | 2399 52.6     | 1063 41.6           | 118 4.0                | 1128 50.5                        | 90 3.9                         |         |
| Household income     |               |                     |                       |                                 |                              |         |
| 1Q                   | 1317 22.5     | 689 49.3            | 80 6.8                 | 517 43.3                         | 31 2.4                         | 0.003   |
| 2Q                   | 1262 23.3     | 637 49.1            | 78 5.6                 | 485 39.9                         | 62 5.3                         |         |
| 3Q                   | 1407 28.6     | 685 44.8            | 86 5.2                 | 571 45.1                         | 65 4.9                         |         |
| 4Q                   | 1171 25.6     | 586 46.0            | 52 4.0                 | 498 46.5                         | 35 3.5                         |         |
| Insurance            |               |                     |                       |                                 |                              |         |
| Medicaid             | 204 3.9       | 108 50.6            | 23 13.1                | 67 33.5                          | 6 2.8                          | <0.001  |
| National health insurance | 4953 96.1 | 2489 47.0           | 273 4.6                | 2004 44.3                        | 187 4.1                        |         |
| Location             |               |                     |                       |                                 |                              |         |
| Urban                | 3965 79.8     | 2014 47.3           | 213 4.6                | 1601 44.3                        | 137 3.8                        | 0.081   |
| Rural                | 1192 20.2     | 583 46.6            | 83 6.3                 | 470 42.1                         | 56 5.0                         |         |
| Physical activity    |               |                     |                       |                                 |                              |         |
| Yes                  | 2277 43.9     | 1090 45.0           | 143 5.4                | 954 45.3                         | 90 4.4                         | 0.069   |
| No                   | 2880 56.1     | 1507 48.9           | 153 4.6                | 1117 42.7                        | 103 3.8                        |         |
| Ever smoking         |               |                     |                       |                                 |                              |         |
| No                   | 3525 66.5     | 2324 63.1           | 126 3.2                | 1035 32.5                        | 40 1.3                         | <0.001  |
| Yes                  | 1632 33.5     | 273 15.5            | 170 8.5                | 1036 66.3                        | 153 9.7                        |         |
| ADL                  |               |                     |                       |                                 |                              |         |
| 0                    | 5116 99.3     | 2574 47.1           | 291 4.9                | 2060 43.9                        | 191 4.1                        | 0.111   |
| 1+                   | 41 0.7        | 23 47.9             | 5 13.6                 | 11 35.6                          | 2 3.0                          |         |
| Comorbidity          |               |                     |                       |                                 |                              |         |
| 0                    | 3026 63.3     | 1507 46.3           | 111 3.2                | 1298 46.4                        | 110 4.1                        | <0.001  |

Continued
of association between the alcohol drinking type at baseline and SCI at follow-up. When compared with NPAD, the aORs of SCI for PrAD were 4.12 (95% CI 1.65 to 10.32) for model 1 (minimally adjusted model), 4.43 (95% CI 1.75 to 11.23) for model 2, 4.13 (95% CI 1.65 to 10.32) for model 3 and 3.76 (95% CI 1.46 to 9.67) for model 4 (fully adjusted model). Among individuals with relatively high cognitive function (K-MMSE score ≥ 27) at baseline (n=3593), alcohol-drinking behaviours at baseline were not statistically significantly associated with SCI at follow-up.

Table 3 presents the results from subgroup analyses with respect to demographic and behavioural characteristics using the fully adjusted model. When compared with NPAD, NAD showed significant positive association with SCI at follow-up among males (aOR=1.62, 95% CI 1.09 to 2.39), while the association was not significant among females (aOR=1.00, 95% CI 0.65 to 1.53). When compared with NPAD, PrAD was not significantly
associated with SCI for both men (aOR=1.74, 95% CI 0.86 to 3.53) and women (aOR=1.79, 95% CI 0.40 to 8.08). Among those with at least one chronic disease at baseline, PrAD showed significant positive association with SCI at follow-up (aOR=3.60, 95% CI 1.61 to 8.07).

DISCUSSION
In this nationally representative cohort study, individuals having PrAD behaviour at baseline experienced faster decline in cognitive function than those with non-problematic drinking behaviour during a 6-year follow-up period. This pattern was observed in the whole population, being more remarkable in people with relatively low-normal K-MMSE score (24–26) at baseline compared with those with high-normal K-MMSE scores (27–30). In addition, we found that a history of PrAD behaviour was significantly related to onset of SCI among individuals who had relatively low-normal cognitive function (24≤K-MMSE score≤26) at baseline. Meanwhile, non-problematic drinking, compared with abstinence, appeared to be protective against the development of SCI, and to be related to a slow decline in cognitive function among men.

Previous studies have shown inconsistent evidence of worse cognitive performance in heavy drinkers and beneficial cognitive function in moderate drinkers. Studies in the USA reported that adults with a history of alcohol use disorders at baseline suffered severe memory impairment.9 10 By contrast, in Eastern European countries, heavy, binge, and problematic drinking at baseline were not consistently associated with cognitive function.7 This difference may be related to difference in cognitive function at baseline or follow-up period. According to our results, while history of problematic drinking was related to faster decline in cognitive performance, people within a normal range but relatively low levels of cognitive function at baseline were at higher risk of development of SCI 6 years later. That is, while problematic drinking may be associated with faster decline in cognitive function and, consequently, higher risk of cognitive impairment, the onset of SCI may not be observed in a short period.

Meanwhile, in the current study, beneficial effects of moderate non-problematic drinking were observed
Table 2  Association of baseline alcohol drinking status with severe cognitive impairment after 6 years' follow-up among Korean adults aged ≥45 years

| Baseline alcohol drinking status | No alcohol drinking | Past alcohol drinking | Non-problematic alcohol drinking | Problematic alcohol drinking | OR for trend |
|---------------------------------|---------------------|-----------------------|----------------------------------|-----------------------------|--------------|
| All (N=5157)                    | (N=2597, n=204)     | (N=296, n=24)         | (N=2071, n=118)                  | (N=193, n=15)              |              |
| Model 1: adjusted OR (95% CI)   | 1.26 (0.93 to 1.72) | 1.02 (0.63 to 1.66)   | 1.00                             | 1.69* (0.91 to 3.17)       | 0.94 (0.81 to 1.11) |
| Model 2: adjusted OR (95% CI)   | 1.26 (0.93 to 1.72) | 0.98 (0.60 to 1.60)   | 1.00                             | 1.69 (0.90 to 3.18)        | 0.94 (0.81 to 1.11) |
| Model 3: adjusted OR (95% CI)   | 1.27 (0.93 to 1.73) | 0.95 (0.58 to 1.55)   | 1.00                             | 1.67 (0.89 to 3.14)        | 0.94 (0.80 to 1.10) |
| Model 4: adjusted OR (95% CI)   | 1.27 (0.93 to 1.74) | 0.89 (0.55 to 1.45)   | 1.00                             | 1.60 (0.85 to 3.04)        | 0.94 (0.80 to 1.10) |

Baseline K-MMSE 24–26 (N=1564) (N=854, n=92) (N=546, n=40) (N=53, n=9)

| Model 1: adjusted OR (95% CI)   | 1.14 (0.72 to 1.81) | 1.41 (0.68 to 2.93)   | 1.00                             | 4.12* (1.65 to 10.32)      | 1.09 (0.87 to 1.37) |
| Model 2: adjusted OR (95% CI)   | 1.16 (0.71 to 1.89) | 1.51 (0.72 to 3.17)   | 1.00                             | 4.43* (1.75 to 11.23)      | 1.09 (0.86 to 1.37) |
| Model 3: adjusted OR (95% CI)   | 1.20 (0.73 to 1.98) | 1.37 (0.66 to 2.83)   | 1.00                             | 4.13* (1.65 to 10.32)      | 1.06 (0.84 to 1.35) |
| Model 4: adjusted OR (95% CI)   | 1.21 (0.72 to 2.01) | 1.30 (0.62 to 2.71)   | 1.00                             | 3.76* (1.46 to 9.67)       | 1.05 (0.82 to 1.35) |

Baseline K-MMSE 27–30 (N=3593) (N=1743, n=112) (N=1525, n=78) (N=140, n=6)

| Model 1: adjusted OR (95% CI)   | 1.34 (0.90 to 2.00) | 0.82 (0.41 to 1.66)   | 1.00                             | 0.92 (0.37 to 2.31)        | 0.87 (0.72 to 1.06) |
| Model 2: adjusted OR (95% CI)   | 1.32 (0.89 to 1.97) | 0.74 (0.37 to 1.51)   | 1.00                             | 0.89 (0.35 to 2.27)        | 0.88 (0.72 to 1.06) |
| Model 3: adjusted OR (95% CI)   | 1.29 (0.87 to 1.92) | 0.74 (0.36 to 1.50)   | 1.00                             | 0.91 (0.36 to 2.33)        | 0.89 (0.73 to 1.08) |
| Model 4: adjusted OR (95% CI)   | 1.29 (0.87 to 1.92) | 0.69 (0.35 to 1.39)   | 1.00                             | 0.90 (0.35 to 2.31)        | 0.89 (0.73 to 1.08) |

N=number of observations; n=number of cases of cognitive impairment (K-MMSE ≤17 in 2012).

Results of multiple logistic regressions. For Korean adults aged≥45 years with normal baseline cognitive function (K-MMSE≥24), alcohol drinking status at baseline (reference: non-problematic drinking) and development of severe cognitive impairment after 6 years of follow-up (K-MMSE ≤17) were measured from the 2006 survey and the 2012 survey, respectively.

Model 1 adjusted for gender and age at baseline (2006 survey).
Model 2 added marital status, health cognitive function, income, educational level and living place at baseline based on model 1.
Model 3 added exercise, smoking status and comorbidity at baseline based on model 2.
Model 4 added baseline K-MMSE score, ADL and depression at baseline based on model 3.

*p<0.001, **p<0.01, *p<0.05, +p<0.1

K-MMSE, Korean Mini-Mental State Examination.
| Baseline alcohol drinking status | Men (N=2528) | Women (N=2629) | Ever smoker (N=1632) | Adjusted OR (95% CI) | OR for trend |
|---------------------------------|-------------|----------------|---------------------|----------------------|-------------|
| No alcohol drinking             | (N=583, n=54) | (N=2014, n=50) | (N=273, n=25)       | 1.62 (1.09 to 2.39)  | 0.88 (0.71 to 1.09) |
| Past alcohol drinking           | (N=258, n=19) | (N=38, n=5)    | (N=170, n=15)       | 0.75 (0.42 to 1.35)  |             |
| Non-problematic alcohol drinking| (N=1511, n=86)| (N=560, n=32) | (N=1036, n=60)      | 1.00                 |             |
| Problematic alcohol drinking    | (N=176, n=13) | (N=17, n=2)    | (N=153, n=11)       | 1.74 (0.86 to 3.53)  |             |
| OR for trend                    |             |               |                     | 1.79 (0.40 to 8.08)  |             |
| Adjusted OR (95% CI)            |             |               |                     | 1.93 (0.87 to 3.97)  |             |
| Never smoker (N=3525)           | (N=2324, n=18) | (N=126, n=7)  | (N=1035, n=37)      | 1.20 (0.66 to 1.76)  | 1.02 (0.77 to 1.36) |
| Adjusted OR (95% CI)            |             |               |                     | 0.89 (0.45 to 1.76)  |             |
| No exercise (N=2277)            | (N=1090, n=125) | (N=143, n=15) | (N=954, n=65)       | 1.28 (0.89 to 1.83)  | 0.91 (0.76 to 1.09) |
| Adjusted OR (95% CI)            |             |               |                     | 0.81 (0.37 to 1.76)  |             |
| Exercise (N=2880)               | (N=1507, n=79) | (N=153, n=9)  | (N=1117, n=53)      | 1.38 (0.91 to 2.09)  | 1.00         |
| Adjusted OR (95% CI)            |             |               |                     | 0.91 (0.49 to 1.69)  |             |
| BMI ≥25 (N=1226)                | (N=624, n=39) | (N=70, n=5)   | (N=491, n=22)       | 1.10 (0.74 to 1.62)  | 1.01 (0.83 to 1.24) |
| Adjusted OR (95% CI)            |             |               |                     | 0.94 (0.43 to 2.04)  |             |
| Adjusted OR (95% CI)            |             |               |                     | 1.00                 |             |
| Adjusted OR (95% CI)            |             |               |                     | 1.00                 |             |
| Age ≥65 (N=1343)                | (N=713, n=10) | (N=136, n=19) | (N=457, n=49)       | 1.47 (0.92 to 2.35)  | 0.70+ (0.49 to 1.01) |
| Adjusted OR (95% CI)            |             |               |                     | 1.38 (0.77 to 2.46)  |             |
| Adjusted OR (95% CI)            |             |               |                     | 1.00                 |             |
| Adjusted OR (95% CI)            |             |               |                     | 1.00                 |             |
| Education ≥college (N=2399)     | (N=1063, n=70) | (N=118, n=6)  | (N=1128, n=55)      | 1.21 (0.80 to 1.83)  | 0.70 (0.71 to 1.12) |
| Adjusted OR (95% CI)            |             |               |                     | 0.58 (0.22 to 1.51)  |             |
| Adjusted OR (95% CI)            |             |               |                     | 1.00                 |             |
| Adjusted OR (95% CI)            |             |               |                     | 1.42 (0.64 to 3.13)  |             |
| Top 50% of income (N=2578)      | (N=1271, n=69) | (N=138, n=14) | (N=1069, n=48)      | 1.17 (0.77 to 1.76)  | 0.96 (0.78 to 1.18) |
| Adjusted OR (95% CI)            |             |               |                     | 1.06 (0.60 to 1.87)  |             |
| Bottom 50% of income (N=2579)   | (N=1326, n=135) | (N=158, n=10) | (N=1002, n=70)      | 1.23 (0.77 to 1.97)  | 0.97 (0.79 to 1.19) |
| Adjusted OR (95% CI)            |             |               |                     | 1.32 (0.68 to 2.58)  |             |
| Adjusted OR (95% CI)            |             |               |                     | 1.00                 |             |
| Adjusted OR (95% CI)            |             |               |                     | 1.00                 |             |
| Adjusted OR (95% CI)            |             |               |                     | 1.00                 |             |

N=number of observations; n=number of cases of cognitive impairment (K-MMSE ≤17 in 2012).
For Korean Adults aged ≥45 years with normal baseline cognitive function (K-MMSE ≥24), alcohol drinking status at baseline (reference: non-problematic drinking) and development of severe cognitive impairment after 6 years of follow-up (K-MMSE ≤17) were measured from the 2006 survey and the 2012 survey, respectively. Multiple logistic regression adjusted for marital status, health insurance, income, educational level, living place, exercise, smoking status, comorbidity, ADL, depression and baseline K-MMSE score from the 2006 survey.

***p<0.001, **p<0.01, *p<0.05, +p<0.1.
BMI, body mass index; K-MMSE, Korean Mini-Mental State Examination.
among men, showing that abstainers, more than non-problematic drinkers, experienced a higher risk of SCI and more rapid decline in cognitive function. While the protective effects of light-moderate alcohol intake have been reported against cognitive impairment,20 21 those beneficial associations were sometimes observed limitedly in specific populations, such as women, but not men, and people with MCI at baseline.3–6 22 It is unknown which factors (ie, different lifestyle or drinking practices) cause those different relationships.

Several mechanisms have been identified to be associated with the links of alcohol drinking behaviours to cognitive impairment. Compared with light to moderate non-problematic drinkers, abstinence and PrAD are associated with higher risk of vascular disease, which may increase the risk of cognitive impairment; that is, vascular dementia.23 Problematic alcohol drinking is also directly related to abnormalities in brain morphology, regional cerebral blood flow and brain trauma.3–24 Furthermore, PrAD combined with other risk factors may be more significantly tied to cognitive impairment. Chronic diseases are known to be directly and indirectly related to cognitive impairment. For example, hypertension, diabetes mellitus and hyperlipidaemia are linked to vascular damage which results in cognitive impairment;25 26 and more directly, abnormal insulin regulation of type 2 diabetes is likely related to cognitive impairment.27 Indeed, our results show that PrAD is more detrimental to cognitive function in an individual with chronic disease.

There are several limitations of this study. First, we used a self-reported measure of alcohol drinking behaviour. It is possible that participants under-report (or over-report) their drinking behaviours.28 Second, longitudinal studies may have a common issue of selection bias due to differential loss to follow-up. Among 7299 participants with normal cognitive function in 2006, 71% were included in the study population, 29% were eliminated due to death, non-responses and missing values. However, the mean values of K-MMSE score at baseline did not differ between two groups (study population: mean=25.12; dropouts: mean=25.23). Therefore, the sample attrition might not have influenced our findings. Last, due to the small sample size for PrAD among women (N=17), we were able to observe only two cases of SCI among women with PrAD at baseline, resulting in a non-significant result. We should be careful in translating the findings.

Despite the limitations, there are several strengths of our present study. First, we used a nationally representative prospective survey. Therefore, the findings from our analysis might be generalisable to the population of Korean adults aged 45 years or older. Particularly, the results from subgroup analyses could provide evidence of necessities of targeted strategy for the prevention of dementia related to alcohol drinking, focusing on specific subpopulations including those with low-normal cognitive function (24≤K-MMSE≤26). Second, in order to address the issue of reverse causation in observational studies, we limited study participants to those with normal cognitive function at baseline (K-MMSE≥26), and investigated the association of drinking behaviours with the outcomes of SCI (K-MMSE≤17) and change in cognitive function over the 6 years of follow-up after adjusting for baseline K-MMSE scores as well as all other covariates. Therefore, the findings could be, to some extent, robust toward resolving the potential issue of reverse causation. Third, this study assessed the relationship between a history of alcohol use disorders and cognitive function, by employing the CAGE questionnaire which is a validated and widely used screening instrument for alcohol use disorders.29 Furthermore, findings from this study show that the CAGE questionnaire could be used as a practical measure to identify individuals at risk of alcohol-related cognitive impairment.

In conclusion, our prospective study shows that a history of problematic alcohol use was a risk factor for rapid cognitive decline as well as the development of SCI, while the protective effects of non-problematic drinking were observed among men. Since the associations may vary across different populations and measurements, caution should also be exercised extrapolating these conclusions. In the future, the detrimental consequences of alcohol on cognitive performance would need to be assessed from a multifactorial perspective. While further research will provide stronger evidence as well as more insight into the relationship between alcohol consumption and cognitive impairment/decline, intervention for individuals with problematic alcohol use behaviour may play a role in prevention of cognitive impairment.

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