보건학 박사학위논문

Health Effects of Mild Alcohol Consumption in Koreans

- Focus on cardiovascular disease -

한국인에서 소량 음주의 건강 영향에 대한 연구

- 심혈관 질환을 중심으로 -

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국문초록

한국인에서 소량 음주의 건강 영향에 대한 연구

- 심혈관 질환을 중심으로

음주는 다양한 질환에 대해 주요한 위험요인으로 여겨진다. 그러나 세계 보건기구에서, 음주는 심혈관 질환에 대해 양면적인 효과를 가지고 있고 소량의 음주는 유익하다고 보고한 바 있다. 또한 최근의 체계적 문헌고찰 연구들 역시 소량의 음주가 사망률을 낮추는 효과가 있다고 발표하였다. 몇몇 선행연구에서는 소량 음주의 유익한 효과가 기준 그룹 (reference)의 잘못된 선택 때문에 나타난다고 지적하고 있다. 특히 건강문제로 금주하게 되는 전 음주자 (former drinker) 때문에 소량 음주의 상대적 보호효과가 발생한다는, 소위 ‘sick quitter effect’가 소량 음주의 보호효과를 유발하는 이유로 지적되었다. 그러나 sick quitter effect를 검증하기 위해 전 음주자 포함 여부에 따라 소량 음주의 효과를 비교한 연구들은 상반된 결과를 보고하고 있다. 또한 sick quitter effect는 건강 상태 변화와 금주와의 관련성을 가정하고

있는데, 건강문제 발생이 금주에 미치는 영향을 분석한 연구는 많지 않다. Sick quitter effect 외에도, 간헐적 음주자 (occasional drinker)를 기준 그룹에 포함시키는 것에 대해 몇몇 연구가 이루어졌으나 명확한 결론을 도출하지 못하였다.

본 연구는 다음과 같은 연구목적을 가지고 있다. 첫째, 체계적 문헌고찰 및 메타분석을 통해 한국인에서 건강에 대한 소량 음주의 영향을 살펴본다. 둘째, 기준 그룹의 특성 분석을 위해 추적기간에 따른 음주량의 변화를 평가하고 건강상태의 변화가 금주에 미치는 영향을 알아본다. 셋째, 한국인 코호트 데이터를 이용하여 소량 음주의 위험도를 평가하고 기준 그룹에 따라 위험도가 다르게 나타나는지 알아본다.

첫 번째, 한국인을 대상으로 음주와 사망률을 분석한 연구들을 국내외 데이터베이스에서 검색하였다. 총 16 건의 연구가 선정되었으며, 그중 총 사망률을 평가한 연구는 9건, 암 사망률 8건, 심혈관 질환 사망률 3건이었다. 메타분석결과 총 사망률에서 소량의 음주가 유의한 효과를 보이지 않았다 (5건 분석, odds ratio: 0.85, 95% confidence interval [CI]: 0.72, 1.01). 암 사망률의 경우 모든 암을 보고한 연구가 3건에 불과하여 메타분석을 실시하지 못했으며, 포함된 3건은 상반된 결과를 보고하였다. 심혈관 질환 사망률 역시 분석 대상수가 부족하여 메타분석을 실시하지 못했고, 포함된 3건의 연구 모두 소량 혹은 적은 빈도의 음주에서 유의하지 않은 보호효과를 보고하였다. 첫 번째 연구 결과 한국인에서 소량의 음주가 총 사망률, 암 사망률, 심혈관 질환 사망률에서 유의한 보호효과가 관련되

어있다는 근거를 찾을 수 없었다.

두 번째, 음주량 변화의 평가를 위해 40-69세의 남녀를 포함한 지역사회기반 코호트 자료를 이용하였다. 모든 대상자는 연구시작시점 및 2년마다 음주량을 측정하였고, 일일 음주량에 따라 비음주자 (0g/일), 소량 음주자 (<15g/일), 과음주자 (≥15g/일)로 분류되었다. 모든 대상자를 포함하여 분석하였을 때 시간이 지남에 음주량은 감소하는 경향을 나타냈고, 전체 대상자 중 64.3%만이 연구시작시점에 측정된 음주상태를 10년의 추적기간 동안 유지하였다. 암의 발생 및 치료는 금주의 가능성을 유의하게 높였으나, 심혈관 질환이나 기타 만성질환의 경우 금주에 대한 영향이 유의하게 나타나지 않았다. 또한 질환의 개수 및 주관적 건강상태를 비교하였을 때, 생애 비음주자와 전 음주자 간에는 건강상태가 유의하게 다르지 않았다. 두 번째 연구 결과는 측정시점의 음주량이 안정적이지 않으며, 암을 제외한 질병의 발생이나 건강상태 악화가 금주로 이어지지 않음을 보여주었다.

세 번째, 음주량과 심혈관 질환 발생의 관련성을 알아보기 위해 심근경색과 관상동맥질환의 발생 여부 및 시점을 평가하였다. 소량의 음주는 비음주자에 비해 심근경색 (Hazard ratio [HR]: 0.44, 95% CI: 0.21, 0.92) 및 관상동맥질환 (HR: 0.61, 95% CI: 0.4, 0.94)에 대해 낮은 위험도를 나타냈다. 연구시작시점의 음주량을 지속하는 사람이 64.3%에 지나지 않으므로 변화된 음주량을 반영하여 분석하였을 경우, 심근경색에서만 소량 음주의 보호효과가 유의하게 나타났다. 기준그룹을 비음주자 (생애 비음주자 + 전

음주자)나 생애 비음주자로 했을 경우 소량 음주의 효과가 유의하게 달라지지 않아 sick quitter effect 는 관찰되지 않았다. 그러나 음주량이 2.5g/일 미만인 간헐적 음주자를 기준그룹에 포함하였을 경우 심근경색 (HR: 0.65, 95% CI: 0.29, 1.45)이나 관상동맥질환 (HR: 0.71, 95% CI: 0.42, 1.19) 모두에서 소량 음주의 보호효과가 유의하지 않았다.

연구결과 건강 문제로 인해 금주하는 sick quitting 현상은 암을 제외한 다른 질환에서는 유의하지 않았고, 기준그룹에 전 음주자 포함여부에 따라 소량 음주의 보호효과가 달라지는 sick quitter effect 도 나타나지 않아 한국인에서 소량 음주의 보호효과는 sick quitter effect 에서 기인하지 않았다. 비음주자에 비교하였을 경우 소량 음주의 보호효과가 유의했으나, 기준그룹에 2.5g/일 미만으로 음주하는 간헐적 음주자를 포함시켰을 경우 소량 음주의 보호효과는 모든 심혈관 질환에서 유의하지 않았다. 또한 비음주자에 비해 간헐적 음주자의 인구사회학적 특성이 음주자와 비슷하게 나타나, 보다 적절한 기준 그룹으로서 간헐적 음주자의 가능성을 보여주었다. 향후 금주자 및 간헐적 음주자, 음주자의 특성 분석 및 비교를 통해 적절한 기준그룹을 대한 지속적인 논의가 필요하다.

주요어: 알코올, 음주, 심혈관 질환, 한국인, 음주 변화, 위험요인, 금주.

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Abstract

Health Effects of Mild Alcohol Consumption in Koreans

– Focus on Cardiovascular Disease

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Alcohol consumption has been considered a major risk factor for various diseases. However, world health organization reported that alcohol consumption showed complex relationship in cardiovascular disease (CVD), which mild alcohol consumption was beneficial. In addition, recent systematic review found beneficial effect of low alcohol consumption on all-cause mortality, CVD-related, and cancer-related mortality. Previous studies have reported that the beneficial effects of mild alcohol consumption were attributed to reference group misclassification. As one of those bias, many studies pointed out ‘sick quitter effect’ which former drinkers abstaining from alcohol because of health concerns or prescription medication. Several studies have

investigated whether alcohol-related risk varies according to the reference group (e.g., former drinkers, non-drinkers, or lifetime abstainers), but they reported controversial results. In addition, sick quitter effect acknowledges the possible association of health conditions with quitting alcohol consumption. Studies assessing relationship between change of health problem and quitting alcohol drinking was not so much. Besides the sick quitter effect, several studies have investigated the effect of mild alcohol consumption using a reference group comprising occasional drinkers. However, a clear conclusion was not reached.

This study had three aims. First, this study aimed to investigate the association between mild alcohol consumption and mortality among Koreans, based on a systematic review and meta-analysis. Second, this study aimed to assess whether the change of health status affected quitting of alcohol drinking. Third, this study aimed to evaluate whether alcohol-related risk varies according to the reference (abstainers, non-drinker including former drinkers, and occasional drinkers) based on a Korean cohort's data.

For the first aim, total 16 Korean studies regarding alcohol-related risks of all-cause mortality, cancer-related mortality, and CVD-related mortality were revealed; nine studies evaluated all-cause mortality, eight studies evaluated cancer-related mortality, and three studies evaluated CVD-related mortality. The meta-analysis did not reveal a significant effect of mild alcohol consumption on all-cause mortality (5 studies,

odds ratio: 0.85, 95% confidence interval [CI]: 0.72, 1.01). Meta-analysis of studies using all-cancer mortality and cardiovascular mortality was not performed based on the limited sample size, and the results of studies were controversial. For cancer-related mortality, the results of previous studies were controversial. For cardiovascular mortality, all three studies reported a non-significant effect of occasional or mild alcohol consumption. Therefore, it appears that mild alcohol consumption is not associated with significant beneficial effects on all-cause mortality, cancer-related mortality, or CVD-related mortality in Koreans.

For the second aim, the change in alcohol consumption was assessed using KoGES data (a community-based cohort study conducted by the Korean Center for Disease Control and Prevention) from 40–69 years old Korean during 2001–2002. Only 64.3% of participants in the present study maintained their baseline-assigned drinking status for the entire 10-year follow-up. Significant association of disease onset or treatment with quitting alcohol drinking was showed in only cancer, but CVD or chronic disease. Health status between abstainer and former was not significantly different based on the number of diseases or perceived health.

For the third aim, the association between alcohol consumption and CVD incidence was investigated. The participants were divided into non-drinkers (0 g/day), mild drinkers (< 15 g/day), and moderate-to-heavy drinkers (≥ 15 g/day). Mild drinkers exhibited a significantly

lower risk of myocardial infarction (hazard ratio [HR]: 0.44, 95% CI: 0.21, 0.92) and coronary artery disease (HR: 0.61, 95% CI: 0.4, 0.94), compared to non-drinkers. When using time-dependent analysis based on the change in alcohol consumption, the beneficial effect of mild alcohol consumption was significant only for myocardial infarction, not for coronary artery disease. The beneficial effect did not change significantly when either non-drinkers or lifetime abstainers were used as the reference group; thus, the sick quitter effect was not observed in the reference group analysis. However, when occasional drinkers who consumed < 2.5 g/day of alcohol were included in the reference group, the beneficial effect of mild alcohol consumption was not significant in myocardial infarction (HR: 0.65, 95% CI: 0.29, 1.45) or coronary artery disease (HR: 0.71, 95% CI: 0.42, 1.19).

The results of this study do not support the sick quitter effect because no diseases other than cancer were associated with quitting alcohol consumption, and the risk of mild alcohol consumption was not so much different compared to non-drinkers or lifetime abstainers. The benefit of mild alcohol consumption was significant compared with non-drinkers; however, when occasional drinkers were included in the reference group, the benefit was no longer significant. Additionally, the sociodemographic characteristics between occasional drinkers and drinkers were more similar to each other than were those between non-drinkers and drinkers. Therefore, occasional drinkers might represent a more appropriate reference group with which to assess the effect of

alcohol consumption. In further studies, deliberation regarding an appropriate reference group for alcohol consumption is needed through the analysis and comparison of characteristics among non-drinkers, occasional drinkers, and non-occasional drinkers.

• Key world: alcohol, cardiovascular, Korean, change of alcohol, risk factors, misclassification.

• Student Number: 2013-30675

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Chapter 1. Introduction

1.1 Background

1.1.1 Alcohol-related risks

Alcohol consumption can lead to various adverse conditions and diseases, and approximately 5.9% of all global deaths and 5.1% of the global burden of disease and injury in 2012 were related to alcohol consumption (WHO, 2014). Although alcohol abuse negatively affects health and mortality (Park et al., 2012; Sull et al., 2009), several studies have reported that mild alcohol consumption has a beneficial effect on mortality, and have depicted this relationship as a J-shaped curve (Bagnardi et al., 2004; Gmel et al., 2003; White et al., 2002). Recent meta-analyses have described the beneficial effect of mild alcohol consumption on not only CVD (Rehm et al., 2003; Ronksley et al., 2011; Zheng et al., 2015), also all-cause mortality (Di Castelnuovo et al., 2006) and cancer-related mortality (Jin et al., 2013).

Several studies have reported that a beneficial effect of alcohol consumption is obtained not only in individuals who consume a mild amount of alcohol, but also in those who consume a more than mild amount. In a study by Mukamal et al., the risk of CVD including nonfatal myocardial infarction, coronary heart disease, and angina pectoris decreased when the level of alcoholic drink consumption increased (Mukamal et al., 2006). Another recent study reported that alcohol consumption was linearly associated with a decreased risk of acute

myocardial infarction, and the hazard ratio for a one-drink increment in the daily alcohol consumption was 0.72 (Gemes et al., 2015).

1.1.2 Mild alcohol consumption

A previous study investigating the relationship between alcohol dose and total mortality reported that intake up to 40 g/day for men and 20 g/day for women was inversely associated with total mortality (Di Castelnuovo et al., 2006). Another meta-analysis of the relationship between alcohol and cardiovascular disease reported a beneficial effect with a dose of 2.5g to 14.9 g/day (Ronksley et al., 2011).

Dietary Guidelines for Americans defines moderate drinking as up to two drinks per day for men and one drink per day for women (U.S. Department of Agriculture et al., 2015), wherein a standard drink contains 14g of pure alcohol (CDC, 2016). So based on this guideline, moderate drinking was 28 g/day of pure alcohol for men and 14 g/day of pure alcohol for women. UK guidelines recommend not drinking more than 14 units of alcohol a week, and they define one unit as 8 g of pure alcohol (UK Department of Health, 2016), so this is equivalent to 16 g/day.

Because the range of mild drinking that showed beneficial effects on health differed in previous studies, this study used 15 g/day as the mild drinking criterion, which was consistent with all the studies.

1.1.3 Alcohol consumption in Korea

According to the World Health Organization (WHO), the average per-capita consumption of ethanol was 6.2 L among total population and it was 17.2 L among drinkers in 2010. In Korea, the per-capita consumption was 12.3 L of ethanol among the general population and 27.5 L of ethanol among Korean drinkers during 2008–2010 (WHO, 2014). Even though Korean prevalence of heavy episodic drinking (consuming 60 g or more of pure alcohol on at least one occasion at least monthly) are lower with 6.0% in general and 13.4% among drinkers than the global prevalence among the general population (7.5%) and among drinkers (16.0%), the percentage of alcohol dependence in Korea (4.7%) is higher than the worldwide average (2.3%) (WHO, 2014). In addition, in Korea, the proportion of high risk drinking was 13%, and the proportion of binge drinking was 35.7% in 2014 (KCDC, 2014).

The effects of alcohol consumption may vary according to race and nationality (Halanych et al., 2010; Mukamal et al., 2008; O'Keefe et al., 2014). Moreover, a meta-analysis of alcohol dose and total mortality revealed geographical variations in this association (Di Castelnuovo et al., 2006). For example, despite the beneficial effect of mild alcohol consumption on all-cause mortality (Di Castelnuovo et al., 2006), no J-shaped curve was observed in African-American or Mediterranean populations (Nunez-Cordoba et al., 2009; Sempos et al., 2003).

Li et al. reported that ethnic differences are attributable in liver size and alcohol-metabolizing enzyme activity (Li et al., 2006). Meta-analysis assessing the associations between the alcohol dehydrogenase (ADH) 2 polymorphism and risk of alcoholic liver cirrhosis showed that

the protective effect of ADH2 polymorphism was more definite in Asians than in Caucasians (He et al., 2015). The prevalence of genes related to alcohol metabolism such as aldehyde dehydrogenase (ALDH) and ADH, differed even among Asian people (Lee et al., 1997). A previous study showed ALDH2*504Lys allele frequency was different among Chinese, Korean, and Japanese groups (Li et al., 2009). In addition, several studies have shown that the impact of those genes was different among Asian people. Yokoyama et al. reported that inactive ALDH2 in Chinese people played a less important role in esophageal cancer than it did in Japanese and Taiwanese people (Yokoyama et al., 2010). Another recent study reported that c2 allele of cytochrome P450 family 2 subfamily E member 1 (CYP2N1) was associated with increased risk of alcohol liver disease in Chinese people, but was non-significant in Japanese and Korean people (Liangpunsakul et al., 2016).

Duranceaux et al. have argued that differences in the rates of alcohol use disorder across Asian groups might reflect not only genetic influences but also environmental ones, such as sociocultural factors. Those authors noted that Koreans showed lower levels of response to alcohol than Chinese subjects, after controlling for genotype (Duranceaux et al., 2008). In addition, WHO has also suggested that culture and context is a factor affecting alcohol consumption and alcohol-related harm. According to a WHO report, the prevalence of alcohol use disorders in Korea (6.3%) is higher than that of China (4.8%) and Japan (3.3%). The prevalence of alcohol dependence is also higher in Korea (4.7%) compared with China (2.4%) and Japan (1.7%). Heavy

episodic drinking rates are 6.0% in Korea, 7.5% in China, and 18.4% in Japan. In Korea, total alcohol consumption and average daily intake are also higher, with 27.5 L and 54.9 g/day, respectively, compared with China (15.1 L and 32.7 g/day) and Japan (10.4 L and 22.4 g/day) (WHO, 2014).

As one of the reasons for high alcohol use disorders and dependence, the Korean drinking culture was cited as a contributory factor, which is affected by social motives such as organizational culture and the social network (Joo, 2009). Kim and Lee investigated factors influencing employees' drinking culture, and reported that conformity and social alcohol drinking motives significantly affected the culture of drinking alcohol (Kim et al., 2015b). Another Korean studies also reported that drinking behaviors was accompanied within relationship of peer groups (Shim et al., 2009), and social motives was the strongest motives among Korean male workers (Kim et al., 2012).

Patterns of alcohol consumption and different contexts may cause different risks for the same level of alcohol consumption. In a recent meta-analysis, the pooled risk of hemorrhagic stroke for low alcohol consumption was 0.76 in a Chinese study, whereas it was 1.15 in a Japanese study (Zhang et al., 2014). Likewise, these genetic factor and specific patterns of alcohol consumption in Korean might cause risk of alcohol consumption different form that in other countries. It is reported that cost caused by alcohol consumption was about 2,260 billion in Korea in 2013 (NHIS, 2015), and various attempts have been suggested to reduce alcohol consumption in Korea (KIHASA, 2005; Inje

University et al., 2006). Although WHO reported that small amount of alcohol could be beneficial for several disease (WHO, 2014), The Korean cancer prevention guideline was recently revised to eliminate alcohol drinking, even at the level of 1 or 2 units/day (NCIC, 2016). For policy making for appropriate drinking, assessing risk of alcohol consumption exactly should be preceded.

1.1.4 Sick quitter effect and reference group classification

Previous study reported that the benefit of low alcohol consumption may be attributable in part to inappropriate selection of the reference group and weak adjustment for confounders (Knott et al., 2015). Three types of reference groups have commonly been used to assess the effects of alcohol consumption: lifetime abstainers; non-drinkers including abstainers and former drinkers; and occasional drinkers.

Several studies reported that non-drinkers are not appropriate as a reference group, because this group includes ex-drinkers with many disorders, and introduced the concept of the "sick quitter effect" (Wannamethee et al., 1988). Stockwell et al. reported that former drinker misclassification (i.e., including former drinkers in the reference group) might increase the alcohol-related risk in the reference group, as many people stop drinking because of health concerns or aging (Stockwell et al., 2012). Other studies have also found that former drinkers were more likely to be heavy smokers and have poor overall health, compared to long-term abstainers (Fillmore et al., 1998), and that the protective effect

of alcohol consumption might be overestimated (Fillmore et al., 2006).

Several studies have analyzed the sick quitter effect, and Fillmore et al. found a significant J-shaped relationship between alcohol consumption and coronary heart disease-related mortality for the pooled group. However, those authors also found that this relation was not significant in a pooled model that excluded studies with former drinker and occasional drinker misclassification errors, as the former and occasional drinkers had a non-significantly higher risk of coronary heart disease, compared to lifetime abstainers (Fillmore et al., 2006). Similarly, Stockwell et al. reported that there was no significant reduction in mortality risk was observed for low-volume risk after adjustment for abstainer biases (Stockwell et al., 2016).

However, another studies reported that former drinker misclassification did not decrease the alcohol-related risk and former drinkers did not have a significantly higher risk (Zeisser et al., 2014). Gemes et al. (Gemes et al., 2015) also investigated the association between alcohol consumption and acute myocardial infarction, and in that analysis, former drinking had no effect.

Sick quitter effect assumed that disease onset and change of health condition would lead to quitting alcohol consumption, so the risk for former drinkers was higher than that for abstainers. Several studies have reported an association between disease status and reduced drinking (Molander et al., 2010; Perreira et al., 2001), but another study has found contrary results (Zins et al., 1999). Previous studies assessing risk among former drinkers have also shown conflicting results. Although some

studies have reported high risk among former drinkers (Chan et al., 2015; Lazarus et al., 1991; Liang et al., 2013), others have shown a lower risk for former drinkers than for abstainers (Andrews-Chavez et al., 2015). To confirm a sick quitter effect, both investigation of the relationship between change of health status and quitting alcohol drinking, and assessment of the risk to former drinkers are needed.

Several studies about effect of alcohol have reported another reference group misclassification; occasional drinkers. One meta-analysis that investigated a reference group classification showed no effect of former drinking; however, this study showed that misclassification of occasional drinking (classifying occasional drinkers as abstainers) significantly decreased the risk of alcohol drinking (Zeisser et al., 2014). Another study showed that occasional drinkers had a lower risk than non-drinkers and a similar risk to mild drinkers (Stockwell et al., 2016). Even though one study suggested that occasional drinkers would be more appropriate reference group (Knott et al., 2015), few studies have assessed the effect of occasional drinking.

To know whether beneficial effect of alcohol consumption was caused by reference group bias, studies comparing alcohol-related risk according to reference group are needed.

1.2 Aim of the study

This study had three objectives. First, this study aimed to evaluate the

alcohol-related risk of mortality in Korea, based on a systematic review and meta-analysis. Second, this study aimed to investigate the change of alcohol consumption and to assess whether change of health status was associated with quitting of alcohol consumption. Third, this study aimed to evaluate the association between alcohol consumption and CVD using a Korean cohort's data, and to investigate whether reference group classification affected it (Figure 1-1).

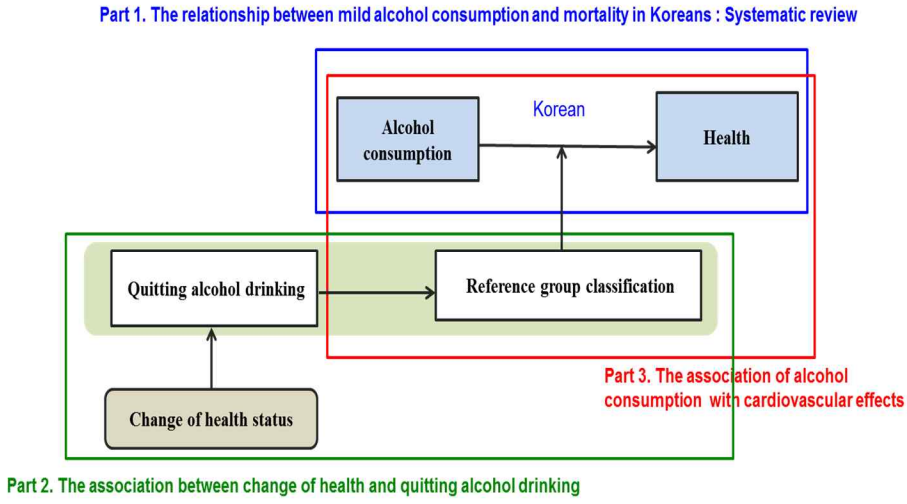


Figure 1-1. Structure of this study

Chapter 2. The relationship between mild alcohol consumption and mortality in Koreans

2.1 Aims

This part aimed to assess the alcohol-related risk of mortality focusing on beneficial effects of mild alcohol consumption in Koreans using systematic review.

2.2 Methods

2.2.1 Literature search and study inclusion criteria

Relevant published studies were selected by searching Medline, Web of Science, KoreaMed, and DBPia databases up to September 30, 2014 without a restriction of study period. Search terms included “alcohol,” “mortality,” and “Korea.” All potentially eligible studies were considered for review, and the reference lists of included studies were examined. Only studies with Korean subjects were included. In addition, studies were eligible for inclusion only if they evaluated all-cause mortality, cancer-related mortality, or cardiovascular mortality as a result of alcohol consumption. When multiple articles had been published for a single study, the latest publication or study with more subjects was used. Two reviewers assessed relevant publications independently, and disagreements were resolved by a third reviewer. Extracted data included

study design, study period, characteristics and number of participants, criteria for drinking, and the risk associated with alcohol consumption.

2.2.2 Data synthesis

For this meta-analysis, studies in which the risk of alcohol consumption was based only on status (e.g., non-drinker/former drinker/current drinker) or frequency were excluded when analyzing the risk of mild drinking. To summarize the effects of alcohol on mortality, the risk estimates and 95% confidence intervals (CI) from each study were extracted using the Cochrane Collaboration software, Review Manager (version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012).

The range of alcohol intake showing a protective effect in previous meta-analyses was variable (Di Castelnuovo et al., 2006; Jin et al., 2013; Ronksley et al., 2011). Considering those studies and guidelines, 15 g/day was used as the mild drinking criterion in this study. Chi-square, tau^2, and Higgins I^2 tests were used to assess heterogeneity. When notable heterogeneity was present (I^2 index $\geq$ 80%), a random-effects model was used.

2.2.3 Quality assessment and publication bias

Two independent reviewers critically appraised the methodological quality of included studies using the Newcastle-Ottawa scale. The Newcastle-Ottawa scale is a quality assessment tool based on selection

of cases and controls (0–4 points for case-control studies and 0–6 points for cohort studies), comparability (0–2 points), and exposure (0–4 points in case-control studies) or outcome (0–5 points in cohort studies). The studies with less than 4 points in case-control studies and less than 6 points in cohort studies were defined as low quality, and these were excluded from the meta-analysis.

2.3 Results

Of a total of 475 identified studies, 429 were excluded after reviewing article titles. Based on a review of abstracts another 30 studies were excluded, and 16 fulfilled the inclusion criteria (Figure 2-1). Of 29 studies, 12 studies were not related to alcohol, 7 did not assess mortality, and subjects did not meet inclusion criteria in one study. Three studies investigating mortality associated with alcohol disorder were excluded (Min et al., 2008; Park et al., 2013; Park et al., 2012), because it is a disease and is not appropriate in the assessment of the effects of typical alcohol use. In addition, another three studies were excluded because they used the same participants as other studies (Jung et al., 2014; Ryu et al., 2014; Sull et al., 2010), and another three studies that did not include appropriate data (Kim et al., 2001; Kim, 2004; Yun et al., 2012).

Total 10 cohorts were included: Juam cohort, Seoul male cohort, Kangwha cohort, National Health and Nutrition Examination survey, Korean National Health Insurance Corporation (KNHIC), Korean

Longitudinal Study on Health and Aging (KLoSHA), Korean Multi-Center Cohort (KMCC), Korean Cancer Prevention Study (KCPS), Korean Elderly Pharmacoepidemiologic Cohort (KEPEC), citizen cohort living in 4 big cities.

Koran Medical Insurance Corporation (KMIC) provides medical insurance to government employees and to private school workers and their dependents (Jee et al., 1998), and now it is a part of the KNHIC. Therefore, studies that used KMIC data (Park et al., 1999) were described as using KNHIC data.

Among studies assessing risk for cancer, two reported alcohol consumption as a risk, based on KCPS data (Jee et al., 2004a; Kimm et al., 2010). Since KCPS was a part of KNHIC (Jee et al., 2004b), there was a possibility of their participants was duplicated in another later study using KNHIC data (Kim et al., 2010). However, the follow-up period of later study was from 2000, and it did not include the follow-up period of the previous two studies, which was from 1993. So the results of the earlier two studies were described separately from those of the later study.

KEPEC was composed of individuals aged 65 years or over who were beneficiaries of the KNHIC (Park et al., 2001). Although some participants in KEPEC were included in the KNHIC, they were all elderly. Owing to their age, these individuals may have different characteristics from the rest of the KNHIC participants. These individuals also have a different study period from that of the later study using KNHIC (Kim et al., 2010), so the studies using KEPEC data (Lim

et al., 2008) were also described separately.

Although several studies may use the same cohort, if they use different measures of alcohol consumption (Sull et al., 2009; Yi et al., 2004) or report different outcomes (Lee et al., 2002; Yi et al., 2010) or additive outcomes (Sull et al., 2009; Yi et al., 2004), their results were also described separately.

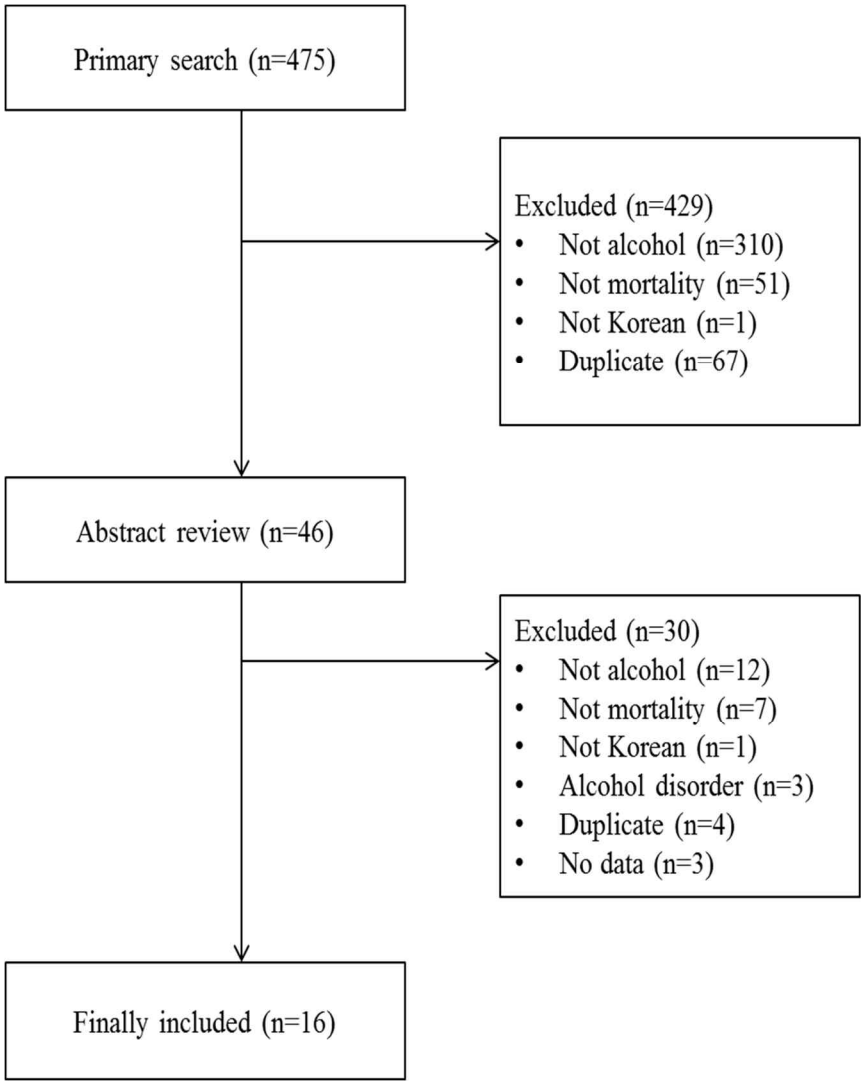


Figure 2-1. Flow diagram of the literature search

The characteristics of 16 included studies are summarized in Tables. Of the 16 studies, five reported on all-cause mortality, six on cancer-related mortality, and one on cardiovascular mortality. Two studies reported all-cause and cancer-related mortality, and the remaining two reported on all-cause and cardiovascular mortality. Ten of the 16 studies used weekly or daily amount as the measure of alcohol consumption, four used drinking frequency, and two used drinking status. A category of no alcohol intake was the reference category in 15 studies, and one study used a mild alcohol group as reference (Jung et al., 2012). Duration of follow-up ranged from 1 to 20.8 years, and sample size varied from 910 to 1,341,393 in the 16 studies.

Table 2-1. Characteristics of studies on alcohol drinking and all-cause mortality

First author (Year)	Study design	Outcome	Study period (Follow-up duration)	Particip-ants	Number of cases (death)	Measures of alcohol consumption	Risk estimate (Confidence Interval)		Criteria of mild drinking
All-cause mortality using alcohol status or frequency (not included in meta-analysis)									
Kim 2007	Cohort (Juam cohort)	All-cause mortality	1995-2001 (6 years)	Aged ≥ 20	3,366 (228)	Status	Men None: 1.0 Former:1.01 (0.57-1.77) Current:0.75 (0.47-1.22)	Women None: 1.0 Former: 1.41 (0.62-3.05) Current: 1.69 (1.01-2.98)	n.r
Rhee 2012	Cohort (Seoul Male cohort)	All-cause mortality	1993-2008 (15 years)	Men aged 40-59	14,533 (990)	Status	None; 1.0 Former: 1.17 (0.98-1.39) Current: 1.40 (1.07-1.83)		n.r
Park 1999	Nest case-control (KNHIC)	All-cause mortality	1993-1997 (4-5 years)	Aged ≥ 40	38,496 (19,258)	Frequency	None: 1.0 Occasional: 1.0 (0.94-1.06) Frequently: 1.17 (1.1-1.26)		n.r
Sull 2009	Cohort (Kanghwa)	All-cause mortality	1985-2005 (20.8years)	Men aged ≥ 55	2,624 (1,984)	Frequency	None: 1.0 Few time a month†: 1.03 (0.89-1.2) Few time a week‡: 1.04 (0.93-1.16) Daily: 1.25 (1.10-1.43)		n.r
All-cause mortality using alcohol amount (included in meta-analysis)									
Yi 2004	Cohort (Kanghwa)	All-cause mortality	1985-1999 (14 years)	Aged ≥ 55	6,292 (2,673)	Weekly amount	Men None; 1.0 **Low: 1.06 (0.92-1.23)** Moderate:1.09 (0.96-1.23) Heavy: 1.35 (1.14-1.60)	Women None: 1.0 **Low: 0.94 (0.77-1.15)** Moderate:1.16 (0.77-1.74)	≤ 70g/ week

Khang 2009	Cohort (National Health and Nutrition Examination Survey)	All-cause mortality	1998-2001 (3 years)	Aged ≥ 30	8,366 (310)	Monthly amount	None: 1.0 Former: 2.03(1.42-2.91) **Minimal: 0.60 (0.39-0.93)** Q1: 1.04 (0.62-1.68) Q2: 1.09 (0.71-1.67) Q3: 1.17 (0.78-1.76) Q4: 1.23 (0.82-1.84)		n.r
Kim 2010	Cohort (KNHIC)	All-cause mortality	2000-2005 (5 years)	Aged 40-69	1,341,393 (19,375)	Daily amount	Men None: 1.0 **1-14.9g: 0.87 (0.84-0.91)** 15-29.9g:0.88 (0.84-0.92) 30-89.9g:1.07 (1.02-1.13) ≥ 90g: 1.29 (1.22-1.37)	Women None: 1.0 **1-14.9g: 0.99 (0.85-1.15)** ≥ 15g: 1.39 (1.08-1.79)	< 30g/ day for men < 15g/ day for women
Jeong 2012	Cohort KLoSHA)	All-cause mortality	2005-2006 (1 year)	Aged ≥ 65	997 (113)	Weekly amount	None: 1.0 **Light: 0.08 (0.01-0.58)** Moderate: 1.15 (0.46-2.85) Heavy: 1.44 (0.81-2.56)		≤ 7drinks /week
Jung 2012	Cohort (KMCC)	All-cause mortality	1993-2004 (11 years)	Aged ≥ 20	16,320 (1,122)	Weekly amount	None: 1.18 (0.96-1.45) **0.1-90g: 1.0** 90.1-252g: 1.29 (0.99-1.66) 252.1-504g: 1.31 (1.00-1.71) ≥ 504.1g: 1.39 (1.05-1.83)		≤ 90g/ week

n.r: not reported, †: almost daily plus 2 to 3 times a week, ‡: 1 to 4 times a month. The group in bold font was analyzed in review or meta-analysis.

KNHIC: Korean National Health Insurance Corporation, KLoSHA: Korean Longitudinal Study on Health and Aging, KMCC: Korean Multi-center Cancer Cohort.

Table 2-2. Characteristics of studies on alcohol drinking and cancer-related mortality

First author (Year)	Study design	Outcome	Study period (Follow-up duration)	Participants	Number of cases (death)	Measures of alcohol consumption	Risk estimate (Confidence Interval)	Criteria of mild drinking
All cancer mortality								
Lee[a] 2002	Cohort (Kangwha)	All cancer mortality	1985-1998 (13 years)	Male aged ≥ 55	2,681 (253)	Frequency	None: 1.0 Light: 0.98 (0.64-1.50) Moderate: 1.01 (0.69-1.48) Heavy: 1.2 (0.89-1.62)	4-12 times /year 1-4 times/ month
Kim[b] 2010	Cohort (KNHIC)	All types of cancer mortality	2000-2005 (5 years)	Aged 40-69	1,341,393 (19,375)	Daily amount	Men None: 1.0 1-14.9g: 0.91 (0.85-0.97) 15-29.9g: 0.93 (0.87-1.0) 30-89.9g:1.06 (0.98-1.15) ≥ 90g: 1.21 (1.11-1.33) Women None: 1.0 1-14.9g: 0.99 (0.85-1.15) ≥ 15g: 1.39 (1.08-1.79)	< 30 g/day for men < 15 g/day for women
Jung 2012	Cohort (KMCC)	All cancer mortality	1993-2004 (11 years)	Aged ≥ 20	16,320 (1,122)	Weekly amount	None: 1.55 (1.15-2.11) 0.1-90g: 1.0 90.1-252g: 1.7 (1.16-2.49) 252.1-504g: 1.84 (1.24-2.72) ≥ 504.1g: 2.07 (1.39-3.09)	≤ 90g/ week
Mortality among cancer patients								
Park 2006	Cohort (KNHIC)	Survival of all cancer patients	1996-2004 (9 years)	Male cancer patients aged ≥ 20	14,578 (7,271)	Weekly amount	None: 1.0 1-124.1g: 0.94 (0.88-1.00) ≥ 124.2g: 1.05 (0.98-1.12)	n.r

Specific type of cancer mortality									
Lee [a] 2002	Cohort (Kangwha)	Stomach cancer	1985-1998 (13 years)	Male aged ≥ 55		Weekly amount	None: 1.0 Light: 2.2 (1.11-4.36) Moderate: 1.32 (0.62-2.79) Heavy: 1.79 (0.998-3.21)		1-4 times/ month
	Cohort (Kangwha)	Liver cancer	1985-1998 (13 years)	Male aged ≥ 55		Weekly amount	None: 1.0 Light: 2.17 (0.68-6.91) Moderate: 1.58 (0.49-5.06) Heavy: 1.45 (0.54-3.9)		1-4 times/ month
	Cohort (Kangwha)	Lung cancer	1985-1998 (13 years)	Male aged ≥ 55		Weekly amount	None: 1.0 Light: 0.1 (0.01-0.76) Moderate: 0.57 (0.26-1.28) Heavy: 0.65 (0.36-1.18)		1-4 times/ month
Jee 2004	Cohort (KCPS)	Liver cancer	1993-2002 (7-9 years)	Aged 30-95	1,283,112 (3,807)	Daily amount	Men None: 1.0 1-24.9g: 1.0 (0.9-1.1) 25-49.9g: 1.0 (0.9-1.2) 50-99.9g: 1.1 (0.9-1.4) ≥ 100g: 1.4 (1.0-1.8)	Women None: 1.0 Drinker: 1.2 (0.9-1.5)	1-24.9g/ day
Lim 2008	Cohort (KEPEC)	Colorectal cancer	1993-1996 1995-2002 (2-7 years)	Aged ≥ 65	14,304 (112)	Daily amount	Never:1.0 0-24g: 0.68 (0.38-1.2) 24-48g: 1.38 (0.66-2.86) 48-72g: 1.22 (0.3-4.98) >72g: 1.28 (0.32-5.21)		≤ 24g/day
Kim [b] 2010	Cohort (KNHIC)	Lung cancer	2000-2005 (5 years)	Aged 40-69	1,341,393 (19,375)	Daily amount	Men None: 1.0 1-14.9g: 0.75 (0.66-0.85) 15-29.9g: 0.78 (0.68-0.9)	Women None: 1.0 1-14.9g: 1.29 (0.91-1.83) ≥ 15g:0.94 (0.45-1.94)	

					30-89.9g:0.93 (0.8-1.08) ≥ 90g: 0.9 (0.74-1.08)	
Liver cancer	2000-2005 (5 years)	Aged 40-69	1,341,393 (19,375)	Daily amount	Men None: 1.0 1-14.9g: 0.92 (0.80-1.05) 15-29.9g: 0.95 (0.82-1.11) 30-89.9g: 1.10 (0.93-1.30) ≥ 90g: 1.23 (1.01-1.51)	Women None: 1.0 1-14.9g: 0.74 (0.44-1.22) ≥ 15g: 1.8 (0.90-3.57)
Stomach cancer	2000-2005 (5 years)	Aged 40-69	1,341,393 (19,375)	Daily amount	Men None: 1.0 1-14.9g: 0.96 (0.83-1.11) 15-29.9g: 1.0 (0.85-1.18) 30-89.9g: 1.05 (0.88-1.26) ≥ 90g: 1.23 (1.00-1.51)	Women None: 1.0 1-14.9g: 0.65 (0.44-0.98) ≥15g: 1.48 (0.85-2.57)
Colorectal cancer	2000-2005 (5 years)	Aged 40-69	1,341,393 (19,375)	Daily amount	Men None: 1.0 1-14.9g: 1.14 (0.90-1.45) 15-29.9g: 1.06 (0.80-1.40) 30-89.9g: 1.32 (0.98-1.77) ≥ 90g: 1.31 (0.90-1.91)	Women None: 1.0 1-14.9g: 0.99 (0.62-1.59) ≥ 15g: 2.51 (1.31-4.82)
Pancreatic cancer	2000-2005 (5 years)	Aged 40-69	1,341,393 (19,375)	Daily amount	Men None: 1.0 1-14.9g: 0.81 (0.61-1.06) 15-29.9g: 0.98 (0.73-1.31) 30-89.9g: 0.81 (0.57-1.14) ≥ 90g: 1.41 (0.99-2.02)	Women None: 1.0 1-14.9g: 0.66 (0.35-1.23) ≥ 15g: 0.50 (0.12-2.05)

	Prostate cancer (men)/ Uterine cancer (women)	2000-2005 (5 years)	Aged 40-69	1,341,393 (19,375)	Daily amount	Men None: 1.0 1-14.9g: 1.32 (0.59-3.0) 15-29.9g: 1.75 (0.72-4.22) 30-89.9g: 2.09 (0.84-5.19) ≥ 90g: 2.39 (0.83-6.89)	Women None: 1.0 1-14.9g: 1.09 (0.50-2.35) ≥ 15g: 1.10 (0.25-4.79)
	Esophageal cancer	2000-2005 (5 years)	Aged 40-69	1,341,393 (19,375)	Daily amount	Men None: 1.0 1-14.9g: 1.23 (0.82-1.85) 15-29.9g: 1.43 (0.92-2.22) 30-89.9g: 2.09 (1.37-3.20) ≥ 90g: 3.33 (2.17-5.12)	
	Leukemia	2000-2005 (5 years)	Aged 40-69	1,341,393 (19,375)	Daily amount	Men None: 1.0 1-14.9g: 0.76 (0.48-1.20) 15-29.9g: 1.00 (0.63-1.60) 30-89.9g: 1.14 (0.68-1.92) ≥ 90g: 1.49 (0.81-2.74)	
	Brain cancer	2000-2005 (5 years)	Aged 40-69	1,341,393 (19,375)	Daily amount	Men None: 1.0 1-14.9g: 1.52 (0.90-2.57) 15-29.9g: 2.05 (1.19-3.53) 30-89.9g: 1.2 (0.58-2.47) ≥ 90g: 2.22 (1.05-4.70)	Women None: 1.0 1-14.9g: 1.10 (0.49-2.47) ≥ 15g: 1.56 (0.37-6.58)
Kimm 2010 Cohort (KCPS)	Esophageal cancer	1993-2006 (14 years)	Aged 30-93	782,632 (996)	Daily amount	None: 1.0 1-24g: 1.9 (1.6-2.3) 25-49g: 2.7 (2.1-3.5) 50-99g: 3.7 (2.8-5.0)	≤ 24g/day

							≥100g: 3.4 (2.2-5.3)		
Yi 2010	Cohort (Kanghwa)	Digestive cancer	1985-2005 (20.8years)	Aged ≥ 55	6,291 (360)	Weekly amount	Men None: 1.0 Low: 1.18 (0.83-1.69) Moderate:1.06(0.73-1.56) High: 1.26 (0.88-1.82)	Women None: 1.0 Low: 1.15 (0.53-2.51) High: 1.63 (0.83-3.19)	<138g/ week for men, <12g/ week for women

[a, b]: Studies marked a or b were the same study, respectively.

n.r: not reported. KEPEC: Koran Elderly Pharmacoepidemiologic Cohort, KNHIC: Korean National Health Insurance Corporation, KMCC: Korean Multi-center cancer Cohort, KCPS: Korean Cancer Prevention Study.

Table 2-3. Characteristics of studies on alcohol drinking and cardiovascular mortality

First author (Year)	Study design	Outcome	Study period (Follow-up duration)	Partici-pants	Number of cases (death)	Measures of alcohol consumption	Risk estimate (Confidence Interval)		Criteria of mild drinking
Meng 1987	Case-control study (citizens living in 4 big cities)	Cardiovascular mortality	1982-1983	Men aged 35-65	910 (190)	Frequency	Men None: 1.0 1-2 times/month: 0.92 1-2 times/week: 1.09 3-4 times/week: 2.27 Everyday: 2.17		1-2 times/ month
Sull 2009	Cohort (Kanghwa)	Cardiovascular mortality	1985-2005 (20.8years)	Men aged ≥ 55	2,624 (1,984)	Frequency	Men None: 1.0 Few times a month†: 0.98 (0.67-1.42) Few times a week‡: 1.06 (0.82-1.37) Daily: 1.36 (1.0-1.84)		n.r
Yi 2004	Cohort (Kanghwa)	Cardiovascular mortality	1985-1999 (14 years)	Aged ≥ 55	6,292 (672)	Weekly amount	Men None: 1.0 < 70g: 0.98 (0.69-1.37) 70-503.9g: 1.06 (0.8-1.39) ≥ 504g: 1.52 (1.06-2.19)	Women None: 1.0 < 70g: 0.92 (0.61-1.38) ≥ 70g: 0.89 (0.33-2.4)	≤70g/week
		Hypertensive disease mortality	1985-1999 (14 years)	Aged ≥ 55	6,292 (672)	Weekly amount	Men None: 1.0 < 70g: 0.51 (0.19-1.37)	Women None: 1.0 < 70g: 0.40 (0.05-2.96)	

					70-503.9g: 0.98 (0.51-1.88) ≥ 504g: 1.43 (0.61-3.32)	≥ 70g: 5.45 (1.25-23.77)
Ischemic heart disease	1985-1999 (14 years)	Aged ≥ 55	6,292 (672)	Weekly amount	Men None: 1.0 < 70g: 1.03 (0.31-3.49) 70-503.9g: 0.38 (0.10-1.48) ≥ 504g: 0.94 (0.19-4.54)	n.r.
Cerebrovascular disease	1985-1999 (14 years)	Aged ≥ 55	6,292 (672)	Weekly amount	Men None: 1.0 < 70g: 1.09 (0.70-1.69) 70-503.9g: 1.08 (0.76-1.54) ≥ 504g: 1.66 (1.03-2.65)	Women None: 1.0 < 70g: 1.20 (0.76-1.91) ≥ 70g: 0.72 (0.18-2.93)

n.r: not reported, †: almost daily plus 2 to 3 times a week, ‡: 1 to 4 times a month,

2.3.1 Mortality

(1) All-cause mortality

Of the two studies using drinking status as a criterion, one reported a significantly high risk only among women (Kim et al., 2007), and the other showed a significant effect on mortality in current drinkers compared with non-drinkers (Rhee et al., 2012). Two studies using frequency as a drinker classification criterion showed no significant results (Park et al., 1999; Sull et al., 2009). In the five studies using amount of alcohol consumed, mild drinkers showed no significant mortality risk in two studies (Jung et al., 2012; Yi et al., 2004), while three reported a significantly lower risk among men (Jeong et al., 2012; Khang et al., 2009; Kim et al., 2010).

The amount of alcohol consumed by groups with the lowest alcohol consumption in the studies was between 10 g/day and 15 g/day; all these studies were included in the meta-analysis as the amounts were considered mild drinking based on previous guidelines. The results of the meta-analysis did not show favorable effects of mild alcohol drinking on total mortality (OR: 0.85, 95% CI: 0.72, 1.01) (Figure 2-2).

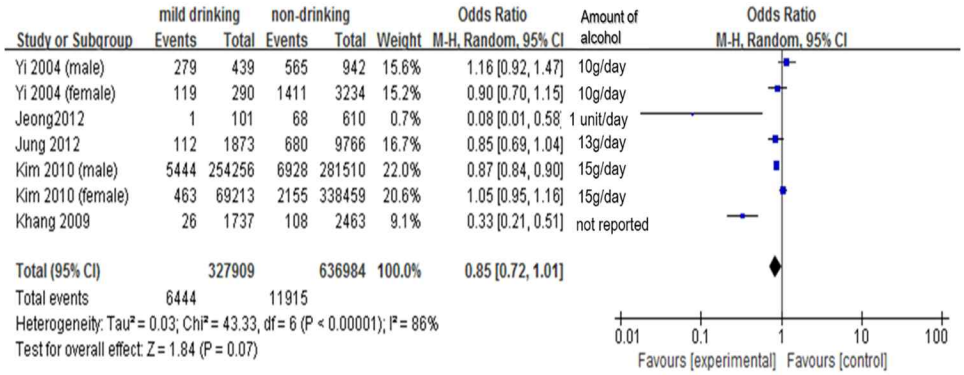


Figure 2-2. Pooled results of mild drinking on the risk of all-cause mortality

(2) Cancer-related mortality

Among eight studies reporting cancer-related mortality, four reported all cancer mortality (Jung et al., 2012; Kim et al., 2010; Lee et al., 2002; Park et al., 2006). Except for one study reporting mortality related to alcohol consumption in cancer patients (Park et al., 2006), only three studies assessed all cancer mortality associated with alcohol consumption. Regarding assessment of risk of mild alcohol consumption using drinking frequency, risk was not significantly lower than that of non-drinkers (Lee et al., 2002). In two studies that used amount of alcohol consumed, one reported a significantly higher risk of cancer mortality among non-drinkers than mild drinkers (Jung et al., 2012); the other study showed that the benefit of mild alcohol consumption was significant for men but not for women (Kim et al., 2010). Meta-analysis for assessing the risk of mild alcohol drinking for cancer-related mortality was not conducted because of the small number of studies.

Six studies assessed the effects of alcohol on hepatocellular carcinoma (Jee et al., 2004a), colorectal cancer (Lim et al., 2008), esophageal cancer (Kimm et al., 2010), digestive cancer (Yi et al., 2010), and various other types of cancer (Kim et al., 2010; Lee et al., 2002). Although several studies reported a beneficial effect of mild alcohol consumption on lung cancer (Kim et al., 2010; Lee et al., 2002) and stomach cancer (Kim et al., 2010), these results were not consistent.

(3) Cardiovascular mortality

Three studies assessed the cardiovascular risk related to drinking alcohol. Although two studies using frequency and one study using alcohol amount as drinking criterion reported lower cardiovascular mortality in occasional or mild drinkers compared with non-drinkers (Meng et al., 1987; Sull et al., 2009; Yi et al., 2004), none of the results were statistically significant. Yi et al also showed that risk of alcohol consumption on various type of cardiovascular mortality including hypertensive disease, ischemic heart disease, cerebrovascular disease (Yi et al., 2004). However, for any of those mortality, mild drinking did not show beneficial effect than non-drinker. Owing to the lack of studies, a meta-analysis of mild drinking as a risk factor for cardiovascular mortality could not be conducted.

2.3.2 Quality assessment and publication bias

Overall, the methodological quality of the included studies was moderate to high. Scores on the Newcastle-Ottawa scales were 4 to 5 points in case-control studies and 6 to 9 points in cohort studies. Exposed and non-exposed groups

were in the same community in all studies, and most studies used structured interviews to ascertain exposure data. Additionally, all cohort studies used independent blind assessment or record linkages to assess outcomes. Based on the results of the quality assessment, none of studies was excluded from the meta-analysis.

Owing to the small number of studies evaluating each outcome, a statistical test to evaluate publication bias could not be conducted. The contour-enhanced funnel plot for publication bias is shown in Figure 2-3. In this figure, the unshaded region in the middle of the funnel plot corresponds to p-values greater than 0.1, the gray shaded region corresponds p-values between 0.1 and 0.05, the dark gray shaded region corresponds to p-values between 0.05 and 0.01, and the region outside of the funnel corresponds to p-values below 0.01. According to this distribution, a possibility of publication bias is indicated by the asymmetry and by the lack of significant studies on the right-hand side of the funnel plot. Therefore, the possibility of publication bias should be considered when applying the results of this study.

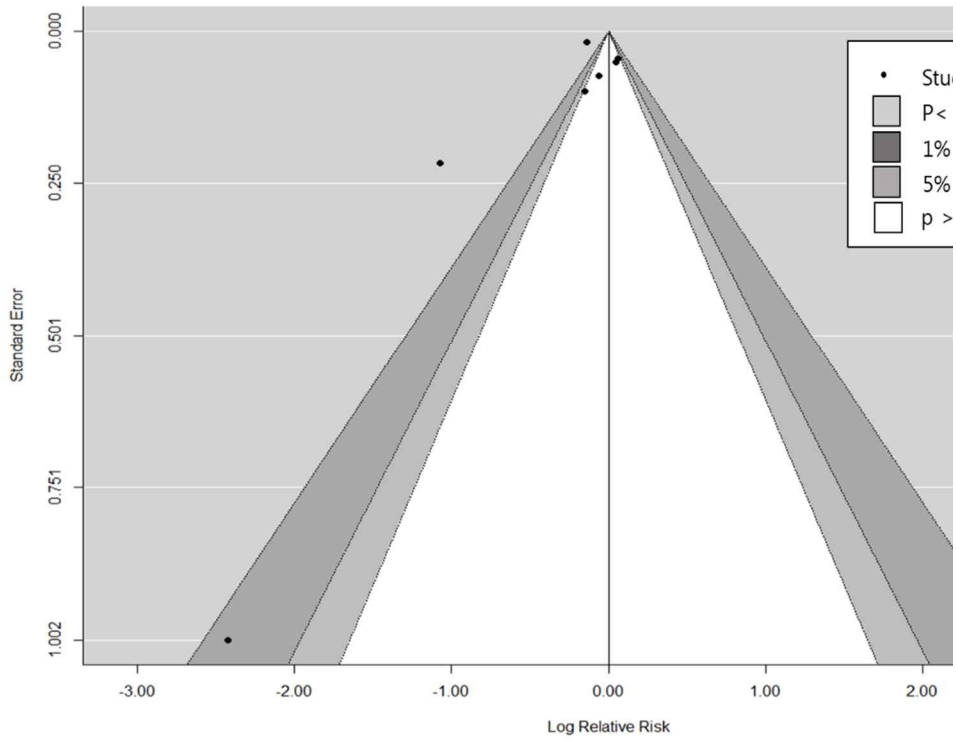


Figure 2-3. Funnel plot for alcohol consumption in relation to all-cause mortality

2.3.3 Heterogeneity test

To assess heterogeneity in meta-analyses, graphical methods, including L'Abbe and Galbraith plots, and statistical methods, such as the Q statistic and Higgins I^2 test, can be used. Since the results of the Galbraith graph (Figure 2-4), and I^2 test (88.7%) indicated significant heterogeneity among the included studies, a random-effects model was used in the meta-analysis. Even after

excluding one study determined to be an outlier by tests of influence, the results of meta-analysis still showed a non-significant effect on all-cause mortality, with a HR of 0.94 (95% CI: 0.82, 1.08).

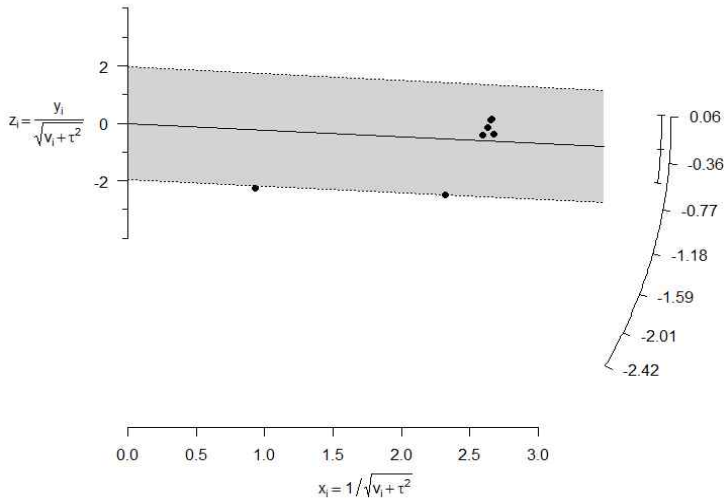


Figure 2-4. Galbraith plot for heterogeneity test

2.4 Discussion

In recent meta-analyses, mild alcohol consumption showed a beneficial effect on all-cause mortality (Di Castelnuovo et al., 2006), cardiovascular mortality (Ronksley et al., 2011), and cancer-related mortality (Jin et al., 2013). However, in this study mild drinking did not demonstrate a protective effect for all-cause mortality and cardiovascular mortality. In cancer-related mortality, mild alcohol consumption showed significant benefit in one study, but did not benefit women in the other study. Overall, no beneficial effect of mild alcohol consumption for all-cause, cancer-related, or cardiovascular mortality was found in the present study. The difference in results could be caused by three factors: the criteria used to define mild drinking, the subjects, and the sample size.

First, the criterion of mild drinking in previous studies was diverse. In the study by Jung *et al.*, a weekly amount of less than 90 g was considered as mild drinking (Jung et al., 2012), while less than 70 g was used in the Yi *et al.* study (Yi et al., 2004). Moreover, Kim *et al.* defined mild drinking as a daily amount of 30 g (Kim et al., 2010), whereas Jee *et al.* designated 25 g/day (Jee et al., 2004a) and Lim and Park preferred 24 g/day (Lim et al., 2008). Unjustified categorization of alcohol consumption might cause inaccurate results in individual studies, and different criteria for mild alcohol consumption between studies make it difficult to compare the results. To accurately assess the effect of alcohol consumption, a consensus on the alcohol intake considered to represent “mild drinking” should first be reached.

Second, the subjects included in this meta-analysis and those in previous ones differed. This review included only the Korean population. Besides

biological factors including race, the effect of alcohol drinking could also differ based on behavioral factors (Poli et al., 2013). While total alcohol per capita in Korea was higher, at 12.3 L of pure alcohol (men: 21, women: 3.9), compared with the world average of 6.2 L, the proportion of heavy episodic drinking was lower (6.0%) than the world average (7.5%) (WHO, 2014). Not only the amount of alcohol and risky drinking, but also the type of beverage has an influence on the effect of alcohol on mortality. Although previous studies reported that wine and beer showed a greater protective effect than spirits on cardiovascular disease and cancer (Arranz et al., 2012; Chiva-Blanch et al., 2013), beer and wine accounted for only 26.6% of total alcohol consumption in Korea (WHO, 2014). Because of these factors, the risk of alcohol consumption could be different even among different Asian populations. Although a recent Chinese study reported that alcohol consumption of less than 1–2 drinks/day showed lower all-cause mortality than that for non-drinkers (Odegaard et al., 2015), this present study and another study in a Japanese population (Marugame et al., 2007) showed no beneficial effects for mild alcohol consumption with respect to total mortality. Further studies assessing the effect of alcohol consumption should consider factors such as drinking patterns and beverage type.

Lastly, there is a possibility that the different results were due to the small number of studies. Whereas previous reviews included between 18 and 84 studies, the number of studies in this review was less than 10 for each outcome. Moreover, the studies including fewer than 10,000 subjects numbered 8 of the total 16 studies. To understand the reasons for these different results, more studies including Korean participants should be conducted to investigate the association between mild alcohol consumption and mortality risk.

Most of the included studies used non-drinkers as a reference group, but it is unclear whether they graded former drinkers as non-drinkers. If some former drinkers quit drinking for health reasons, analyzing these subjects as non-drinkers could lead to biased results. Further misclassification, for example including occasional drinkers as non-drinkers or low-level drinkers, could bias risk estimates (Zeisser et al., 2014). Appropriate classification of drinkers is important in assessing the risks of alcohol consumption.

In this review, several studies used different criteria for men and women (Kim et al., 2010; Yi et al., 2010), while others applied the same criteria and analyzed both sexes together. In a previous meta-analysis investigating alcohol and total mortality, 2 to 4 drinks per day for men and 1 to 2 drinks per day for women were inversely associated with total mortality (Di Castelnuovo et al., 2006). Women may be more vulnerable to alcohol-related risk, and men and women exhibit different drinking patterns (Organization, 2014). Participants' characteristics, such as sex, should be considered when assessing the impact of alcohol.

The age of the subjects in each study was diverse. Moreover, several studies chose subjects according to their residential area (Yi et al., 2004; Yi et al., 2010) while others enrolled participants based on health examination (Kim et al., 2010). Such variations might have contributed to population heterogeneity in this meta-analysis.

To test for publication bias, a contour-enhanced funnel plot was used in this study. Statistical methods to test publication bias, such as Begg's test or Egger's test, were not used, as they are not recommended for meta-analyses including less than 10 studies (NECA, 2011). The results of funnel plot showed the possibility of publication bias among previous studies. Despite a

possible protective effect of alcohol consumption, no beneficial effect of mild alcohol drinking in this study could support even the careful use of alcohol consumption in Koreans.

Previous studies have attributed the apparent benefits of alcohol to antioxidant capacity, anti-inflammatory effects, and the change in lipid profiles (Arranz et al., 2012). Rimm *et al.* reported that alcohol intake is causally related to a lower risk of coronary heart disease through changes in lipids and hemostatic factors (Rimm et al., 1999). Furthermore, another study revealed that alcohol has anti-inflammatory effects by reducing plasma fibrinogen and interleukin-1α levels (Estruch et al., 2004). However, high-dose ethanol increases mortality (Di Castelnuovo et al., 2006), and Carnevale and Nocella reported that long-term alcohol consumption involves increased oxidative stress and the production of pro-inflammatory cytokines and adhesion molecules (Carnevale et al., 2012). The biological mechanism of alcohol on health and mortality should be further assessed through additional studies.

Chapter 3. The association between health changes and cessation of alcohol consumption

3.1 Background

3.1.1 Changes in alcohol consumption over time

Many studies have assumed that alcohol consumption would remain relatively stable among subjects during their respective study periods. Perreira and Sloan found that approximately 70% of their subjects exhibited relatively stable alcohol consumption over a 6-year period (Perreira et al., 2001), while another study found the same over a 1-year period (Bacharach et al., 2004). Paavola et al. assessed health behaviors among participants at 15, 21, and 28 years old. Their findings showed that alcohol consumption was significantly associated with earlier consumption (Paavola et al., 2004).

However, other studies have reported conflicting results. WHO reported that the quantity of alcohol consumption declines with age, but frequency increases (WHO, 2014). Jenkins et al. reviewed the changes in consumption among control groups in intervention studies and found a decreased of 11.5%–46.0% in most of the included studies (Jenkins et al., 2009). McCambridge et al. investigated whether questioning participants about their alcohol consumption led to reduced consumption, and found a negative association between the baseline and 6-month scores for those with alcohol-use disorders. They suggested that part of the reduction seen in the control groups was likely related to regression to the mean (McCambridge et al., 2014). Moreover, a 6-

year longitudinal study found that 19% of drinkers and 12% of non-drinkers exhibited a change in drinking status (Eigenbrodt et al., 2001).

Observation studies have also reported that alcohol consumption was not consistent. Benzies et al. evaluated changes in health-related behaviors among middle-aged women, and found correlation coefficients of 0.74 for alcohol consumption frequency and 0.63 for alcohol amount over a 4-year period (Benzies et al., 2008). Another study found reductions in the proportion of participants who consumed alcohol, and their total alcohol consumption, over 10 years (Moos et al., 2004).

Stability of alcohol consumption can vary based on participants' characteristics, such as sex, age, or drinking status. Kerr et al. analyzed the stability of alcohol consumption in three studies measuring alcohol consumption more than three times, and found high inter-measurement correlations for adults with inter-measurement intervals of < 5 years, though the correlations were low for inter-measurement intervals of > 5 years, younger participants, and heavy drinkers (Kerr et al., 2002). Brennan et al. investigated drinking patterns among 55–65 year olds for 10 years, and recorded correlation coefficients of 0.31–0.54 for men and 0.61–0.76 for women (Brennan et al., 2010). They also found that heavy drinkers exhibited less-stable consumption habits (Brennan et al., 2010).

3.1.2. Factors associated with change in alcohol consumption

Sex

Previous studies indicate that men and women exhibit different patterns of change in their alcohol consumption. Molander et al. found that the number of

drinks per month was stable among women, but that this measure increased among men (Molander et al., 2010). Furthermore, women are more likely to decrease or stop drinking (Perreira et al., 2001). In Park's study, female drinkers were more likely to quit drinking during follow-up monitoring and were also more likely to keep abstaining than men (Park et al., 2009). However, another study reported that male sex was associated with a faster age-related reduction in alcohol consumption (Moore et al., 2005). Brennan et al. conducted a 10-year study of drinking patterns among 55–65-year-olds, and found correlation coefficients of 0.31–0.54 for men and 0.61–0.76 for women (Brennan et al., 2010).

Age

Previous studies indicate an association between older age and lower alcohol consumption (Kemm, 2003). For example, Eigenbrodt et al.'s cross-sectional study revealed an inverse association between drinking prevalence and age, and a reduction in drinking prevalence during the 6-year follow up (Eigenbrodt et al., 2001). Longitudinal studies of alcohol consumption also generally show age-related changes (Moore et al., 2005), which often involve reduced consumption or a transition to non-drinker status. However, several studies have reported stable alcohol consumption over multi-year evaluation periods (Benzies et al., 2008; Brennan et al., 2010).

Marriage

Becoming a widow or widower is associated with increased alcohol consumption, but the effect of getting married and divorced are not consistent;

these factors are associated with both decreases and increases in alcohol consumption (Perreira et al., 2001). Karlamangla et al. found that getting married was associated with a reduction in the frequency of heavy drinking (Karlamangla et al., 2006). Another study reported that predictors of attempts to quit drinking and factors leading to successful quitting varied among individuals with alcohol abuse or dependence; for example, being single increased the likelihood of attempting to quit, while being married increased the odds of success (Chiappetta et al., 2014).

Employment

A study of the effect of employment status on alcohol consumption revealed that retirement increased the likelihood of periodic heavy drinking, compared with working individuals (Bacharach et al., 2004). Other studies show that retirement is associated with increased (Perreira et al., 2001) or frequent alcohol consumption (Molander et al., 2010). Furthermore, employment type can affect alcohol consumption; Syden et al. found that self-employed women exhibited more stable alcohol consumption than women who worked as manual labourers (Syden et al., 2014).

Education level

Moore et al. reported that higher education levels predicted greater alcohol consumption at baseline and slower age-related decreases in drinking (Moore et al., 2005). Similarly, another study found that higher education levels predicted increased daily drinking (Molander et al., 2010).

Smoking

Smoking status is associated with greater alcohol consumption at baseline (Moore et al., 2005), and Zins et al. found that smoking status is associated with increased alcohol consumption (Zins et al., 1999). Other research indicates that quitting smoking is related to a reduction in the incidence of heavy drinking (Berg et al., 2015; Karlamangla et al., 2006) or alcohol use disorder (Cavazos-Rehg et al., 2014). However, Kahler et al. reported that quitting smoking did not lead to significant change in alcohol use (Kahler et al., 2010).

Social support and self-efficacy

Among chronic liver disease patients, drinking motives, drinking refusal self-efficacy, diagnosis of the disease was significant in drinking habits (Kim et al., 2013). Another study showed that age and lower perceived emotional support were associated with increased likelihood of former drinking in women (Andrews-Chavez et al., 2015).

Health status

Although some studies have reported that the number of baseline health conditions does not affect changes in consumption (Brennan et al., 2010), many other researchers have presented conflicting findings. Walton et al. found that drinking habits were not stable among problem drinkers, with participants indicating health concerns as a common reason for changing their drinking habits (Walton et al., 2000).

A previous Korean study showed that the awareness and treatment of hypertension/diabetes were significantly associated with a low rate of alcohol consumption (Choi, 2007). Zins et al. found that self-perception of poor health and taking of sleeping pills were associated with cessation of alcohol consumption (Zins et al., 1999). Similarly, Perreira and Sloan found hospitalization and chronic conditions were associated with reduced consumption (Perreira et al., 2001), while another study found that a severe medical diagnosis, including diabetes, stroke, myocardial infarction, cancer, and hospitalization, during the follow-up period were associated with fewer units of consumption per month (Molander et al., 2010).

3.2 Aims

Previous studies have assumed many drinkers quit consuming alcohol because of health problems, and that pre-existing health problems caused higher risk for former drinkers. As a result, in studies assessing the risks of alcohol consumption, health risks would be inflated among non-drinkers—a group that includes former drinkers—and the relative health risk for mild drinkers would be underestimated.

This part of the study had two aims: 1) assess changes in alcohol consumption over time and 2) determine whether changes in health condition affect cessation of alcohol consumption.

3.3 Method

3.3.1 Study population

This study used data from the Korean Genome and Epidemiology Study (KoGES), a community-based cohort study conducted by the Korean Center for Disease Control and Prevention. A total of 10,038 participants aged 40–69 years at baseline and living in one of two Korean cities (Ansung and Ansan) were recruited in 2001–2002 and followed-up for 10 years. The Seoul National University Institutional Review Board approved the study.

3.3.2 Baseline examination

Trained physicians and nurses collected baseline data using standardized methods and with stringent levels of quality control. Data on demographic characteristics, medical history, and lifestyle risk factors were obtained through a standardized questionnaire. Participants underwent health examinations every 2 years from baseline. Information on health behaviors, including alcohol consumption and medical histories of participants, was obtained at every assessment.

3.3.3 Alcohol consumption

Participants were classified as “current drinker,” “never drinker,” and “ex-drinker” based on their reply to the question on drinking status. They were asked, “Do you drink any alcoholic beverages?” with follow-up questions to assess the frequency and amount of consumption at one time for each type of alcohol. For drinkers, the amount of alcohol consumed was converted to grams

of ethanol per day. This quantity was multiplied by the percentage of alcohol of each type of beverage (6% for Korean *makgeolli*, 4.5% for beer, 15% for rice wine, 13% for regular wine, 22% for spirits, 40% for liquor). Grams of alcohol per day were then summed across the six types of beverages and multiplied by 0.7893, the concentration of ethanol. Based on the calculated daily amount of ethanol, participants were classified as non-drinker (0 g/day), mild drinker (< 15 g/day), or moderate-to-heavy drinker (≥ 15 g/day).

3.3.4 Change in alcohol consumption

Among 10,038 initial participants, only 9,001 were included analysis, with the exception of 1,037 with no follow-up data. Changes in alcohol consumption were assessed every 2 years, based on the difference between the baseline and assessment consumption values. Stability of alcohol consumption over time was assessed using correlation analysis, and changes in consumption were compared between the drinker groups using a mixed model.

3.3.5 Factors associated with quitting drinking

Of the 9,001 participants, 8,923 (abstainer: 4,116, former: 570, current: 4,235) reported their drinking status at baseline. Of the current drinkers, 198 reported their alcohol consumption as zero. After these were excluded, only 4,037 were considered drinkers at baseline. To find factors associated with quitting alcohol consumption, the drinkers were divided into quitters and non-quitters. Only participants whose alcohol consumption was zero both at the 8-year and 10-year measurements were considered to have quit drinking. Of the 4,037 drinkers at baseline, 673 were considered quitters by this definition, and

3,364 were considered non-quitters.

Demographics at baseline and changes in those variables among participants were compared. Analysis of change involved comparison of values at baseline and 8 years later. When participants' data were missing at 8 years, their previous follow-up data were forwarded to know whether the change in variables had occurred. Factors deemed related to quitting alcohol consumption were included in analysis. The baseline covariates were defined as sex, age group, marital status, educational level, employment status, baseline presence of chronic disease, and baseline perception of health. Changes in marital status, employment status, smoking, and perceived health status were also assessed from baseline to the 10-year follow-up (Figure 3-1).

Perceived health and presence of disease at baseline, and change in those variables were assessed to analyze the impact of change in health status on quitting alcohol consumption. Disease onset and treatment were evaluated to investigate their association with quitting alcohol consumption, and the assessed diseases were categorized into three groups: cardiovascular disease (CVD), cancer, and other chronic diseases. The CVD group included hypertension, myocardial infarction, heart failure, coronary artery disease, hyperlipidemia, peripheral artery disease, stroke, transient ischemic heart disease, and arrhythmia. The cancer group included various types of cancer, such as lung cancer, stomach cancer, liver cancer, colon cancer, pancreatic cancer, uterine cancer, and breast cancer. Other chronic diseases included diabetes, gastritis, hepatitis, kidney disease, tuberculosis, and pulmonary disease (Table 3-1).

Only if disease onset occurred before quitting drinking could the disease be considered to have affected the decision to quit. In the case of CVD and

chronic disease, the individual might have quit alcohol consumption a short time before diagnosis, as disease progress is typically slow. Therefore, when disease diagnosis occurred before quitting or before the first measurement subsequent to quitting, it was considered as a positive entry for the disease occurrence variable.

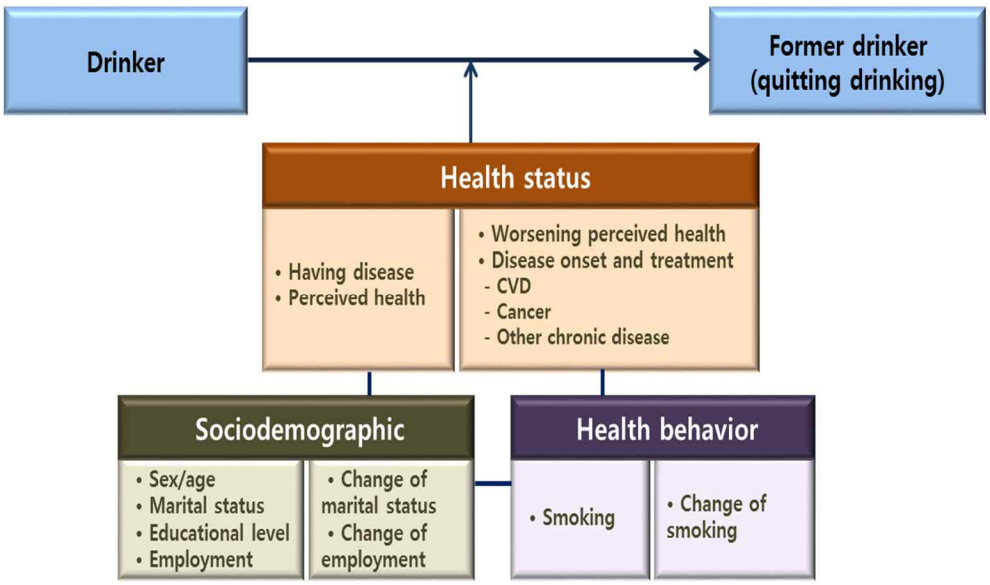


Figure 3-1. Analytic model of factors related to quitting alcohol drinking

Logistic analysis was conducted to determine factors associated with quitting alcohol consumption.

$$\log\left[\frac{\Pr(Y=1)}{1-\Pr(Y=1)}\right] = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \varepsilon$$

Y = 0: continued consuming alcohol (reference group)

Y = 1: quit consuming alcohol

X_1: baseline demographic variables

X_2: changes in the demographic variables

X_3: health conditions

Table 3-1. Independent and dependent factors of study design.

Category	Factor		Definition
Dependent variable	Quitting alcohol consumption		0: continued consuming alcohol 1: quit consuming alcohol
Variables at baseline	Sex		0: male 1: female
	Age		0: aged 40–49 at baseline 1: aged 50–59 at baseline 2: aged 60–69 at baseline
	Marital status		0: not married/divorced/separated 1: married
	Educational level		0: middle school graduate or lower 1: high school graduate or higher
	Employment		0: employed 1: unemployed
	Current smoking		0: non-smoker 1: smoker
	Having chronic disease		0: no 1: yes
	Perceived health		0: poor 1: average 2: good
Change in variables	Marital status		0: maintained status or married 1: divorced or separated
	Employment		0: maintained status or became employed 1: became unemployed
	Smoking		0: maintained smoking status 1: quit smoking
Change in health status	Perceived health		0: maintained or improved 1: worsened
	Disease onset	Cardiovascular disease	0: no 1: yes
		Cancer	0: no 1: yes
		Other chronic diseases	0: no 1: yes
	Disease treatment	Cardiovascular disease	0: no 1: yes

	Cancer	0: no 1: yes
	Other chronic diseases	0: no 1: yes

3.3.6 Comparing health status among abstainer, former, and current drinker

The numbers of diseases for abstainers, former drinkers, and current drinkers were compared to analyze health conditions. After excluding participants with no follow-up data or drinking status data at baseline, 8,923 cases were included.

Among the abstainers at baseline, participants who did not drink any alcohol for the 10-year follow-up period were considered part of the abstainer group. For non-abstainers at baseline, those whose alcohol consumption was zero at both the 8- and 10-year follow-ups were considered former drinkers. The remaining participants were considered current drinkers. The number of CVD, cancer, and chronic disease occurrences in each group were compared using analysis of variance, and categorical variables were evaluated using the χ^2 test. All analyses were performed using R statistical software (version 3.1), and $p < 0.05$ was considered statistically significant.

3.4 Result

3.4.1 Change in alcohol consumption

The baseline characteristics and changes in the characteristics were analyzed for each alcohol consumption group. Consumption increased over time in non-drinkers and mild drinkers, but moderate-to-heavy drinks were less likely over time to consume alcohol. The mean consumption of non-drinkers at baseline was 1.83 g/day after 2 years and 1.56 g/day after 10 years. The mean baseline consumption of mild drinkers was 4.75 g/day, and the changes during the follow-up period ranged from 4.72 g/day at 2 years to 3.37 g/day at 10 years. The moderate-to-heavy drinkers exhibited reduced consumption ranging from −5.51 g/day at 2 years to −11.82 g/day at 10 years. Consumption increased among all participants until the 6-year follow-up, though at 8 and 10 years was lower than baseline (Table 3-2). When only the participants followed-up for 10 years were analyzed, non-drinkers and mild drinkers still showed increased consumption, whereas moderate-to-heavy drinkers showed decreased consumption over the follow-up period (Supplement 1).

Table 3-2. Changes in alcohol consumption from baseline at every 2 years in each group

	Mean alcohol consumption*			
	Non-drinker (n = 4,964)	Mild drinker (n = 2,380)	Moderate-to-heavy drinker (n = 1,657)	Total (n = 9,001)
Baseline	0 ± 0	4.75 ± 4.02	42.63 ± 32.45	9.10 ± 21.35
Change after 2 years	1.83 ± 12.39	4.72 ± 13.72	− 5.51 ± 36.89	1.25 ± 19.91
Change after 4 years later	1.78 ± 9.70	3.78 ± 14.13	− 7.68 ± 40.52	0.58 ± 20.53
Change after 6 years later	1.50 ± 7.91	3.62 ± 14.47	− 7.79 ± 39.75	0.33 ± 19.97
Change after 8 years later	1.57 ± 8.44	3.05 ± 16.73	− 9.63 ± 40.90	− 0.07 ± 20.96
Change after 10 years later	1.56 ± 16.18	3.37 ± 15.75	− 11.82 ± 37.77	− 0.34 ± 22.25

*All values are mean ± standard deviation.

The correlations of alcohol consumption amounts among all participants were analyzed at each time point. Although the correlation coefficient for the baseline and 2-year consumption amounts was 0.59, this value decreased to 0.47 at the 10-year follow-up. Correlation coefficients ranged from 0.44 to 0.65 (Table 3-3). In men the range was 0.39–0.59, and in women 0.36–0.61. When the 6,219 participants followed-up for 10 years were analyzed, the correlation coefficient between each measurement was 0.42–0.64, and the difference between analysis including all participants and only the participants followed-up for 10 years was small (Supplement 2).

Table 3-3. Correlation between alcohol consumption at each measurement among all participants (n = 9,001)

Variables	baseline	2 years	4 years	6 years	8 years	10 years
Baseline	-					
2 years	0.59**	-				
4 years	0.56**	0.58**	-			
6 years	0.55**	0.58**	0.62**	-		
8 years	0.51**	0.53**	0.59**	0.65**	-	
10 years	0.47**	0.44**	0.48**	0.52**	0.54**	-

*: $p<0.05$, **: $p<0.01$

In a mixed model for change in alcohol consumption over time by drinker category at baseline, consumption decreased 0.18 g/day for one period (2 years). The effect of the drinker category at baseline on change in alcohol consumption was significant. While non-drinkers and mild drinkers consumed an average of 0.23 g/day and 0.39 g/day more, respectively, for one period, moderate-to-heavy drinkers consumed about 2.27 g/day less.

Changes in consumption differed between the sexes, with a mean decrease of 0.32 g/day in men and 0.04 g/day in women for one period. Male non-drinkers (0.74 g/day for one period) and mild drinkers (0.76 g/day for one period) showed a greater increase in consumption over time than women (0.05 g/day in non-drinkers, −0.04 g/day in mild drinkers). In moderate-to-heavy drinkers, consumption decreased, but the decline was greater in women (−3.52 g) than men (−2.21 g) for one period (Table 3-4).

Table 3-4. Mixed model for change in alcohol consumption over time (n = 9,001)

	Model 1*						Model 2**					
	Male		Female		Total		Male		Female		Total	
	β (se)	p-value	β (se)	p-value	β (se)	p-value	β (se)	p-value	β (se)	p-value	β (se)	p-value
Time	-0.32 (0.09)	<0.001	-0.04 (0.02)	0.009	-0.18 (0.04)	<0.001	0.74 (0.16)	<0.001	0.05 (0.02)	0.012	0.23 (0.06)	<0.001
Mild drinker	-	-	-	-	-	-	7.03 (0.97)	<0.001	3.26 (0.16)	<0.001	5.87 (0.45)	<0.001
Moderate-to-heavy drinker	-	-	-	-	-	-	43.0 (0.94)	<0.001	29.79 (0.48)	<0.001	42.29 (0.51)	<0.001
Time* mild drinker	-	-	-	-	-	-	0.02 (0.22)	0.93	-0.09 (0.04)	0.017	0.16 (0.1)	0.11
Time*(Moderate-to-heavy drinker)	-	-	-	-	-	-	-2.95 (0.21)	<0.001	-3.57 (0.12)	<0.001	-2.5 (0.11)	<0.001
Intercept	19.18 (0.45)	<0.001	1.47 (0.08)	<0.001	9.91 (0.23)	<0.001	1.7 (0.68)	0.013	0.15 (0.08)	0.048	0.6 (0.26)	0.02

*Model 1 included only time variables.

**Model 2 included time and drinker category at baseline.

3.4.2 Factors associated with quitting alcohol consumption

Drinkers at baseline were assessed on whether they continued to drink, and their characteristics were subsequently compared. Analysis of participants who continued drinking or quit drinking revealed significantly more men who continued drinking than quit drinking ($p < 0.001$). Participants 40–49 years old were numerous in both groups, though this age group was significantly more common among those who continued drinking ($p < 0.001$). Single people were more likely to quit drinking ($p < 0.001$), but the proportion of participants unemployed ($p = 0.26$) or who had a chronic disease ($p = 0.83$) was not significantly different. In the quit-drinking group, participants who reported poor self-perceived health status were strongly represented, whereas the kept-drinking group showed a higher proportion with good or average self-perceived health status ($p < 0.001$).

The group that quit drinking exhibited a higher percentage of people who separated or divorced ($p = 0.02$). Prevalence of people losing a job ($p = 0.06$) or quitting smoking ($p = 0.43$) was not significantly different between those who continued and those who quit.

The group that quit drinking also exhibited significantly lower prevalence of worsened perceived health status ($p < 0.001$) and higher prevalence of CVD ($p = 0.85$), cancer ($p < 0.001$), and other chronic diseases onset ($p < 0.51$). The prevalence of CVD ($p = 0.18$), cancer ($p = 0.002$), and other chronic disease treatment ($p = 0.14$) were all higher in quit-drinker group, but only cancer onset and cancer treatment were statistically significant (Table 3-5).

Table 3-5. Demographic data of groups that continued drinking and quit drinking

		Drinking status N (%)		Total	p-value
		Kept drinking (n = 3,364)	Quit drinking (n = 673)	(n = 4,037)	
Baseline					
Male		2,595 (77.1)	315 (46.8)	2,910 (72.1)	< 0.001
Age	40 –49	1,928 (57.3)	295 (43.8)	2,223 (55.1)	< 0.001
	50 – 59	805 (23.9)	196 (29.1)	1,001 (24.8)	
	60 – 69	631 (18.8)	182 (27.0)	813 (20.1)	
Separated or divorced		185 (5.5)	65 (9.7)	250 (6.2)	< 0.001
Low education level		1,482 (44.2)	378 (56.3)	1,860 (46.2)	< 0.001
Unemployed		604 (18.0)	108 (16.1)	712 (17.7)	0.26
Chronic disease		1526 (45.4)	309 (45.9)	1835 (45.5)	0.83
Perceived health	Poor	802 (23.9)	231 (34.4)	1,033 (25.6)	< 0.001
	Average	1,319 (39.3)	246 (36.6)	1,565 (38.8)	
	good	1,237 (36.8)	195 (29.0)	1,432 (35.5)	
Change of baseline					
Separated or divorced		124 (3.7)	39 (5.8)	163 (4.0)	0.02
Became unemployed		167 (5.0)	46 (6.9)	213 (5.3)	0.06
Smoking	Maintained	2,887 (86.1)	584 (87.3)	3,471 (86.3)	0.43
	Quit	468 (13.9)	85 (12.7)	553 (13.7)	
Worsened perceived health		1,548 (46.0)	259 (38.5)	1,807 (44.8)	< 0.001
Disease onset	Cardiovascular	676 (21.8)	142 (22.2)	818 (21.9)	0.85
	Cancer	39 (1.3)	33 (5.2)	72 (1.9)	< 0.001
	Other chronic disease	565 (18.2)	124 (19.4)	689 (18.4)	0.51
Disease treatment	Cardiovascular	209 (21.2)	59 (25.5)	268 (22.1)	0.18
	Cancer	9 (0.9)	9 (4.0)	18 (1.5)	0.002
	Other chronic disease	88 (12.2)	24 (17.3)	112 (13.0)	0.14

Table 3-6 shows the factors associated with quitting alcohol consumption. Model 1 analyzed the effect of baseline characteristics on quitting. Age and sex affected quitting, as women (OR: 3.95, 95% CI: 3.19, 4.91) and older people (OR: 1.7 in 50–59 years old; OR: 2.08 in 60–69 years old) were more likely to stop. Marital status, educational level, employment status, current smoking, and having a chronic disease did not significantly affect the likelihood of quitting. Participants with good perceived health were less likely to quit than were participants with poor perceived health ($p = 0.002$).

In model 2 that included the significant baseline characteristics and change in baseline characteristics, becoming single was not significant. Individuals losing a job (OR: 1.47, 95% CI: 1.01, 2.12) or quitting smoking (OR: 1.3, 95% CI: 0.99, 1.71) had greater odds of quitting drinking, while those with worsening perceived health (OR: 0.77, 95% CI: 0.63, 0.93) showed a divergent effect. Those with occurrence of cancer (OR: 3.9, 95% CI: 2.34, 6.46) had greater odds of quitting, though occurrence of CVD (OR: 0.88, 95% CI: 0.7, 1.1) and other chronic disease (OR: 1.05, 95% CI: 0.83, 1.33) were not statistically significant in that area.

Model 3 analyzed the effect of receiving treatment for a disease on quitting alcohol consumption. The likelihood of quitting was significantly higher in those receiving cancer treatment (OR: 3.48, 95% CI: 1.07, 10.63) than those with no disease treatment, though no significant effect was found for CVD (OR: 0.99, 95% CI: 0.61, 1.58) and those in the group for other chronic diseases (OR: 1.63, 95% CI: 0.93, 2.8) (Table 3-6).

Table 3-6. Logistic regression of analyses of quitting alcohol consumption

		Cessation of alcohol consumption					
		Model 1*		Model 2**		Model 3***	
		Exp(B) (CI)	p-value	Exp(B) (CI)	p-value	Exp(B) (CI)	p-value
Baseline character							
Sex (ref: male)		3.95 (3.19, 4.91)	<0.001	4.45 (3.67, 5.41)	<0.001	4.27 (2.78, 6.64)	<0.001
Age, years (ref: 40-49)	50-59	1.7 (1.36, 2.12)	<0.001	1.71 (1.37, 2.13)	<0.001	1.87 (1.17, 2.98)	<0.01
	60-69	2.08 (1.62, 2.68)	<0.001	2.0 (1.59, 2.53)	<0.001	1.26 (0.65, 2.35)	0.49
Marriage status (ref: single)		1.02 (0.74, 1.44)	0.89	-	-	-	
Education level (ref: low)		1.06 (0.86, 1.3)	0.58	-	-	-	
Employment status (ref: employed)		1.15 (0.91, 1.46)	0.24	-	-	-	
Current smoking		0.87 (0.7, 1.08)	0.19	-	-	-	
Having chronic disease		0.96 (0.8, 1.15)	0.64	1.02 (0.85, 1.23)	0.82	1.02 (0.68, 1.55)	0.92
Perceived health (ref: poor)	Average	0.81 (0.65, 1.0)	0.05	0.85 (0.68, 1.07)	0.17	0.78 (0.49, 1.24)	0.29
	Good	0.7 (0.55, 0.88)	0.002	0.79 (0.62, 1.02)	0.07	0.83 (0.48, 1.42)	0.49
Change from baseline							
Separated/ divorced/widowed		-		0.97 (0.63, 1.45)	0.89	0.84 (0.29, 2.11)	0.72
Became unemployed		-		1.47 (1.01, 2.12)	0.04	0.8 (0.26, 1.99)	0.65
Quit smoking (ref: maintained)		-		1.3 (0.99, 1.71)	0.056	0.89 (0.44, 1.7)	0.73
Worsened perceived health		-		0.77 (0.63, 0.93)	<0.01	0.38 (0.25, 0.57)	<0.001
Disease onset (ref: none)	Cardiovascular	-		0.88 (0.7, 1.1)	0.26	-	-
	Cancer	-		3.9 (2.34, 6.46)	<0.001	-	-
	Other chronic	-		1.05 (0.83, 1.33)	0.66	-	-
Disease	Cardiovascular	-			-	0.99 (0.61, 1.58)	0.97

treatment (ref: none)	Cancer	-			-	3.48 (1.07, 10.63)	0.03
	Other chronic	-			-	1.63 (0.93, 2.8)	0.08
Intercept		0.03 (0.01, 0.06)	<0.001	0.02 (0.02, 0.03)	<0.001	0.03 (0.01, 0.08)	<0.001
Pseudo R^2		0.1569		0.237		0.8185	
Akaike information criteria		3270.3		3072.2		688.29	

*Model 1 included only the baseline variables. **Model 2 included the change in variables and disease onset.

**Model 3 included the change in variables and disease treatment.

3.4.3 Comparing health status among abstainer, former, and current drinkers

Among 4,116 abstainers and 572 former drinkers at baseline, 3,139 (76.2%) and 270 (47.2%) remained non-drinkers during the follow-up period. Of 4,235 current drinkers, only 2,334 (55.1%) maintained their measured amount of alcohol consumption (e.g., mild drinkers maintained consumption of < 15 g/day). Therefore, based on the findings from our 10-year follow-up, 64.3% (70.4% of non-drinkers, 67.0% of mild drinkers, and 42.8% of moderate-to-heavy drinkers) maintained their measured alcohol consumption.

In comparison of health status, the 8,923 participants were categorized as abstainers, former drinkers, or current drinkers based on their drinking status at baseline and their alcohol consumption during the follow-up period. Among the 4,116 abstainers at baseline, 3,139 remained non-drinkers during the follow-up period, and were considered abstainers in this analysis. Among the abstainers and former drinkers at baseline, 411 (10.0%) and 66 (11.5%) were categorized as former drinkers because their alcohol consumption was zero at

the 8- and 10-year follow-ups after previously having been drinkers. In this analysis, 3,139 participants were abstainers, 1,470 were former drinkers, and 4,314 were drinkers (Table 3-7).

Table 3-7. Change in drinking status based on follow-up data

Drinking status at baseline	Change in drinking	N (%)	Drinking status at 8-10 years' follow up
Abstainer (n = 4,116)	Keeping non-drinking	3,139 (76.2%)	Abstainer
	Start drinking and quitting again	411 (10.0%)	Former drinker
	Start drinking	566 (13.8%)	Current drinker
Former drinker (n = 572)	Keeping non-drinking	270 (47.2%)	Former drinker
	Start drinking and quitting again	66 (11.5%)	Former drinker
	Start drinking	236 (41.3%)	Current drinker
Current drinker (n = 4,235)	Quit drinking	723 (17.0%)	Former drinker
	Keeping drinking	3,512 (83.0%)	Current drinker

The number of disease variables was lowest in current drinkers (0.52 in CVD, 0.029 in cancer, 0.66 in chronic disease, 1.21 in total). Although the number of CVD (0.59 former, 0.61 abstainer) and chronic disease (0.67 former, 0.68 abstainer) cases was lower in former drinkers than in abstainers, and the number of cancer cases was significantly higher in former drinkers (0.076 former, 0.047 abstainer). The difference in the number of disease variables between abstainers and former drinkers was not significant in any of CVD ($p = 0.74$), chronic disease ($p = 0.99$), or total disease ($p = 0.051$), with the exception of cancer ($p < 0.001$).

Individuals reporting good perceived health were most prevalent among current drinkers, while those reporting poor perceived health were most prevalent among abstainers. The difference in perceived health between abstainers and former drinkers was marginally significant ($p = 0.051$) (Table 3-8).

Table 3-8. Number of disease variables in abstainers, former drinkers, and current drinkers at 10-year follow-up

		Abstainer (n = 3,139)	Former (n = 1,470)	Current (n = 4,314)	p-value between groups	
Number of cardiovascular disease		0.61 ± 0.9	0.59 ± 0.89	0.52 ± 0.87	Abstainer-former Abstainer-current Former-current	0.74 < 0.001 0.035
Number of cancer		0.047 ± 0.23	0.076 ± 0.29	0.029 ± 0.18	Abstainer-former Abstainer-current Former-current	< 0.001 0.0012 < 0.001
Number of chronic disease		0.68 ± 0.92	0.67 ± 0.91	0.66 ± 0.91	Abstainer-former Abstainer-current Former-current	0.92 0.59 0.94
Number of total disease		1.33 ± 1.41	1.33 ± 1.38	1.21 ± 1.35	Abstainer-former Abstainer-current Former-current	0.99 < 0.001 0.01
Perceived health	Poor	1,148 (36.6)	496 (33.8)	972 (22.5)	Abstainer-former Abstainer-current Former-current	0.051 < 0.001 < 0.001
	Average	1,149 (36.6)	591 (40.2)	1,862 (43.2)		
	good	842 (26.8)	382 (26.0)	1,480 (34.3)		

3.5 Discussion

Previous studies have reported conflicting results about individuals' changes in alcohol consumption. While several studies have during follow-up found that consumption rates remained stable (Bacharach et al., 2004; Paavola et al., 2004; Perreira et al., 2001), others have shown decreases over time (Benzies et al., 2008; Jenkins et al., 2009; Moos et al., 2004). In the present study, the average amount of alcohol consumed among drinkers decreased by 0.18 g/day after 2 years. In previous studies, a correlation of 0.63 was found for alcohol consumption in each of 4 consecutive years (Benzies et al., 2008), and coefficients of 0.31–0.76 were reported during a 10-year period (Brennan et al., 2010). The present study found a correlation of 0.47–0.65 between every two measurements, and the 10-year correlation coefficient was 0.47.

Although overall alcohol consumption decreased over time in this study, the direction varied by the amount of consumption at baseline (increased among non-drinkers and mild drinkers, but decreased among moderate-to-heavy drinkers). Baseline consumption also affected the magnitude of change, as the 10-year differences were 1.56 g/day among non-drinkers and 11.82 g/day among moderate-to-heavy drinkers. Additionally, characteristics of participants were related to changes in consumption. Reduction of consumption for one period was higher in men, at 0.32 g/day on average compared with 0.04 g/day for women. These results indicate that studies of changes in alcohol consumption should account for the effects of baseline consumption and participants' characteristics.

The correlations of alcohol consumption with other variables at each measurement period did not greatly differ both for individuals who remained

in, or dropped out of, the study. The study demonstrated that disease treatment affected quitting drinking. Therefore, when people were lost to follow-up because of disease treatment or because they were dying from a disease, they may have changed their drinking behavior. Stability of alcohol consumption between participants followed-up for 10 years and the full sample, including those who dropped out, was not markedly different. This may have been because the prevalence of people who dropped out for disease treatment was low, or because these reasons for dropout were not detected over the long measurement interval.

Only 64.3% of the participants maintained their reported baseline level of alcohol consumption throughout the follow-up period. Even among lifetime abstainers at baseline, only 76.2% remained non-drinkers. Analyzing the effect of alcohol consumption based only on the amount of consumed alcohol at baseline may bias the risk of alcohol consumption. It is therefore important to properly define groups of drinkers based on follow-up data rather than one-time measurement, and to analyze the effect of alcohol consumption with due consideration of changes in consumption.

Previous studies have verified the assumption of a “sick quitter” effect in which people cease alcohol consumption because of their health problems. Although Brennan et al. reported that baseline health condition was not related to changes in drinking (Brennan et al., 2010), several studies have found that health status and disease at baseline were in fact associated with quitting (Perreira et al., 2001; Zins et al., 1999). Receiving a medical diagnosis during follow-up has also been associated with decreased alcohol consumption (Molander et al., 2010). The results of the present study indicate that disease onset significantly increased the likelihood of quitting, but the effect of this

factor varied according to disease type. Cancer significantly increased the likelihood of quitting, but CVD and other chronic diseases (e.g., diabetes or pulmonary disease) had no significant effect. One study showed that colorectal cancer survivors are more likely than a matched population group to be heavy drinkers (Hawkes et al., 2008), yet the present study showed that cancer onset and cancer treatment were positively associated with quitting alcohol consumption. Therefore, future studies of diseases' effects on health behavior need to consider the type of disease, rather than simply the presence of disease.

The present study did not show higher risk among former drinkers compared with lifetime abstainers. Several studies have investigated the purported high risk among former drinkers—another factor in the sick quitter effect. In a study comparing self-reported health among abstainers and former and current drinkers, health status was worst among former drinkers, followed by abstainers, and best among current drinkers (Liang et al., 2013). It was also reported that poor self-reported health was positively associated with being a former drinker (Chan et al., 2015), and former drinkers had the highest prevalence of poor health among abstainer, former, and current drinkers (Liang et al., 2013). However, Andrew et al. showed fair/poor perceived health status among former drinkers was more prevalent (58%) than that among moderate drinkers (55%), but lower than that among lifetime abstainers (83%) (Andrews-Chavez et al., 2015). Similarly, in the present study, prevalence of poor perceived health was greatest in abstainers, and the difference between abstainers and former drinkers was not significant. This study also showed that the number of disease variables was greater in abstainers than in former drinkers, which poses problems for any assumption that the health status of former drinkers is worse than that of abstainers. Need exists for further studies,

using objective indexes, to assess the health status of former drinkers and abstainers.

There are two limitations in the present study. First, self-efficacy and support factors were not considered in the analysis of factors associated with quitting alcohol consumption. Several studies have reported that motivation, self-control, and emotional support are important in quitting (Andrews-Chavez et al., 2015; Jung, 2012). The present study could not consider those factors in the analysis because the cohort data did not include them. Although the objective of this study was to assess the effect of health problems on cessation of alcohol consumption, the absence of consideration for motivational factors could be considered a limitation.

Second, identifying factors related to quitting alcohol consumption by assessing health data could cause measurement error because health is not a definitive reason by which people quit drinking. Although many previous studies have analyzed patients' characteristics or health status to investigate the factors affecting quitting alcohol consumption (J Choi, 2007; Perreira et al., 2001), further studies are needed that identify factors by surveying people about their reasons for quitting.

Chapter 4. The association of alcohol consumption with cardiovascular effects

4.1 Aims

This part of the study aimed to assess the relationship between alcohol consumption and risk of cardiovascular disease in a Korean cohort based on a different reference group to evaluate the sick quitter effect.

4.2 Methods

4.2.1 Study population

As in chapter 3, this part of the study used data from the Korean Genome and Epidemiology Study (KoGES), a community-based cohort study conducted by the Korean Centers for Disease Control and Prevention.

4.2.2 Baseline examination

As described in chapter 3, participants underwent health examinations every 2 years from baseline. Information on health behaviors, including alcohol consumption and medical histories of participants, was obtained at every assessment. Such health behaviors include alcohol consumption, smoking, exercise, stress, and dietary behavior.

4.2.3 Alcohol consumption

The frequency and the amount of alcohol consumed were assessed at baseline and in the follow-up period. Based on the amount of ethanol per day, the participants were classified as non-drinker (0 g/day), mild drinker (< 15 g/day), or moderate-to-heavy drinker (≥ 15 g/day).

4.2.4 Covariates

Throughout the analysis, sex and age (40s, 50s, and 60s) were adjusted. Participants were classified as current smokers or non-smokers (including ex-smokers). To assess health status, they were investigated for the presence of chronic diseases including hypertension, diabetes, and cancer. Perceived health was subdivided into bad, average, and good. Body mass index (BMI) was calculated as weight divided by the square of the height (kg/m^2), and participants were divided by a cutoff criterion of BMI > 25. Income was dichotomized as < or ≥ $1,500 (equivalent) per month (Table 4-1).

Table 4-1. Independent and dependent factors of study design

Category	Factor	Definition of Factor
Independent factor	Alcohol consumption amount per day	Non: 0 g/day Mild: < 15 g/day Moderate-to-heavy: ≥ 15 g/day
Covariate	Age	0: aged 40-49 at baseline 1: aged 50-59 at baseline 2: aged 60-69 at baseline
	Sex	0: male 1: female
	Marital status	0: not married/divorced/separated 1: married
	Income	0: less than 1,500,000 won/month 1: 1,500,000 won/month or more
	Educational level	0: middle school graduate or lower 1: high school graduate or higher
	Employment	0: employed 1: unemployed
	Having chronic disease	0: no 1: yes
	Current smoking	0: non-smoker 1: smoker
	Obesity (BMI)	0: not obese (BMI < 25) 1: obese (BMI ≥ 25)
	Physical activity	0: less than 3 times/week 1: 3 times/week or more
	Perceived Health	0: poor 1: average 2: good
Dependent factor	Myocardial infarction incidence	0: no 1: yes
	Coronary artery disease incidence	0: no 1: yes

4.2.5 Follow-up data collection

At every 2-year assessment, each participant was surveyed for whether these diseases had been diagnosed and when they occurred. In this study, CVD outcomes included myocardial infarction and coronary artery disease such as angina. The disease end point was the time at which the participant was diagnosed. Person-time of each participant was calculated from the data at baseline examination to disease end points or censoring. Information on alcohol use was also collected at every follow-up.

4.2.6 Statistical analysis

Cox proportional hazards regression models were adjusted for baseline sex, age, chronic disease, smoking, obesity, and perceived health. To identify the sick-quitter effect, risk of alcohol consumption on CVD was evaluated considering different types of reference group, including non-drinker and lifetime abstainer (Figure 4-1). All statistical analyses were conducted using R statistical software (version 3.1), and χ^2 tests were used for categorical variables to test for differences among alcohol consumption groups. A value of $p < 0.05$ was considered statistically significant.

$$\log h_i(t) = \alpha(t) + \beta_1\chi_{i1} + \beta_2\chi_{i2} + \ldots + \beta_k\chi_{ik}$$

In this prospective study, alcohol consumption was measured every 2 years over the span of 10 years. The amount of consumed alcohol may change over time, and a previous study showed that analysis using only baseline data on alcohol consumption and a confounder could lead to biasing of the risk of alcohol consumption on myocardial infarction (Ilomaki et al., 2012). In

addition, in chapter 3 of this study, the amount of consumed alcohol did not remain stable throughout the follow-up period. Therefore, a Cox proportional hazard model for time-dependent variable was also conducted to clarify whether the risk of alcohol consumption would be different using this analysis. Covariates also changed over time, and these changes were considered in this analysis.

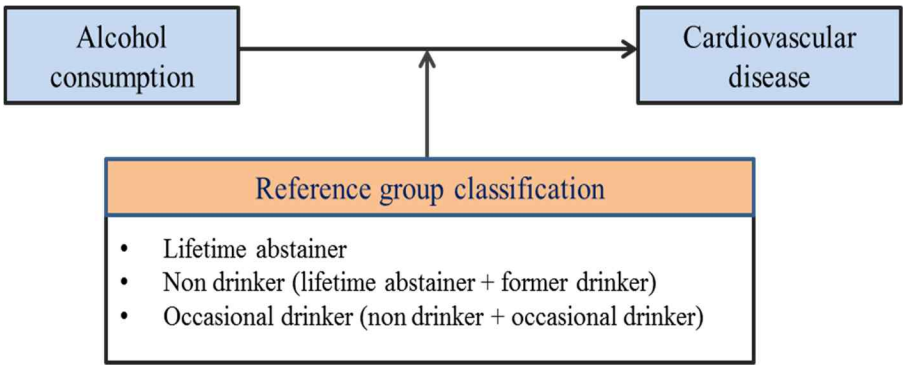


Figure 4-1. Frame of data analysis

4.3 Results

4.3.1 Demographic data

After excluding participants who had CVD at baseline, and participants without any follow-up data among people recruited for the cohort, only 8,330 participants were included in the analysis and 6,139 were ultimately followed-up for 10 years. The characteristics of participants at baseline and over 10

years of follow-up were compared to assess their comparability. Significant differences were only identified in income, education level, current smoking status, and perceived health (Supplement 3).

Table 4-2 presents baseline characteristics of the participants are presented in accordance with degree of alcohol consumption. During 10-year follow-up in 2001–2002, 236 participants reported having CVD events (myocardial infarction: 61, coronary artery disease: 180, both: 5). Older participants aged 60–69 were most prevalent in the non-drinker group (31.8%) compared with mild drinkers (20.2%) and moderate-to-heavy drinkers (21.2%). Men comprised only 27.4% of non-drinkers, but 94.2% of moderate-to-heavy drinkers. The percentage with low income (< $1,500 equivalent per month) was highest among the non-drinker group (59.4%), followed by mild drinkers (46.3%) and moderate-to-heavy drinkers (40.2%). Having a chronic disease was also highest among non-drinkers (47.4%), but the difference among drinker groups was not statistically significant. The percentage of smokers was lowest in non-drinkers (13.0%), followed by mild drinkers (29.0%) and moderate-to-heavy drinkers (55.7%). Among non-drinkers, the proportion of those assessing their health as bad was highest, at 39.5%, compared with the other drinker groups (25.3% in mild, 25.4% in moderate-to-heavy) (Table 4-2).

Table 4-2. Demographic characteristics of participants according to alcohol consumption

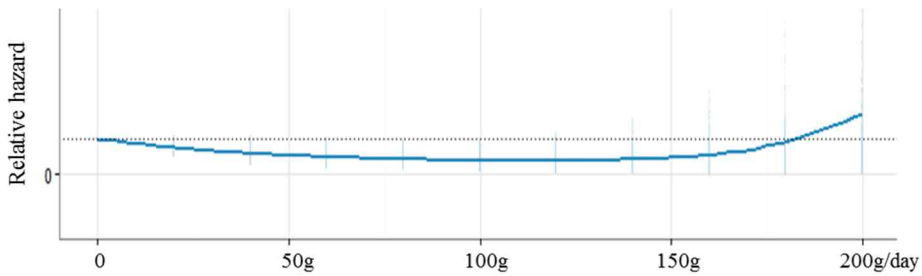
Characteristics		Alcohol consumption (n = 8,330)				p-value
		Non-drinker (n = 4,612)	Mild drinker (n = 2,192)	Moderate-to-heavy drinker (n = 1,526)	Total (n = 8,330)	
Age, years	40-49	1,855 (40.2)	1,166 (53.2)	855 (56.0)	3,876 (46.5)	< 0.001
	50-59	1,289 (27.9)	583 (26.6)	348 (22.8)	2,220 (26.7)	
	60-69	1,468 (31.8)	443 (20.2)	323 (21.2)	2,234 (26.8)	
Sex (male)		1,265 (27.4)	1,234 (56.3)	1,437 (94.2)	3,936 (47.3)	< 0.001
Marital status (married)		4,002 (87.6)	2,022 (92.5)	1,453 (95.4)	7,477 (90.3)	< 0.001
Low income (less than $1,500/month)		2,663 (59.4)	1,008 (46.3)	610 (40.2)	4,281 (52.4)	< 0.001
Low educational level		2,975 (65.4)	1,.077 (49.3)	657 (43.1)	4,709 (57.0)	< 0.001
Unemployed		476 (10.4)	343 (15.7)	291 (19.2)	1,110 (13.4)	< 0.001
Having chronic disease		2,185 (47.4)	988 (45.1)	680 (44.6)	3,853 (46.3)	0.069
Current smoking		587 (13.0)	632 (29.0)	849 (55.7)	2,068 (25.1)	< 0.001
Obesity		2,016 (43.7)	888 (40.5)	638 (41.9)	3,542 (42.5)	0.038
Physical activity		1,535 (34.7)	843 (39.0)	607 (40.3)	2,985 (36.9)	< 0.001
Perceived health	Bad	1,805 (39.5)	554 (25.3)	387 (25.4)	2,746 (33.8)	< 0.001
	Normal	1,534 (33.6)	886 (40.5)	568 (37.3)	2,988 (35.7)	
	Good	1,233 (27.0)	748 (34.2)	569 (37.3)	2,550 (30.5)	

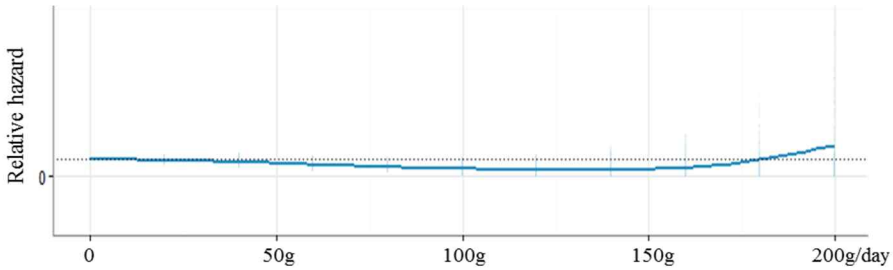
All values were described as number (percentage).

4.3.3 Cardiovascular disease

The hazard ratio (HR) of myocardial infarction was lower among drinkers, though not significant in the groups (0.62 in mild drinkers, 0.67 in moderate-to-heavy). In the model adjusted for age, sex, having a chronic disease, smoking, obesity, physical activity, and socioeconomic factors, the risk in mild drinkers (HR: 0.44, 95% CI: 0.21, 0.92) and moderate-to-heavy drinkers (HR: 0.42, 95% CI: 0.19, 0.93) was significantly lower than that for non-drinkers.

For the crude model of coronary artery disease, the risk was significantly lower among mild drinkers (HR: 0.57, 95% CI: 0.39, 0.84), and still remained significant in the adjusted model, with HR of 0.61 (95% CI: 0.4, 0.94). The risk in moderate-to-heavy drinkers (HR: 0.68, 95% CI: 0.41, 1.12) was not statistically significant (Table 4-3). Figure 4-2 details the relative hazards of alcohol consumption on CVD incidence. Although risk of alcohol was higher in heavy drinkers (more than 150 g/day), lower alcohol consumption showed lower risk compared with that in non-drinkers for myocardial infarction and coronary artery disease.





(A) Myocardial Infarction, (B) Coronary artery disease

Figure 4-2. Relative hazards of alcohol consumption on cardiovascular disease incidence

Table 4-3. Hazard ratio of cardiovascular disease by alcohol consumption categories

	Alcohol consumption		
	Non-drinker (n = 4,612)	Mild drinker (n = 2,192)	Moderate-to-heavy drinker (n = 1,526)
Myocardial Infarction			
Person-years of follow-up	39,833	19,383	13,324
Events	40	12	9
Crude model	1.00	0.62 (0.32,1.17)	0.67 (0.33, 1.39)
Multivariate-adjusted model [a]	1.00	0.44* (0.21, 0.92)	0.42* (0.19, 0.93)
Coronary artery disease			
Person-years of follow-up	39,519	19,310	13,236
Events	118	33	29
Crude model	1.00	0.57** (0.39, 0.84)	0.73 (0.49, 1.1)
Multivariate-adjusted model [a]	1.00	0.61* (0.4, 0.94)	0.68 (0.41, 1.12)

*: $p< 0.05$, **: $p< 0.01$. Values were described as hazard ratio (95% confidential incidence)

[a]: Sex, age, marriage status, educational level, employment, income, chronic disease, smoking, obesity, physical activity was adjusted in multivariate-adjusted model

4.3.4 Time-dependent analysis

The alcohol-related risk of CVD varied depending on the use of simple and time-dependent Cox proportional hazards models. For example, alcohol consumption protected against myocardial infarction when alcohol consumption was assumed to be constant, even in moderate-to-heavy drinkers.

However, when the analysis considered change in consumption, only mild consumption was associated with significant beneficial effects (2-year lag model, HR: 0.36, 95% CI: 0.14, 0.9; 4-year lag model, HR: 0.31, 95% CI: 0.1, 0.93; 6-year lag model, HR: 0.19, 95% CI: 0.04, 0.88) against myocardial infarction. Moreover, mild alcohol consumption provided protection against coronary heart disease with the simple Cox model, though this benefit disappeared with the time-dependent Cox model (2-year lag model, HR: 0.83, 95% CI: 0.52, 1.32; 4-year lag model, HR: 0.56, 95% CI: 0.31, 1.04; 6-year lag model, HR: 1.08, 95% CI: 0.57, 2.06; 8-year lag model, HR: 1.05, 95% CI: 0.4, 2.79) (Table 4-4). Supplement 4 shows the results of time-dependent analysis using covariates at baseline and at each measurement time (Supplement 4).

Table 4-4. Multivariate-adjusted hazard ratio for cardiovascular disease incidence by time-dependent analysis

		Alcohol consumption					
		Myocardial Infarction			Coronary artery disease		
		Non-drinker	Mild drinker	Moderate-to-heavy drinker	Non-drinker	Mild drinker	Moderate-to-heavy drinker
Simple Cox		1.00	0.44* (0.21, 0.92)	0.42* (0.19, 0.93)	1.00	0.61* (0.4, 0.94)	0.68 (0.41, 1.12)
Time-dependent Analysis	0y lag	1.00	0.47 (0.22, 1.04)	0.69 (0.32, 1.47)	1.00	0.78 (0.52, 1.16)	0.75 (0.45, 1.24)
	2y lag	1.00	0.36* (0.14, 0.9)	0.58 (0.24, 1.38)	1.00	0.83 (0.52, 1.32)	0.89 (0.52, 1.52)
	4y lag	1.00	0.31* (0.1, 0.93)	0.53 (0.2, 1.43)	1.00	0.56 (0.31, 1.04)	0.77 (0.4, 1.48)
	6y lag	1.00	0.19* (0.04, 0.88)	0.39 (0.12, 1.24)	1.00	1.08 (0.57, 2.06)	1.25 (0.6, 2.61)
	8y lag	1.00	0.36 (0.07, 1.85)	0.31 (0.06, 1.69)	1.00	1.05 (0.4, 2.79)	0.56 (0.14, 2.27)

*: $p < 0.05$. Values were described as hazard ratio (95% confidential incidence)

[a]: Sex, age, marriage status, educational level, employment, income, chronic disease, smoking, obesity, physical activity was adjusted

4.3.5 Reference classification

Three models were used to assess whether the risk of CVD would differ based on reference group classification. As shown in Table 4-5, the risk of myocardial infarction among drinker groups was significant whether the reference group was non-drinkers (HR: 0.5 in mild, 0.38 in moderate-to-heavy) or lifetime abstainers (HR: 0.45 in mild, 0.34 in moderate-to-heavy). For coronary artery disease incidence, in a model using non-drinkers as the reference group, mild drinkers showed a significantly lower risk, at 0.59. When the reference group was lifetime abstainers, the risk of coronary artery disease in mild drinkers was still significant, at 0.57. Furthermore, in the model including only lifetime abstainers as the reference group, the risk of myocardial infarction (HR: 0.5) and coronary artery disease (HR: 0.59) was lower than that in the model including non-drinkers (0.45 in myocardial infarction, 0.57 in coronary artery disease). The risk in former drinkers was lower than that among lifetime abstainers, with HR of 0.72 (95% CI: 0.29, 1.8) for myocardial infarction and 0.86 (95% CI: 0.47, 1.55) for coronary artery disease.

When occasional drinkers were included with non-drinkers in the reference group, the beneficial effect of mild alcohol consumption was not statistically significant. Although the risk of mild alcohol consumption was still lower than that in the reference group, it was not significant for either myocardial infarction (HR: 0.65, 95% CI: 0.29, 1.45) or coronary artery disease. (HR: 0.51, 95% CI: 0.23, 1.12) (Table 4-5).

Sociodemographic characteristics were compared among non-drinkers, occasional drinkers, and non-occasional drinkers to assess whether occasional

drinkers could be an appropriate reference group. In this analysis, occasional drinkers were often positioned between the other two groups. For example, the prevalence of low income or low educational level among occasional drinkers was higher than that among non-occasional drinkers and lower than that among non-drinkers (Table 4-6).

Table 4-5. Multivariate-adjusted hazard ratio for cardiovascular disease incidence by reference group classification

Reference group	Alcohol consumption							
	Myocardial Infarction				Coronary artery disease			
	Ref	Former drinker [a] (n = 713)	Mild drinker (n = 2,192)	Moderate-to-heavy drinker (n = 1,526)	Ref	Former drinker (n = 713)	Mild drinker (n = 2,192)	Moderate-to-heavy drinker (n = 1,526)
Non-drinker (n = 4,612)	1.0	-	0.44* (0.21, 0.92)	0.42* (0.19, 0.93)	1.0	-	0.61* (0.4, 0.94)	0.68 (0.41, 1.12)
Lifetime abstainer (n = 3,824)	1.0	0.84 (0.35, 1.98)	0.41* (0.19, 0.9)	0.39* (0.16, 0.91)	1.0	0.97 (0.56, 1.71)	0.61* (0.39, 0.95)	0.67 (0.39, 1.14)
Occasional drinker (n = 5,512)	1.0	-	0.65 (0.29, 1.45)	0.51 (0.23, 1.12)	1.0	-	0.71 (0.42, 1.19)	0.75 (0.46, 1.23)

*: $p < 0.05$. Values were described as hazard ratio (95% confidential incidence).

Sex, age, marriage status, educational level, employment, income, chronic disease, smoking, obesity, physical activity was adjusted.

[a] Among 4,612 non-drinker, 3,824 was lifetime abstainer, 531 was former drinker, 182 was current drinker, and 75 had no data about drink history. Total 713 including 531 former drinkers and 182 current drinkers was considered as former drinker in this analysis.

Table 4-6. Comparison of sociodemographic characteristics among non-drinkers, occasional drinkers, and non-occasional drinkers

Characteristics		Alcohol consumption (n = 8,330)			p-value
		[A] Non-drinkers (n = 4,612)	[B] Occasional drinkers (n = 900)	[C] Non-occasional drinkers (n = 2,818)	
Age, years	40-49	1,855 (40.2)	447 (49.7)	1,574 (55.9)	A-B: < 0.001 B-C: < 0.001
	50-59	1,289 (28.0)	265 (29.4)	666 (23.6)	
	60-69	1,468 (31.8)	188 (20.9)	578 (20.5)	
Sex (male)		1,265 (27.4)	300 (33.3)	2,371 (84.1)	A-B: < 0.001 B-C: < 0.001
Marital status (married)		4,002 (87.6)	815 (90.8)	2,660 (94.6)	A-B: 0.009 B-C: < 0.001
Low income (less than $1,500/month)		2,663 (59.4)	447 (50.0)	1,171 (41.9)	A-B: < 0.001 B-C: < 0.001
Low educational level		2,975 (65.4)	500 (55.7)	1,234 (43.9)	A-B: < 0.001 B-C: < 0.001
Unemployed		476 (10.4)	120 (13.4)	514 (18.3)	A-B: 0.01 B-C: < 0.001
Having chronic disease		2,185 (47.4)	413 (45.9)	1,255 (44.5)	A-B: 0.43 B-C: 0.50
Current smoking		587 (13.0)	155 (17.3)	1,326 (47.2)	A-B: < 0.001 B-C: < 0.001
Obesity		2,016 (43.7)	392 (43.6)	1,134 (40.3)	A-B: 0.96 B-C: 0.09
Physical activity		1,535 (34.7)	360 (40.4)	1,090 (39.3)	A-B: 0.001 B-C: 0.58
Perceived health	Poor	1,805 (39.5)	264 (29.3)	677 (24.1)	A-B: < 0.001 B-C: 0.001
	Average	1,534 (33.5)	355 (39.4)	1,099 (39.1)	
	Good	1,233 (27.0)	281 (31.2)	1,036 (36.8)	

Group A, non-drinkers; Group B, occasional drinkers; Group C, non-occasional drinkers. The p-value of A–B represented the difference between non-drinkers and occasional drinkers, and that of B–C represented the difference between occasional drinkers and non-occasional drinkers.

4.4 Discussion

The present study could not find prevalence of higher risks among former drinkers when compared with lifetime abstainers. The protective effect of alcohol consumption remained in two models: including former drinkers as abstainers and excluding former drinkers from abstainers. In view of this result, the sick quitter effect might not cause the beneficial effect of mild drinking on CVD. However, the beneficial effect of mild consumption disappeared when occasional drinkers were included in the reference group.

A recent study that used occasional drinkers as a reference group reported no benefits from moderate alcohol consumption (Rostron, 2012), and in a study by Zeisser et al. (Zeisser et al., 2014), classifying occasional drinkers as abstainers shifted the risk of alcohol consumption downward. Another meta-analysis reported that occasional drinkers had lower risk than abstainers (Stockwell et al., 2016); the present study showed similar results.

The lower risks of occasional drinkers compared with lifetime abstainers may owe to three factors apart from the benefit of alcohol found in occasional drinking. The first may be the poor health status of lifetime abstainers. Ng Fat et al. showed that lifetime abstainers have poorer health than drinkers, even before starting drinking (Ng Fat et al., 2012). They also reported that using lifetime abstainers as a reference group may overestimate the benefit of moderate alcohol consumption. This is because people with long-standing illness were found more likely to remain non-drinkers throughout adulthood (Ng Fat et al., 2014). The second factor is unresolved confounding. UK governmental guidelines asserted that the people who can afford to drink at older ages might have better health status than those who cannot (UK

Department of Health, 2016). Even though the present study included various covariates—such as marriage status, income, employment, and education level — to avert this problem, there is a possibility that the benefits of occasional drinking owe to resolved confounding. The third possible contributing factor is the benefits of a social network. In Korea, drinking alcohol is often accompanied by social activity (Joo, 2009; Kim et al., 2015a; Shim et al., 2009), and social networks have been considered as modifying variables for the relationship between alcohol consumption and its consequences (Rehm et al., 1996). Several studies have reported that occasional drinking with friends can be socially beneficial (Odegaard et al., 2015) and have positive effect on stress reduction and social integration (Tsugane, 2012). Thus, social activity accompanied by alcohol consumption may be a protective factor against the risk of CVD.

Although many studies have assessed the effects of alcohol by using lifetime abstainers as the reference group, occasional drinkers would be a more appropriate reference group for a number of reasons.

First, the validity of lifetime abstainers might not be high. One study that investigated the stability and validity of lifetime abstention reported that use of lifetime abstainers as a sole comparison group could cause problems, especially when based on a one-time measurement (Liu et al., 2010). Another study reported that consistency of drinking status in test-retest analysis was only 74.4% for lifetime abstainers, but 94.7% for current drinkers (Greenfield et al., 2014). In the present study, only 76.2% of lifetime abstainers continued to abstain over the 10-year period.

Second, occasional drinkers have characteristics comparable with those of drinkers. Previous studies have shown that occasional drinking would be

more normative and might be not enough to yield biological health benefits (Stockwell et al., 2016). Rostron et al. found that, among infrequent drinkers who consumed < 12 units in a single year as a reference group (this population had lower mortality than never drinkers), the differences seen did not owe to alcohol consumption but rather to other unobserved differences (Rostron, 2012). Another study reported that occasional drinkers have personal and lifestyle characteristics similar to those of low-volume drinkers (Knott et al., 2015). In the present study, occasional drinkers showed intermediate characteristics between non-drinkers and drinkers. Therefore, using occasional drinkers as the reference group could decrease bias and the effects of confounders.

Although alcohol consumption showed a protective effect against myocardial infarction and coronary heart disease when considering only the baseline alcohol consumption, it was significant only for myocardial infarction and not for coronary heart disease when it was analyzed with consideration of change in alcohol consumption. The amount of consumed alcohol at baseline was not stable; therefore, assessing the effect of alcohol without considering the amount of change over time may cause bias. Further studies on the risk of alcohol consumption must therefore measure consumption repeatedly over time and consider change in consumption in performing data analyses.

The drinker group in this study was initially divided into four subgroups: non-drinkers, and mild, moderate, and heavy drinkers. This was for the purpose of more specifically investigating the effect of alcohol consumption. However, the number of cardiovascular events was low in the heavy drinker group, and statistical power was as low as 15%. When summing moderate and heavy drinkers, power elevated to 50%. This value was still low; however,

when comparing non-drinkers and mild drinkers, group power was 82%. This study was meaningful because it showed the effect of mild alcohol consumption.

Various factors could affect the association between alcohol consumption and mortality. The World Health Organization suggested that alcohol-related harm was decided by three factors: volume of alcohol consumed, pattern of drinking, and quality of alcohol consumed (WHO, 2014). Alcohol-related risk showed a dose–response relationship, and the risk increased when alcohol was consumed without food. Additionally, the cardioprotective effect disappeared in heavy episodic drinking. Unrecorded alcohol, including homemade or illegal alcohol, could trigger problems such as methanol poisoning. The US National Institute of Alcohol Abuse and Alcoholism has also reported age, sex, race, taking food with alcohol, speed of alcohol consumption, drug use, and family history as factors affecting risk associated with alcohol consumption (NIAAA, 2004).

Biological factors, such as age and sex, could affect the alcohol-related risk of mortality. Arndt et al. found that a J-/U-shaped association was limited to men > 35 years old, and that 25–34-year-old men exhibited a positive dose–response relationship (Arndt et al., 2004). Other studies found that the beneficial effect may be limited to men aged 50–64 years old, and women ≥ 65 years old (Knott et al., 2015), and that the dose of alcohol that provided protective effects was lower among women (Di Castelnuovo et al., 2006). Rehm et al. reported a significant J-shaped association of drinking and mortality among male drinkers, though the differences between the drinking categories were much smaller for women (Rehm et al., 2001). WHO reported that women reach a higher blood alcohol concentration than men when

consuming the same amount, which is attributed to lower body weight, smaller liver capacity for metabolizing alcohol, and a higher proportion of body fat (WHO, 2014). Studies assessing the effects of alcohol consumption should also consider factors affecting the associated risk of CVD.

The effects of alcohol consumption can also differ based on the type of outcome measured. Rehm et al. reported that the effects were stronger on mortality than morbidity for several disease and injury categories (Rehm et al., 2010). Another study assessing risk among former drinkers found increased risk for the group compared with abstainers for ischemic heart disease mortality, but a non-significant risk for morbidity (Roerecke et al., 2010). Further studies evaluating the effects of alcohol consumption should carefully consider the specific outcomes and measures to be used.

Comparison of risk of alcohol consumption for CVD and cancer

The present study showed no protective effect of mild alcohol consumption for cancer, including liver cancer, lung cancer, stomach cancer, colon cancer, pancreatic cancer, breast cancer, and uterine cancer. Cancer events numbered 106 in non-drinkers, 58 in mild drinkers, and 37 in moderate-to-heavy drinkers. In the adjusted model, the cancer risk of the drinker group was higher than that of the non-drinker group, although the difference was not statistically significant (HR: 1.3, 95% CI: 0.91, 1.85 in mild drinkers, HR: 1.19, 95% CI: 0.75, 1.91 in moderate-to-heavy drinkers). Because WHO has reported a causal link between alcohol and cancer, but showed complex effects in CVD (WHO, 2014), the effects of alcohol consumption may differ by disease type.

One study reported that alcohol increased high-density lipoprotein levels, reduced low-density lipoprotein susceptibility, and increased omega-3 fatty

acids. Therefore, moderate alcohol consumption was found associated with antiatherogenic and antithrombotic properties (Di Castelnuovo et al., 2010). An understanding of the mechanism of alcohol in CVD and cancer is needed to determine the reason alcohol showed different effects on these diseases. Further studies assessing the effect of alcohol consumption on intermediate cardiovascular end points, such as hypertension or diabetes, and various factors related to cancer, would advance this understanding.

Chapter 5. Public health implications

5.1 Importance of this study

Unlike many other risk factors for disease, alcohol consumption has been associated with both harmful and protective effects. Mild alcohol consumption has been found to have beneficial effects against CVD, though previous studies have reported the effects may differ depending on factors such as race. The first implication of the present study was that it verified the effect of mild alcohol consumption among Koreans. Although previous studies have reported that the effect of alcohol consumption differed by race because of genetic factors or drinking patterns, an insufficient number of studies have assessed the effects of consumption among Korean populations. Not only the result of the meta-analysis, but also findings from cohort data in this study could provide evidence to inform alcohol consumption guidelines and policies for Korean populations.

The second implication of this study was that it showed the importance of the reference group when assessing the effects of alcohol consumption. Several studies asserted that the benefits of mild alcohol consumption were due to former drinker bias, though these results have been disputed. The present study evaluated the effects of former drinker status on alcohol-related risk of mortality, and found that the benefit of mild alcohol consumption was unrelated to the sick quitter effect. However, when compared with occasional drinking, no benefit of alcohol consumption was found. The beneficial effects of mild alcohol consumption may differ based on whether occasional drinkers

are included in the reference group. Therefore, this study provides insight into consideration of an appropriate reference group of alcohol drinkers.

Third, this study also verified the possibility that the beneficial effects of mild alcohol consumption may be partially attributable to measurement bias owing to the failure to consider changes in alcohol consumption; participants' drinking status and amounts consumed at baseline changed over time. Although mild alcohol consumption was beneficial when considering only baseline consumption, it was only partially significant after considering the change. Therefore, this study illustrates the importance of considering this change over time when analyzing the effects of alcohol consumption.

Fourth, this study showed the importance of repeated, ongoing measurement of alcohol consumption. The study investigated the change in consumption over time and revealed that it was affected by baseline consumption and participants' characteristics. Many prospective studies assessing alcohol consumption have assumed that consumption at baseline was consistent during follow-up. This study, however, showed differing change and variation according to the participant. In addition, the study indicates that appropriate classification of people as abstainers or former or current drinkers requires repeated measurement. Even abstainers or former drinkers changed their drinking status during the study period; therefore, further studies of consumption, and policy for it, need to evaluate it in periods and consider the participants' characteristics.

Last, this study did not support the previously described higher risk of CVD among former drinkers compared with non-drinkers. Although disease onset or treatment significantly affected whether participants stopped drinking, the impact differed by disease type. This study also compared health status

between abstainers and former drinkers to evaluate the assumption of former drinker bias. Objective and subjective health statuses did not differ the two groups, but cancer prevalence differed significantly. Although the effects of being a former drinker were not found to be significant in this study, they could be significant among a population with a higher prevalence of cancer.

5.2 Limitations

Credibility of assessment of alcohol consumption has been pointed out as a limitation of studies on alcohol's effects. Rehm et al. noted that such assessment and its outcomes present methodological problems in studies on alcohol-related health risks (Rehm et al., 2003). Another study showed that the quantity of alcohol consumed differed according to the assessment methods, especially in harm drinking (Clemens et al., 2008; Rehm et al., 1999). Self-reported drinking has been used in numerous studies, despite it presenting the possibility of heavy drinkers underestimating consumption (Northcote et al., 2011). More objective methods need to be developed to assess amounts of alcohol consumed.

In analyses of the effect of health problems on changes in alcohol consumption, disease onset and treatment were included as objective indexes of health problems. However, apart from treatment, the severity of the disease could also be related to such changes. For example, Perreira et al. reported that hospitalizations were associated with reduced drinking (Perreira et al., 2001). To understand the relationship between health problems and alcohol consumption, further studies should consider not only disease onset and

treatment, but also severity of disease, such as disease stage or hospitalization.

Objective assessment of CVD incidence is also needed. In this study, myocardial infarction and other coronary artery diseases were assessed via interview, which including asking participants whether they had been diagnosed in a hospital. CVD incidence was analyzed to test the validity of these data. The prevalence of myocardial infarction and coronary artery disease were 0.7% and 2.9% in this study, respectively. These figures are similar to the findings of a 2010 nationwide study in Korea that indicated prevalence rates of 0.7% and 2.3%–2.8%, respectively (MOHW & KCDC et al., 2011). The incidence of myocardial infarction was higher among participants with coronary heart disease (2.8%) than among those without (0.7%) ($p = 0.005$). The prevalence of risk factors, including smoking, family history of CVD, and obesity, was higher among people with CVD than those without (Supplement 5). These findings may confirm the validity of outcome assessment within this study, but further studies that include medical record review are needed to more objectively assess disease incidence.

5.3 Conclusion

The meta-analysis of Korean studies did not identify beneficial effects of mild alcohol consumption against mortality, but our cohort analysis revealed that mild alcohol consumption protects against myocardial infarction as compared with nondrinking. Using only baseline alcohol consumption, the benefits of mild alcohol consumption were found to be significant both in patients with myocardial infarction and those with coronary artery disease.

However, the reported alcohol consumption at baseline changed throughout the follow-up period, and only 64.3% of participants maintained their assigned drinking status. When considering the change in consumption, the effect of mild consumption was significant only for myocardial infarction and not for coronary artery disease.

Although the risk associated with mild alcohol consumption was significantly lower than that associated with nondrinking, this benefit was not statistically significant when compared with that of occasional drinking. Because occasional drinkers had more socioeconomic characteristics in common with drinkers than with non-drinkers, inclusion of occasional drinkers in the reference group would be more appropriate. This study showed no benefit associated with mild alcohol consumption compared with occasional drinking of < 2.5 g/day.

Furthermore, the study did not detect a significant sick quitter effect because the alcohol-related risk of mortality did not change significantly when lifetime abstainers or non-drinkers, including former drinkers, were used as the reference group. The health statuses of former drinkers and abstainers did not significantly differ in terms of the number of perceived health or disease variables, with the exception of cancer.

Further studies assessing the effect of alcohol consumption must consider the reference group classification, as the effects of consumption vary depending on this classification. Future studies must also repeatedly measure participants' consumption to detect changes in the consumption over time, and should consider these changes in the data analysis.

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Supplement 1. Changes in alcohol consumption from baseline at every 2 years among participants followed up for 10 years in each group (n = 6,219)

	Mean alcohol consumption			
	Non-drinker (n = 3,417)	Mild drinker (n = 1,691)	Moderate-to-heavy drinker (n = 1,111)	Total (n = 6,219)
Baseline	0 ± 0	4.73 ± 4.04	41.41 ± 30.73	8.68 ± 20.25
Change after 2 years	1.8 ± 13.37	4.48 ± 13.09	-4.4 ± 34.69	1.43 ± 19.16
Change after 4 years later	1.59 ± 8.57	4.05 ± 14.81	-7.31 ± 36.67	0.7 ± 18.76
Change after 6 years later	1.49 ± 8.01	3.71 ± 14.87	-7.56 ± 39.01	0.45 ± 19.59
Change after 8 years later	1.53 ± 8.32	3.13 ± 17.38	-9.57 ± 40.99	-0.01 ± 20.98
Change after 10 years later	1.56 ± 16.18	3.37 ± 15.75	-11.82 ± 37.77	-0.34 ± 22.25

Values were described as mean ± standard deviation.

Supplement 2. Correlations between alcohol consumption at each measurement among participants followed up for 10 years (n = 6,219)

Variables	Baseline	2 years	4 years	6 years	8 years	10 years
Baseline	-					
2 years	0.59**	-				
4 years	0.59**	0.6**	-			
6 years	0.55**	0.59**	0.64**	-		
8 years	0.51**	0.54**	0.60**	0.63**	-	
10 years	0.47**	0.44**	0.48**	0.52**	0.54**	-

**: $p < 0.01$

Supplement 3. Demographic characteristics of participants at baseline and at 10 years of follow-up

Characteristics		Participants		p-value
		Baseline (n = 8,330)	10 years' follow-up (n = 6,139)	
Sex (male)		3,936 (47.3)	2,842 (46.3)	0.261
Marital status (married)		7,477 (90.3)	5,552 (90.9)	0.262
Low income (less than $1,500/month)		4,281 (52.4)	2,995 (49.7)	0.002
Low educational level		4,709 (57.0)	3,338 (54.7)	0.008
Unemployed		1,110 (13.4)	812 (13.3)	0.842
Having chronic disease		3,853 (46.3)	2,784 (45.3)	0.287
Current smoking		2,068 (25.1)	1,401 (23.1)	0.005
Obesity		3,542 (42.5)	2,648 (51.6)	0.471
Physical activity		2,985 (36.9)	2,254 (37.7)	0.339
Perceived health	Bad	2,746 (33.1)	1,900 (31.1)	0.033
	Normal	2,988 (36.1)	2,282 (37.3)	
	Good	2,550 (30.8)	1,928 (31.6)	

All values were described as number (percentage).

Supplement 4. Risk of mild alcohol consumption on CVD using time-dependent analysis

		Myocardial Infarction			Coronary artery disease		
		Changed covariates	Changed covariates and lagged smoking	Changed covariates and baseline smoking	Changed covariates	Changed covariates and lagged smoking	Changed covariates and baseline smoking
Time-dependent effect of mild alcohol consumption	0y lag	0.47 (0.22, 1.04)	-		0.78 (0.52, 1.16)	-	
	2y lag	0.35* (0.14, 0.88)	0.36* (0.14, 0.9)	0.35* (0.14, 0.88)	0.84 (0.53, 1.34)	0.83 (0.52, 1.32)	0.83 (0.52, 1.33)
	4y lag	0.3* (0.1, 0.9)	0.31* (0.1, 0.93)	0.3* (0.1, 0.91)	0.58 (0.31, 1.05)	0.56 (0.31, 1.04)	0.57 (0.31, 1.04)
	6y lag	0.2* (0.04, 0.9)	0.19* (0.04, 0.88)	0.19* (0.04, 0.87)	1.08 (0.57, 2.06)	1.08 (0.57, 2.06)	1.08 (0.57, 2.06)
	8y lag	0.37 (0.07, 1.93)	0.36 (0.07, 1.85)	0.36 (0.07, 1.85)	1.05 (0.4, 2.79)	1.05 (0.4, 2.79)	1.05 (0.4, 2.79)

*: $p < 0.05$

Supplement 5. Prevalence of risk factors among participants according to CVD incidence

Characteristics	Myocardial infarction			Coronary artery disease		
	Not having (n = 8,269)	Having (n = 61)	p-value	Not having (n = 8,150)	Having (n = 180)	p-value
Hypertension	1,239 (15.0)	18 (29.5)	0.003	1,208 (14.8)	49 (27.2)	< 0.001
Diabetes	539 (6.5)	9 (14.8)	0.02	523 (6.4)	25 (13.9)	< 0.001
Smoking	2,044 (25.0)	24 (39.3)	0.015	2,013 (25.0)	55 (31.1)	0.08
Obesity	3,505 (42.4)	37 (60.7)	0.006	3,462 (42.5)	80 (44.4)	0.66
Family history of CVD	1,228 (14.9)	4 (6.6)	0.101	1,206 (14.8)	26 (14.4)	0.97

All values were described as number (percentage)