의학석사 학위논문

한국인 사망과 관련된 건강 행태요인의 복합위험도에 관한 코호트 연구

Combined Life-style Factors and All-causes and Cancer-specific Mortality in Korea - The Korean Multi-center Cancer Cohort Study -

2013 년 2 월

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이 논문을 의학석사 학위논문으로 제출함

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정은주의 의학석사 학위논문을 인준함

2013년 2월

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ABSTRACT

Objectives

Lifestyle factors such as obesity, smoking habit and alcohol drinking habit are known to be associated with increased risk of all-cause mortality in Korea. However, little has examined the association of combined life-style factors with the risk of mortality.

Methods

The study population of 15,740 participants over 20 years old was selected from the Korean Multi-center Cancer Cohort (KMCC) study. Information on lifestyle factors was obtained through structured questionnaire interview. The total number of persons who completed the follow-up through the Death Certificate database of the National Statistical Office was 145,218.4 person-years by the end of December 31, 2008. The total number of death during the study period was 1,094 persons, and 474 deaths were due to cancer and 229 persons were due to cardio-vascular diseases. Each risk factor was dichotomized based on the previous study as follows; body mass index (BMI) under 22.6 or over 27.5 kg/m^2 versus 22.6~27.5 kg/$m^{2;}$; current or past smokers

versus non-smokers; non-drinkers or drinkers with alcohol amount of 90 gram per week or more versus drinkers less than 90 grams per week. Combined effect of three risk factors was estimated in two different ways; according to the number of risk factors qualitatively, and to the combined risk scores ranged from 0 to 14 quantitatively. The hazard ratios (HRs) and 95% confidence intervals (CI) for mortality were estimated by Cox's proportional hazard regression model adjusting for age, sex, locality, education, marriage, and the past history of chronic diseases.

Results

The risk of dying was 1.47 times (95% CI = 1.27~1.69) in BMI, 1.50 times (95% CI=1.25~1.79) in smoking habit, and 1.36 times (95% CI=1.08~1.72) higher in alcohol drinking habit than the baseline hazard. The HRs for cancer death was 1.35 (95% CI=1.10~1.66) in BMI, and 1.75 (95% CI=1.32~2.33) in smoking habit, but not statistically significant in alcohol drinking habit.

The HRs for both all-causes mortality and cancer mortality showed linearly increasing pattern with statistical significant according to the number of risk factor ($p<0.001$). Overall, the combined effect of

lifestyle factors was more prominent in female. Particularly noteworthy was that the risk of dying increases according to the combined risk score increasing ($p<0.001$). Subjects with highest score (10~14) had significantly at the greatest risk of deaths (HR=3.46, 95% CI=1.89-6.32). The risk of dying was more prominent in female and participants under age<60.

Conclusions

This study confirms abnormal BMI, smoking habit and alcohol drinking habit are major risk factor of premature deaths, as well as cancer death in Korea. Combined effect of lifestyle factors would additively be associated with marked increased risks of both all-causes and cancer-specific death in Korea.

Keywords: risk factor, risk score, premature death, cancer death, combined health effect, cohort study, KMCC study, Korean

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LIST OF ABBREVIATIONS

BMI: Body Mass Index

KMCC: Korean Multi-center Cancer Cohort

ICD: International Classification of Diseases

CVD: CardioVascular Disease

CVA: CerebroVascular Attack

COPD: Chronic Obstructive Pulmonary Disease

INTRODUCTION

Recent publication on "Global Status Report on non-communicable diseases(NCDs)" by WHO(World Health Organization), indicates that the NCDs are the leading causes of death all around the world, killing more people than all other causes combined. Of the 57 million global deaths, 36 million were due to NCDs, and shows cancers are responsible for 27% of all NCD deaths under the age of 70 in 2008 [1]. Contrary to the general belief that the NCDs afflict mostly high-income populations, however, the evidence tells nearly 80% of NCD deaths occur in low- and middle-income countries. Asia occupies 2/3 of world population, and of the 12 million global new cancer cases, almost half of them occur in Asia in 2008. Cancer has become a leading cause of deaths in many Asian countries.

Risk of NCDs including cancer is well known to be closely related with many lifestyle factors, i.e., smoking, obesity, diet, alcohol drinking, physical exercise, and sleep patterns [1]. Lifestyle factors such as alcohol drinking [2], cigarette smoking [3] were associated with an

increased risk of all-cause mortality in the Korean Multi-center Cancer Cohort (KMCC) study. A lot of evidence indicates that lifestyle factors such as relative weight [4-6] are also associated with an increased risk of premature mortality, cardiovascular disease (CVD), and cancer.

Most of the studies published so far demonstrated independent effect of a risk factor with adjustment for other covariates with the statistical model. Since lifestyle factors are highly correlated with each other, however, each factor should thus be regarded as one component of the risk factors, not just as a covariate which needs statistical adjustment in a multivariate manner. Assessment of the combined effect of several lifestyle factors could emphasize the predictive value of individual probability being diagnosed as having a disease or mortality in terms of public health significance and primary prevention as well.

A recent prospective cohort study of 71,243 women aged 40 to 70 years of the Shanghai Women's Health Study (SWHS) found a 43% reduction in risk of all-cause mortality who reported normal weight, lower waist-hip ratio, daily exercise, never exposed to spouse's

smoking, higher daily fruit and vegetable intake, compared to women with none of these risk factors [7]. Another prospective cohort study among 4,886 individuals at least 18 years old from a United Kingdom reported a 3.5-fold increase in risk of all-cause mortality for participants with 4 poor health lifestyle factors compared with those with no poor health lifestyle factors (nonsmoker, fruits and vegetables consumed more than 3 times daily, more than 2 hours physical activity per week, and weekly consumption of less than 14 units of alcohol (in women) and more than 21 units (in men)) [8]. A cohort study among 20,244 British men and women aged 45-79 years similarly reported a 4-fold increase in risk of all-cause mortality for participants with no lifestyle factors compared to participants who had four health lifestyle factors (nonsmoker, plasma vitamin C levels indicative of ≥5 daily serving of fruits and vegetables, moderate alcohol intake, and physically active) [9]. Of the lifestyle factors-mortality studies, however, 1 study sampled only aged 40- to 70-year-old female residents of urban counties in Shanghai, China [7], another study was restricted to 45- to 79-year old residents of Norfolk, England [9], whereas the number of participants of the third study was so small [8], thus limiting statistical power or the generalizability of these studies.

Most studies on the combinations of established lifestyle factors and mortality have been conducted in the United States and countries in Western Europe, but, little in Asia including Korea. This study was designed to estimate the combined effects of abnormal BMI(Body Mass Index), smoking, and alcohol drinking on the risk of all-causes and cause-specific mortality through a population-based cohort study in Korea, where the NCDs including cancer has been leading causes of death for the last 20 years.

MATERIALS & METHODS

Study population and follow-up for outcomes

Eligible subjects were selected from the Korean Multi-center Cancer Cohort (KMCC) study. The rationale and design of KMCC is described in detail elsewhere [10]. Briefly, KMCC is a community-based prospective cohort of male and female volunteers recruited from 1993 through 2004 from 4 rural and urban areas in Korea. Information on general lifestyle including smoking habit and alcohol drinking habit, physical activity, diet, reproductive factors, and pesticide exposures were obtained through structured questionnaire interviews. Body weight and height were measured directly by well-trained medical staffs at the time of recruitment. Blood samples and spot urine samples were also collected. Serum, plasma and buffy coat samples were stored at -70℃. The study protocol was approved by the institutional review boards of the Seoul National University Hospital.

A total of 20,059 subjects were participated in the KMCC between 1993 and 2004. Among them, 1,527 participants due to missing information on locality, 1,484 participants who were younger than 20 years old at the time of enrollment, 43 participants with missing of date of birth, and 1,265 subjects due to missing information on at least one of the lifestyle factors, i.e., BMI, smoking habit, and alcohol drinking habit were excluded. The number of final study population included in the analysis was 15,740 persons (Fig. 1).

The total number of persons who completed the follow-up through the Death Certificate database of the National Statistical Office was 145,218.4 person-years by the end of December 31, 2008. Information on the date of death and causes of death was obtained from the Death Certificate database from the Korea National Statistics Office. Cause of death was classified by the tenth Revision of the International Classification of Disease (ICD-10) as follows; all-causes death (A00-Z99), all types of cancer death (C00-C97), cardiovascular disease (CVD) death (I00-I99), and deaths due to non-cancer, non-CVD deaths (A00-B99 or D00-H95 or J00-Z99) (Table 1). As results, the total number of death during the study period was 1,094

persons, and 474 deaths were due to cancer and 229 persons were due to cardio-vascular diseases among them,

Measurement of lifestyle factors

BMI, smoking habit, and alcohol drinking habit were chosen as the variables of major concern on lifestyle factors, because they have been examined to be closely associated with all causes-mortality in this cohort study[2, 3], and other large cohort study based on longitudinal observation among more than 1 million Asians [4].

At the baseline interview, all lifestyle factors were collected through direct interview with structured questionnaire by well-trained interviewers. Height and weight were used to calculate BMI as current weight divided by height squared (kg/m^2). Inquiry on smoking habits included smoking status (never, ex- or current smoker), age at starting or quitting smoking, the number of cigarettes per day, and the number of years of smoking [3]. Participants were asked to answer questions on whether they have ever drank alcoholic beverages; 'yes', 'yes, but not now', or 'no' , and 'have you ever drunk alcohol?', as used in the National Alcohol Survey [11]. Concerning the alcohol drinking

habits, participants were divided into 3 groups as ‘never drinkers’, ‘past drinkers’, and ‘current drinkers’, with the latter two also denoted as “drinkers” in this paper. The frequency of alcohol consumption was also measured as ‘more than 2 times a day’, ‘daily’, ‘4 to 6 times a week’, ‘2 to 3 times a week’, ‘weekly’, ‘2 to 3 times a month’, or ‘less than once a month’. The question on the preference of alcoholic beverage included ‘soju’, ‘beer’, and ‘rice wine (makkoli)’. Average amount of alcoholic consumption over the past one year was asked as ‘how much do you dring alcoholic beverage at one sitting’. To calculate the alcohol consumption quantitatively, we multiplied the amount of alcohol in a drink by the concentration of each beverage and the frequency of alcohol intake per week and weight of each beverage by multiplying 0.8 by the volume [2].

Classification of risk lifestyle factors

Risk scores of lifestyle factors were calculated based on the three lifestyle factors: underweight or overweight, current or past smoking, and nondrinker or more than 90 gram per week (Table 2). There was parameter estimates in the multiple logistic regression model which

was increased risk compared to reference group and provided rationale for included specific groups for each individual behavior to risk group (Table 3).

Risk level of each lifestyle factor was defined based on the previous cohort studies [2-4] as follows; underweight (BMI less than 22.6 kg/m^2) or overweight (BMI over 27.5 kg/m^2) compared to the normal range of BMI (22.6 ~ 27.5 kg/m^2); current smoker or ex-smoker compared to never-smokers; non-drinker or heavy drinker (over 90 gram of alcohol per week) compared to moderate drinker (1-90 gram of alcohol per week) (Table 3).

Estimation of the combined effect

Combined effect of three risk factors was estimated in two different ways; according to the number of risk factors qualitatively, and to the combined risk scores ranged from 0 to 14 quantitatively. Firstly, by adding simply the number of risk factor in random order of underweight/overweight, smokers, and drinkers, the combined risk of each category for all-causes or cancer-specific mortality were measured. Quantification of the combined risk by counting number of

risk factors may, however, mislead the fact that the magnitude of the effects regarding on mortality is not always equal.

Alternatively, in order to assess the combined risk of mortality more quantitatively, risk scores were used by weighting the effects of each lifestyle factor based on the regression equation of the Cox proportional hazard model [12].

For the weighted factor score, we used the percentage of the ß coefficient of each factor to the sum of the ß coefficients of each factor in the Cox proportional hazards regression model with all three factors. After determining the reference values for each, we computed how far each risk factor was from the baseline category in terms of the coefficient. By entering a particular individual's risk factor profile, a risk of all-cause mortality over a specified time frame can be generated [12], and it was assessed as 1-year difference in this study. And then, the constant for the risk score system that will correspond to one risk score was defined. The constant, B was reflected the increase in risk associated with 1-year increase in age, it was 0.07591.

We then weighted them with risk scores proportional to the β regression coefficient values, and risk scores were rounded to the nearest integer. (Table 4) A risk score was calculated for each study participant and they were grouped according to their total risk scores and all-cause or cause-specific mortalities, and hazard ratios were calculated. This assessment of factors as a score has been described previously, and for most risk profiles, there was very good agreement between the estimated produced by the risk score system and those produced by the models [12].

It has been categorized the weighted lifestyle scores to 4 levels, where the distribution of the categories is nearly bell-shaped with that of the 4 categories of the combined lifestyle score, and it was not same with analyses stratified by chronic disease, due to insufficient number of participants in specific categories.

Statistical analysis

To describe the baseline characteristics by gender, study population was compared by chi-square test for categorical variables and t-test or ANOVA for continuous variables. Hazard ratios (HRs) and

corresponding 95% confidence intervals (95% CI) of risk factors for all-causes and disease-specific mortality were obtained based the regression coefficients and its standard error from the Cox's proportional hazards regression models with follow-up time as time-scale.

All models were adjusted for sex, age groups (20-29, 30-39, 40-49, 50-59, 60-69, ≥70), geographic locality (Haman, Chungju, Youngil and Uljin), educational level(none, 1-12, ≥13 years), marital status (single, married, separate or bereaved, divorced) and the past history of the chronic diseases of hypertension or diabetes mellitus. HRs for all-cause mortality were shown as stratified by sex, and age group ≤60 and >70 years.

Linear trends were evaluated using the Wald test, treating the numbers of lifestyle as a continuous variable, and p-values < 0.05 were taken to indicate statistically significant comparisons [13].

The joint effect of risk factors has been measured for every combination of two lifestyle factors considered in this study. Hazard

ratios for all-cause mortality was assessed by compared to subjects who did not have any risk lifestyle factor [13].

Sensitivity analyses were run applied excluding the all-cause mortality that had occurred in the first 2 years of follow-up. Additionally, we examined the relationship between risk scores and mortality in the individuals with prevalent chronic disease excluded from the main analyses (data not shown). All the statistical analyses were done with SAS Windows Version 9.3 (Cary, NC, USA).

RESULTS

The general characteristics of the study population are shown in Table 5. Both male and female were more likely to be middle or older age of 40-69 years. Female are more likely to be less educated, never smoker, while male are more likely to be current smokers, and current drinkers of over 90 grams/week. Mean value of BMI was 23.1 ± 3.1 kg/m^2 for male and 23.9 ± 3.4 kg/m^2 for female. Women are more likely to have chronic disease than men (Table 5).

During the mean follow-up of 9.26 years with 145,218.4 person-years, 1,094 deaths were observed. Cancer was the leading cause of death (43.3%), followed by cardiovascular disease (20.9%). Among cancer deaths, the leading sites were lung cancer (n=113), liver cancer (n=89), and stomach cancer (n=87) (Table 6).

Adjusted HR of individual risk factors for mortality

Table 7 shows HRs for all-cause mortality according to individual risk factors. Adjusted HRs of BMI (underweight or overweight versus normal weight) was 1.47 (95% CI 1.27~1.69), 1.50 (95% CI 1.25~1.79) for smoking habit (current smokers or ex-smokers versus non-smokers) and 1.36 (95% CI 1.08~1.72) alcohol drinking habit (non-drinkers or heavy drinkers versus moderate drinkers). All the HRs was statistically significant, even stratifying by male and female, except alcohol drinking habit in women.

Similar findings can be observed in the association of risk factors for cancer mortality in Table 8. Adjusted HRs of BMI (HR, 1.35; 95% CI, 1.10~1.66) and smoking habit (HR, 1.75; 95% CI, 1.32~2.33) for cancer mortality were statistically significant in both genders. Smoking habit showed the highest risk of dying due to cancer in male (HR, 1.85; 95% CI, 1.26~2.70).

Adjusted HRs of BMI for CVD mortality in men and women (HR, 1.28; 95% CI, 0.95~1.73) and in men (HR, 1.53; 95% CI, 0.97~2.42) were not statistically significant (Table 9). Meanwhile, adjusted HRs for non-cancer and non-CVD mortality according to risk factors were

1.89 (95% CI, 1.47 to 2.42) for BMI, 1.48 (95% CI, 1.08−1.95) for smoking habit and 2.17 (95% CI, 1.34−3.49) for alcohol drinking, showing statistically significant association in both male and female. The association of BMI and alcohol drinking was statistically significant in male, while only BMI was significant in female (Table 10).

Adjusted HR of combined risk factors for mortality

Table 11 shows age− and sex−standardized mortality rates and adjusted HRs with 95% CIs for various indices of mortality according to the number of risk factors in this population. There was a linear increasing pattern of standardized rate of all−causes mortality with an increasing number of risk factors ($p<0.001$). Compared to the reference group of normal BMI, non−smoker and moderate drinker), individuals with three risk factors had approximately double risk of dying due to all−causes mortality (HR=3.42, 95% CI=1.87~6.26). Such a dose−dependent relationship was also found the standardized rates of cancer mortality ($p<0.01$), where the highest HRs was 2.70 (95% CI=1.19~6.15) among individuals with three risk factors. Similar

findings can be observed the standardized rates for non-cancer, non-CVD mortality, but not for CVD mortality.

Table 12 shows the matrix of joint hazards of risk factors for all-causes mortality observed in this study by gender. Combination of abnormal BMI and smoking habit shows HR of 3.35 (95% CI= 1.75~6.44) and women (HR, 5.66; 95% CI, 2.14-14.99). A combination of risk BMI and alcohol drinking habit showed a statistically significant hazard ratio of 2.28 (95% CI, 1.24-4.18) for men and women, and 2.69 (95% CI, 1.19-6.08) for women. A combination of risk among alcohol drinkers and smokers showed statistically significant hazard ratios in men and women (HR, 2.29; 95% CI, 1.24-4.24). Smoking alone without other risk factors showed high hazard ratios in women (HR, 6.44; 95% CI, 2.07-20.04), whereas there was no combination of lifestyle factors which has been statistically significant association with all-cause mortality in men.

Alternatively, Table 13 shows HRs with 95% CIs for all-cause mortality according to the risk score of risk factors of an individual. There was a somewhat monotonic increase in age- and sex-

standardized rate and risk of all-cause mortality was observed with an increasing risk score of risk factors. Individuals with 5~9 risk score of lifestyle factors has approximately two times the risk of all-cause mortality relative to those with no hazardous lifestyle factors, and it's getting bigger with 10~14 risk score of lifestyle factors that they has three times the risk of all-cause mortality. Also, among participants who were younger than 60 years, a monotonic increased risk was shown with an increasing risk score of hazardous lifestyle factors, and a statistically significant association was found in more than 10 risk score (Table 13). Also, among men and women, a monotonic increased risk was shown with an increasing risk score of hazardous lifestyle factors. A statistically significant association was found in more than 5 risk score and those with 10~14 risk score of lifestyle factors has four times the risk of all-cause mortality in women. In addition, among male participants with 10-14 risk score, they had statistically significant increased hazard ratio of 2.72 (95% CI, 1.13-6.59) (Table 13).

To evaluate the possible influence of reverse causation it has been performed analyses that excluded first 2 years of follow-up, and then there was an almost same result, although there was a slightly

strengthened positive association of the risk of death with particular categories of score (Table 14).

DISCUSSION

This study confirms abnormal BMI, smoking habit and alcohol drinking habit are major risk factor of premature deaths, as well as cancer death. Combined effect of lifestyle factors would additively be associated with a marked increased risk of both all-causes and cancer-specific death in Korea. The present study supports the risk behaviours increase the probability of deaths in Korea.

In this analysis, we found that the risk of all-cause, cancer, cardiovascular disease (CVD) and non-cancer, non-CVD mortality was significantly higher in participants who had the highest combined risk lifestyle score compared with participants who had the lowest score. Approximately male and female participants with hazardous lifestyle factors represented by unhealthy weight (underweight or overweight); history of smoking; and nondrinking or heavy alcohol consumption were at a significantly increased risk of all-cause mortality. Participants, who had underweight or overweight, had smoked ever experienced a significant increased risk of overall cancer

mortality. The evidence that individual lifestyle factors such as BMI, smoking status, and alcohol consumption influence health is well-known so far [4, 5, 14-17].

Particularly noteworthy was that the risk of dying increases according to the combined risk score increasing. The higher risk for both all-cause deaths and cancer deaths showed linear increasing ($p<0.001$). Subjects with the higher score (0~14) had significantly at greater risk of all-cause mortality (HR=3.46, 95% CI=1.89-6.32).

This results are compatible with those of two prospective studies of an increased risk of premature mortality [9] or incident stroke [18]. This suggests that the combined risk lifestyle factors should be assessed with age of death and considered it could be increase the risk of premature death or incidence of specific disease. The combination of risk lifestyle factors showed a particularly increased risk for all-cause mortality of 2.72 for males and 4.17 for females with 10 to 14 risk score in this study.

Combinations of BMI in risk range and ever smoking increased risk of all-cause mortality of 3.35-fold higher risk of all-cause mortality, combinations of BMI and alcohol consumption increase of 2.28-fold higher risk of all-cause mortality compared to those with no risk lifestyle factors. The group with alcohol consumption and smoking status altogether had a 2.29-fold higher risk of all-cause mortality than the group with no risk behavior. However, females had a strengthened result more than among both males and females, moreover, alcohol consumption alone increased risk of all-cause mortality in females, although males had no statistically significant results in joint relative risk of lifestyle factors. This suggests that females were exempted from the dangers of alcohol use or smoking, and they might be more sensitive to risk lifestyle factors than males. This results was compatible with a case-control study in Japan [19], and it has been made almost same hypotheses with those of joint hazard ratios and mortality in this study.

Lifestyle factors are highly correlated generally, and only recently have these factors been examined in combination, but few studies have investigated the combined effect of these factors. Khaw et al examined the combined impact of not smoking, not being physically inactive,

having a moderate alcohol intake, and a having a high fruit and vegetable intake on mortality among males and females aged 45 to 79 years followed up for about 11 years. The study concluded that there was a strong trend of decreasing mortality risk associated with an increasing number of positive lifestyle factors, with those who had 4 positive lifestyle factors having about one-quarter the mortality risk of those who had none[9]. A large multicenter European study that reported that in 2,339 males and females aged 70 to 90 years in 11 European countries, the combination of four factors-adherence to Mediterranean diet, moderate alcohol use, being physically active, and nonsmoking- was associated with a mortality rate one third of those who did not have these lifestyle factors [20].

A limitation of previously published studies is that most studies have been conducted in the United States of Western Europe, whereas few studies have examined the combined lifestyle factors in relation to mortality among Asian populations. In a cohort study of Japanese, which included 62,106 males and females aged 40-79 years, subjects who were not currently smoking, did not heavily drink, walked 1 hour or more per day, slept 6.5 to 7.4 hour per day, ate green-leafy

vegetables almost daily and had a BMI between 18.5 and 25 kg/m2 experienced a significant decrease in risk of all-cause mortality [21]. In a cohort study of china, which included 71,243 females aged 40 to 70 years, subjects who were normal weight, had lower waist-hip ratio, exercise daily, were never exposed to spouse's smoking, ate higher daily fruit and vegetable intake experience a significant decrease in risk of all-cause mortality and CVD mortality, and cancer mortality [7]. However these studies were restricted to specific age, thus it might be limited for the generalizability.

The selected lifestyle factors overlapped with well-known risk lifestyle factors. However, previous risk score such as so-called 'Alameda 7' did not weight different risk factors [22-24], even though there are differences between risk factors in terms of the number of lifestyle factors and in magnitude of their respective effects on mortality. It has been used a scoring system to weight individual lifestyle factors by calculating their effect size on mortality, and the group with 10 to 14 scores had a 3.46-fold higher risk of all-cause mortality than the group with 0 score of lifestyle factors in this study. It could be suggested that the combined effects of lifestyle factor might

be assessed by not summed number of risk lifestyle factors, but also weighted one in terms of their impact on mortality.

The scoring system used in this study has been widely used to develop for cardiovascular diseases [25–27]. However, limitations of using this scoring system rather than the Cox model is that, to achieve simplicity in use, we lose some of the information that is only captured using the entire Cox model [28].

In this scoring system, a small number of lifestyle factors such as BMI, smoking status, and alcohol consumption were included, and their magnitude size of risk on mortality was applied in the dichotomized form, so risk scores of the lifestyle factors were discrete. This makes that distribution of subjects is not statistically normal distribution, and there are little difference between hazard rations according to risk scores and the number of risk lifestyle factors.

However, in this scoring system, only modifiable factors were included, so this results are more available to motivate patients to adopt healthier lifestyle factors than previous health risk score such as Framingham risk score included non–modifiable lifestyle factors (i.e. age, gender) [29, 30], even though, theoretical and statistical models

were used to develop this scoring system, applying it to the general population remains to be validated.

This study has several strengths. First, our mortality data was collected from the National Death Certificate System, which covers more than 95% of the deaths in the whole population. Second, the present study was from the population-based prospective cohort study in Korea, which has been selected as one of the genome cohort studies with biologic materials bank and risk factor questionnaire data in the world by the NCI-USA in 2006. Third, this study population has their unique characteristics compared to those in previous studies and all subjects in this study were of the same ethnicity, Korean. Fourth, our research studied the relationship between combined lifestyle factors and all-causes and cause-specific mortality. In addition, we can find the mortality from all-causes, overall cancer, CVD, and non-cancer non-CVD, simultaneously. Other strengths include all lifestyle factors were collected through direct interview with structured questionnaire by well-trained interviewers and various anthropometric indices were measured directly using standard methods at the time of the physical examination.

There are limitations need to be considered. First, risk scores of the lifestyle factors were not statistically normal distributed, in addition, models for weighted risk score in the study had not been validated, applying it to the general population may not be appropriate. However, it has been thought that these results would be likely to be statistically normal distributed when we include more lifestyle factors and refine the category of each behavior. Therefore, further evaluation which applied it to the general population to be validated and lifestyle factors to refined is required. Second, the lifestyle factors were dichotomized, which may lead to underestimation of risk because there are graded associations among some of the lifestyle factors. However, the 3 lifestyle factors were given unequal weight, which take into account that the lifestyle factors have varying degrees of impact on all-cause, and cause-specific mortality. Third, we relied on self-report of diagnosed hypertension and diabetes mellitus, which results in some misclassification. Fourth, because each lifestyle factor was assessed at the baseline only, we could not consider the changes over time. The validity of the results could have increased if we had performed repeated measures because the lifestyle factors might have changed after the enrollment period. However, repeated measures could not

weaken the significant association between individual lifestyle factors and total and cause-specific mortalities in this study, but would help to reinforce the association more clearly. Fifth, the number of subjects and follow-up duration were limited in the analysis of cause-specific mortality, such as cancer, CVD, and non-cancer non-CVD mortality stratified by sex. Sixth, residual confounding is likely because this was an observational study and such studies are unable to adjust for all known and unknown confounding variables.

In summary, a prospective cohort study was performed to examine the association of combined life-style factors with the risk of mortality in Korea. This study confirms abnormal BMI, smoking habit and alcohol drinking habit are major risk factor of premature deaths, as well as cancer death. The risk of dying was 1.47 times in BMI, 1.50 times in smoking habit, and 1.36 times higher in alcohol drinking habit than the baseline hazard. The HR for cancer death was 1.35 in BMI, and 1.75 in smoking habit. The HRs for both all-causes mortality and cancer mortality showed linearly increasing pattern with statistical significant. Conclusively, combined effect of lifestyle factors would additively be associated with a marked increased risk of both all-causes and

cancer-specific death in Korea. The present study supports the risk behaviours increase the probability of deaths in Korea.

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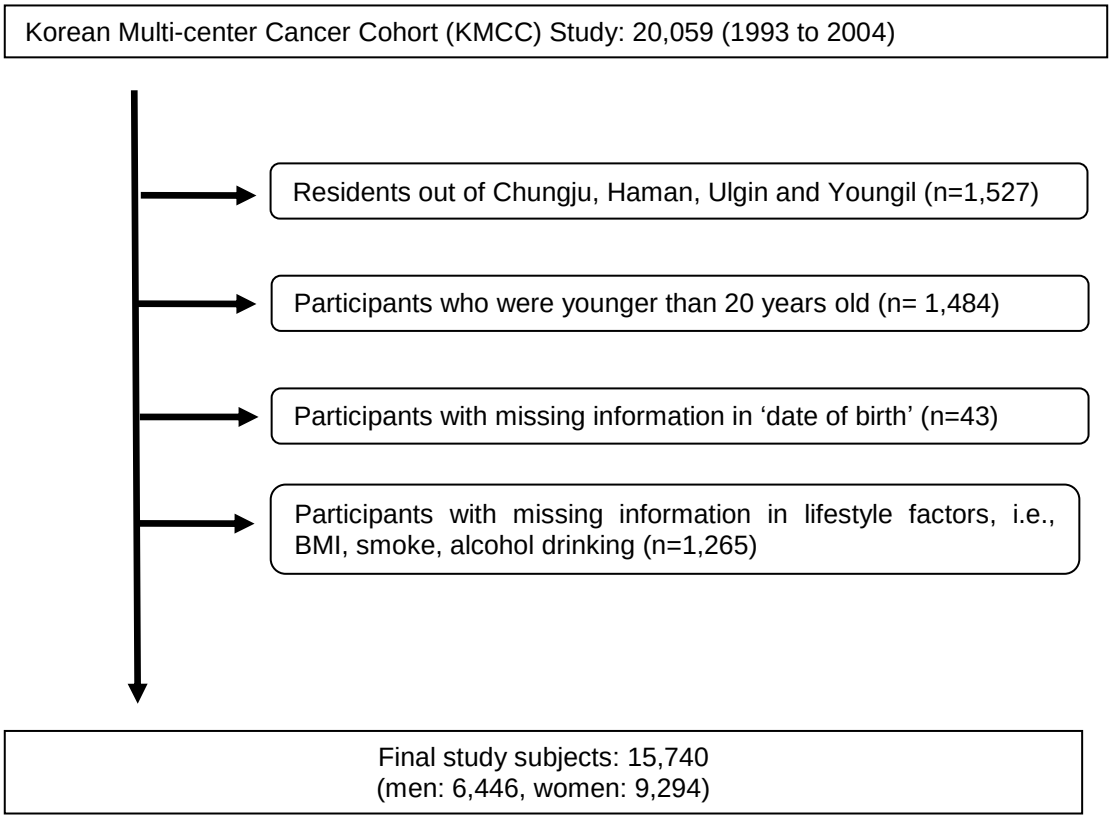

Fig. 1. Study subjects selected from the Korean Multi-center Cancer Cohort study on the combined effect of lifestyle factors on mortality.

Table 1. Classification of the cause of death based on the ICD-10*

Cause of death	ICD-10 code
All-cause death	A00-Z99
Cancer death	C00-C97
Cardiovascular disease(CVD) death	I00-I99
Non-cancer, non-CVD death	A00-B99
	D00-H95
	J00-Z99

* International Classification of Diseases

Table 2. Definition of lifestyle factors

Lifestyle factors	Referent level	Risk level
BMI	22.6 ~ 27.5 kg/m^2	< 22.6 or ≥ 27.5 kg/m^2
Smoking habit	Non-smoker	Current or past smoker
Alcohol drinking habit	≤ 90g/week	Nondrinker or drinking habit >90g/week

BMI = Body Mass Index
Lifestyle factors classified into referent and risk level based on the previous cohort studies as follows; 'BMI' from Zheng et al. 2011[4], 'Smoking habit' from Lee et al. 2010[3], and 'Alcohol drinking habit' from Jung et al.. 2012[2].

Table 3. Hazard ratio and 95% confidence interval of all-causes mortality according to the level of lifestyle factors in the Korean Multi-center Cancer Cohort study, 1993-2008

Lifestyle factors	Categories	No. of cohort (%)	No. of death (%)	HR (95% CI) †
Total		15,740 (100)	1,094 (100)	
BMI (kg/m^2**)**				
	<22.6	6,205 (39.4)	649 (59.3)	1.51 (1.31-1.75)
	22.6~27.5	7,702 (48.9)	368 (33.6)	1.0
	≥27.5	1,833 (11.7)	77 (7.0)	1.15 (0.87-1.50)
Smoking habit				
	never smoker	9,760 (62.0)	403 (36.8)	1.0
	ex-smoker	1,582 (10.1)	168 (15.4)	1.08 (0.86-1.37)
	current smoker	4,398 (27.9)	523 (47.8)	1.60 (1.33-1.92)
Alcohol drinking habit (grams/week)				
	non-drinker	10,429 (66.3)	684 (62.5)	1.27 (0.99-1.62)‡
	1 - 90	2,522 (16.0)	105 (9.6)	1.0
	>90	2,789 (17.7)	305 (27.9)	1.56 (1.20-2.01)

†Hazard ratios and 95% confidence intervals were based on Cox's proportional hazard model, adjusting for age, sex, educational level, marital status, geographic area, and past history of chronic disease

‡ emarginal significance 0.05 cationa

Table 4. Risk scores associated with each of the lifestyle factors

Risk factor	Categories	Reference value	ß (regression coefficient)	Risk scores= ß/B†
BMI	<22.6 or ≥27.5	1	0.38271	5
	22.6~27.5	0	0	0
Smoking status	Smoker	1	0.40308	5
	Never smoker	0	0	0
Alcohol consumption	Never drinker or >90gram/week	1	0.30990	4
	0~90 gram/week	0	0	0

† B reflects the increase in risk associated with 1-year increase in age.

Table 5. General characteristics of the study population at the time of enrollment factors in the Korean Multi-center Cancer Cohort study

Characteristics		Both		Male	Female	p-value
		No.	(%)	No. (%)	No. (%)†	
Total		15,740	100	6,446 (40.9)	9,294 (59.1)	
Age in years						<0.001
	20-29	574	3.7	303 (4.7)	271 (2.9)	
	30-39	1,736	11.0	777 (12.1)	959 (10.3)	
	40-49	3,079	19.6	1,232 (19.1)	1,847 (19.9)	
	50-59	4,075	25.9	1,550 (24.1)	2,525 (27.2)	
	60-69	4,462	28.4	1,820 (28.2)	2,642 (28.4)	
	≥70	1,814	11.5	764 (11.9)	1,050 (11.3)	
Educational attainment (years)						<0.001
	none	3,290	20.9	705 (10.9)	2,585 (27.8)	
	1-12	11,866	75.4	5,334 (82.8)	6,532 (70.3)	
	≥13	526	3.3	370 (5.7)	156 (1.7)	
	missing	58	0.4	37 (0.6)	21 (0.2)	
Smoking habit						<0.001
	never smoker	9,760	62.0	1,268 (19.7)	8,492 (91.4)	

	ex-smoker	1,582	10.1	1,426 (22.1)	156 (1.7)	
	current smoker	4,398	27.9	3,752 (58.2)	646 (7.0)	
Alcohol drinking habit (grams/week)						<0.001
	non-drinker	10,429	66.3	2,677 (41.5)	7,752 (83.4)	
	0.01-90	2,522	16.0	1,296 (20.1)	1,226 (13.2)	
	>90	2,789	17.7	2,473 (38.4)	316 (3.4)	
BMI (mean±SD, kg/m^2)				23.1±3.1	23.9±3.4	<0.001
Marital status						<0.001
	single	570	3.6	363 (5.6)	207 (2.2)	
	married	11,726	74.5	5,355 (83.1)	6,371 (68.6)	
	separated, bereaved, divorced	2,410	15.3	330 (5.1)	2,080 (22.4)	
	missing	1,034	6.6	398 (6.2)	636 (6.8)	
Past history of chronic disease‡		2,263	14.4	802 (12.5)	1,461 (15.8)	<0.001

† Defined as having past history of hypertension or diabetes mellitus obtained from direct questionnaire interview.

Table 6. Number of deaths observed during the follow-up period of factors in the Korean Multi-center Cancer Cohort study

Cause of death		ICD-10	No. of deaths	%
All-causes death		A00-Z99	1094	100
Cancer death				
	All	C00-C99	474	43.3
	Lung and bronchus	C34	113	10.3
	Esophagus	C15	9	0.8
	Stomach	C16	87	8.0
	Colorectum	C18-C20	26	2.4
	Liver	C22	89	8.1
	Pancreas	C25	29	2.7
	Biliary tract	C24	22	2.0
	Other cancers	-	99	9.0
CVD		I00-I99	229	20.9
Cerebrovascular disease		I60-I69	139	12.7
	Cerebral hemorrhage	I60-I62	55	5.0
	CVA/infarct	I63	27	2.5
	Other cerebrovascular disease	I64-I69	57	5.2
Liver disease		K70-K77	42	3.8
Diabetes mellitus		E10-E14	40	3.7
COPD		J40-J47	46	4.2
Hypertension		I10-I12	22	2.0
Others		-	263	24.0

CVD: cardiovascular disease;
CVA: cerebrovascular accident;
COPD: chronic obstructive pulmonary disease

Table 7. Hazard ratio and 95% confidence interval of all-cause mortality according to lifestyle factors in the Korean Multi-center Cancer Cohort study

	Lifestyle factors	All-causes mortality	
		HR (95% CI)†	p-value
Both			
	No. of deaths	1,094	
	BMI	**1.47 (1.27-1.69)**	<.001
	Smoking habit	**1.50 (1.25-1.79)**	<.001
	Alcohol drinking habit	**1.36 (1.08-1.72)**	0.009
Male			
	No. of deaths	697	
	BMI	**1.56 (1.31-1.87)**	<.001
	Smoking habit	**1.46 (1.14-1.85)**	0.002
	Alcohol drinking habit	**1.37 (1.03-1.81)**	0.03
Female			
	No. of deaths	397	
	BMI	**1.34 (1.07-1.67)**	0.012
	Smoking habit	**1.47 (1.13-1.92)**	0.005
	Alcohol drinking habit	1.38 (0.89-2.13)	ns

†Hazard ratios and 95% confidence intervals were based on Cox's proportional hazard model, adjusting for age, sex, educational level, marital status, geographic area, and past history of chronic disease

BMI (22.6~27.5 vs <22.6 or ≥27.5); smoking habit (never smoker vs smoker); alcohol drinking habit (0~90 gram/week vs never drinker or > 90 gram/week)

Table 8. Hazard ratio and 95% confidence interval of cancer mortality according to lifestyle factors in the Korean Multi-center Cancer Cohort study

	Lifestyle factors	Cancer mortality	
		HR (95% CI)†	p-value
Both			
	No. of deaths	474	
	BMI	**1.35 (1.10-1.66)**	0.005
	Smoking habit	**1.75 (1.32-2.33)**	<.001
	Alcohol drinking habit	1.09 (0.79-1.50)	ns
Male			
	No. of deaths	334	
	BMI	**1.53 (1.18-1.98)**	0.001
	Smoking habit	**1.85 (1.26-2.70)**	0.002
	Alcohol drinking habit	0.97 (0.69-1.39)	ns
Female			
	No. of deaths	140	
	BMI	1.03 (0.72-1.49)	ns
	Smoking habit	**1.66 (1.04-2.63)**	0.03
	Alcohol drinking habit	1.69 (0.78-3.64)	ns

†Hazard ratios and 95% confidence intervals were based on Cox's proportional hazard model, adjusting for age, sex, educational level, marital status, geographic area, and past history of chronic disease

BMI (22.6~27.5 vs <22.6 or ≥27.5); smoking habit (never smoker vs smoker); alcohol drinking habit (0~90 gram/week vs never drinker or > 90 gram/week)

Table 9. Hazard ratio and 95% confidence interval of CVD mortality according to lifestyle factors in the Korean Multi-center Cancer Cohort study

	Lifestyle factors	CVD mortality	
		HR (95% CI)†	p-value
Both			
	No. of deaths	229	
	BMI	1.28 (0.95-1.73)	ns
	Smoking habit	1.21 (0.83-1.77)	ns
	Alcohol drinking habit	1.23 (0.73-2.05)	ns
Male			
	No. of deaths	111	
	BMI	1.53 (0.97-2.42)	0.066
	Smoking habit	1.09 (0.62-1.90)	ns
	Alcohol drinking habit	1.23 (0.61-2.46)	ns
Female			
	No. of deaths	118	
	BMI	1.11 (0.74-1.66)	ns
	Smoking habit	1.26 (0.76-2.09)	ns
	Alcohol drinking habit	1.16 (0.53-2.51)	ns

†Hazard ratios and 95% confidence intervals were based on Cox's proportional hazard model, adjusting for age, sex, educational level, marital status, geographic area, and past history of chronic disease

BMI (22.6~27.5 vs <22.6 or ≥27.5); smoking habit (never smoker vs smoker); alcohol drinking habit (0~90 gram/week vs never drinker or > 90 gram/week)

Table 10. Hazard ratio and 95% confidence interval of non-cancer, non-CVD mortality according to lifestyle factors in the Korean Multi-center Cancer Cohort study

	Lifestyle factors	Non-cancer non-CVD mortality	
		HR (95% CI)†	p-value
Both			
	No. of deaths	391	
	BMI	**1.89 (1.47-2.42)**	<.001
	Smoking habit	**1.45 (1.08-1.95)**	0.014
	Alcohol drinking habit	**2.17 (1.34-3.49)**	0.002
Male			
	No. of deaths	252	
	BMI	**1.74 (1.28-2.37)**	<.001
	Smoking habit	1.26 (0.86-1.85)	0.233
	Alcohol drinking habit	**2.94 (1.55-5.55)**	<.001
Female			
	No. of deaths	139	
	BMI	**2.23 (1.46-3.39)**	<.001
	Smoking habit	1.51 (0.99-2.32)†	0.058
	Alcohol drinking habit	1.31 (0.64-2.71)	0.462

†Hazard ratios and 95% confidence intervals were based on Cox's proportional hazard model, adjusting for age, sex, educational level, marital status, geographic area, and past history of chronic disease

BMI (22.6~27.5 vs <22.6 or ≥27.5); smoking habit (never smoker vs smoker); alcohol drinking habit (0~90 gram/week vs never drinker or > 90 gram/week)

Table 11. Hazard ratio and 95% confidence interval† of mortality according to lifestyle factors in the Korean Multi-center Cancer Cohort study

	Number of lifestyle factors				
	0	**1**	**2**	**3**	**p for trend**
All-causes mortality					
Total person-years	6420.4	51371.2	63862.8	23564.0	
No. of deaths	11	195	453	435	
Standardized rate‡	28.1	154.2	195.4	298.8	
HR (95% CI)	1.0	1.73 (0.94-3.19)†	**2.36 (1.30-4.30)**	**3.42 (1.87-6.26)**	<.001
Cancer mortality					
No. of deaths	6	80	196	192	
Standardized rate‡	5.8	44.9	63.4	94.9	
HR (95% CI)	1.0	1.36 (0.59-3.12)	1.89 (0.84-4.27)	**2.70 (1.19-6.15)**	<.001
CVD mortality					
No. of deaths	2	63	94	70	
Standardized rate‡	0.5	73.6	53.2	63.4	
HR (95% CI)	1.0	3.10 (0.76-12.70)	3.02 (0.74-12.30)	4.07 (0.98-16.82)†	0.120
Non-cancer, non-CVD mortality					
No. of deaths	3	52	163	173	
Standardized rate‡	21.8	35.7	78.9	140.5	
HR (95% CI)	1.0	1.66 (0.52-5.33)	3.04 (0.97-9.55)†	**4.84 (1.53-15.29)**	<.001

†Hazard ratios and 95% confidence intervals were based on Cox's proportional hazard model, adjusting for age, sex, educational level, marital status, geographic area, and past history of chronic disease, and lifestyle factors in the sequence of BMI, smoking habit, and alcohol drinking habit
BMI, smoking habit, alcohol drinking habit was used to count the number of the lifestyle factors.

BMI (22.6~27.5 vs <22.6 or ≥27.5); smoking habit (never smoker vs smoker); alcohol drinking habit (0~90 gram/week vs never drinker or > 90 gram/week)
‡ Age and sex-standardized mortality rate per 10,000 person-years using age and sex distribution of KMCC study

Table 12. Joint hazard ratio and 95% confidence interval of various combinations of lifestyle factors for all-cause mortality in the Korean Multi-center Cancer Cohort study

Risk factors	Both			Male			Female		
	BMI†	Smoking habit‡	Alcohol drinking habit§	BMI†	Smoking habit‡	Alcohol drinking habit§	BMI†	Smoking habit‡	Alcohol drinking habit§
BMI									
Person-years	5523.2	5775.2	39751.2	938.0	5006.0	4105.6	4585.2	769.2	35645.6
No. of death	13	56	222	4	43	50	9	13	172
HR (95% CI) ‖	1.28 (0.56-2.90)	**3.35 (1.75-6.44)**	**2.28 (1.24-4.18)**	1.09 (0.29-4.05)	2.38 (0.94-6.02) ¶	1.81 (0.72-4.56)	1.50 (0.52-4.31)	**5.66 (2.14-14.99)**	**2.69 (1.19-6.08)**
Smoking habit									
Person-years		4815.2	18336.4		4333.2	15608.8		482.0	2727.6
No. of death		25	175		19	158		6	17
HR (95% CI) ‖		1.94 (0.94-4.00)¶	**2.29 (1.24-4.24)**		1.23 (0.45-3.33)	1.86 (0.76-4.54)		**6.44 (2.07-20.04)**	1.98 (0.78-5.04)
Alcohol drinking habit									

Person-years		41032.8	4946.0	36086.8
No. of death		157	39	118
HR (95% CI) ‖		1.75 (0.95-3.23)†	1.45 (0.57-3.69)	0.06 (0.91-4.68)

† BMI: <22.6 or ≥27.5 km/m^2

‡ Smoking status: Ever smoking

§ Alcohol consumption: Never drink or more than 90 gram/week

‖ Hazard ratios and 95% confidence intervals were based on Cox's proportional hazard model, adjusting for age, sex, educational level, marital status, geographic area, and past history of chronic disease, and lifestyle factors in the sequence of BMI, smoking habit, and alcohol drinking habit

Number of lifestyle factors was included BMI, smoking habit, and alcohol drinking habit

BMI (22.6~27.5 vs <22.6 or ≥27.5); smoking habit (never smoker vs smoker); alcohol drinking habit (0~90 gram/week vs never drinker or > 90 gram/week)

¶ emarginal significance 0.05 cationa

Table 13. Hazard ratio and 95% confidence interval of all-cause mortality according to risk scores calculated based on the lifestyle factors in the Korean Multi-center Cancer Cohort study

		Total risk score‡				
		0	**4**	**5, 9**	**10, 14**	**p for trend**
Both						
	Total person-years	6420.4	41032.8	68426.0	29339.2	
	No. of deaths	11	157	435	491	
	Multivariate HR (95% CI)†	1.0	1.75 (0.95-3.23) ‖	**2.21 (1.21-4.03)**	**3.46 (1.89-6.32)**	<0.001
Male						
	Total person-years	1509.6	4946.0	24985.6	24938.8	
	No. of deaths	5	39	231	422	
	Multivariate HR (95% CI)†	1.0	1.45 (0.57-3.69)	1.76 (0.72-4.27)	**2.72 (1.13-6.59)**	<0.001
Female						
	Total person-years	4910.8	36086.8	43440.4	4400.4	
	No. of deaths	6	118	204	69	
	Multivariate HR (95% CI)†	1.0	2.06 (0.91-4.68)	**2.57 (1.14-5.80)**	**4.17 (1.80-9.68)**	<0.001
HR for premature death§						
	Total person-years	4585.6	27568.0	43262.8	15486.0	
	No. of deaths	4	42	115	102	
	Multivariate HR (95% CI)†	1.0	1.68 (0.60-4.70)	2.37 (0.87-6.42)	**3.60 (1.31-9.92)**	0.006

† Hazard ratios and 95% confidence intervals were based on Cox's proportional hazard model, adjusting for age, sex, educational level, marital status, geographic area, and past history of chronic disease, and lifestyle factors in the sequence of BMI, smoking habit, and alcohol drinking habit

‡ BMI, smoking habit, alcohol drinking habit was used to assess the risk score of the lifestyle factors, BMI (22.6~27.5 vs <22.6 or ≥27.5); smoking habit (never smoker vs smoker); alcohol drinking habit (0~90 gram/week vs never drinker or > 90 gram/week)

§ Deaths under 60 years old

‖ emarginal significance 0.05 cationa

Table 14. Hazard ratios for all-cause mortality by total risk score of lifestyle factors in participants excluding deaths in the first two years of follow-up (N=15,403)

	Total risk score				
	0~4	**5~6**	**7~9**	**10~14**	**p for trend**
All-cause mortality					
Total person-years	47404.4	10324.0	57970.8	29191.2	
No. of deaths	125	26	301	366	
Standardized rate†	106.5	96.8	149.1	219.1	
Multivariate HR (95% CI)	1.0	0.98 (0.64-1.52)	**1.41 (1.14-1.75)**	**2.18 (1.73-2.75)**	<.001
Cancer mortality					
No. of deaths	54	13	135	170	
Standardized rate†	25.4	34.5	51.7	63.1	
Multivariate HR (95% CI)	1.0	1.04 (0.56-1.93)	**1.40 (1.01-1.95)**	**2.09 (1.48-2.97)**	<.001
CVD mortality					
No. of deaths	45	7	68	54	
Standardized rate†	59.9	41.6	42.8	40.7	
Multivariate HR (95% CI)	1.0	0.92 (0.41-2.05)	0.99 (0.67-1.46)	1.22 (0.77-1.93)	0.728
Non-cancer non-CVD mortality					
No. of deaths	26	6	98	142	
Standardized rate†	21.2	20.7	54.7	115.3	
Multivariate HR (95% CI)	1.0	1.01 (0.39-2.64)	**2.17 (1.40-3.37)**	**4.09 (2.58-6.48)**	<.001

Adjusted for age, sex, educational level, marital status, geographic area
† Age and sex-standardized mortality rate per 10,000 person-years using age and sex distribution of KMCC study

Table 15. Summary of study results on alcohol consumption for disease or mortality risk

Ref	Author	Control selection	Country	Age	Study period	Outcome	No. of cases	No. of control (cohort)	Comments
Cohort study									
[31]	Hansen, et al. 2011		Denmark	50-64	1993-2006	Acute coronary syndrome	860; 271	195493 (M); 226678 (F)	The Diet, Cancer and Health study, Denmark; Drinking quantity per week
[32]	Thygesen, et al. 2008		Denmark	>20	1976-2003	All-cause mortality	2686	12698†	The Copenhagen City Heart Study, Denmark; Drinking quantity per week
[33]	Nicholson, et al. 2005		Russia	>30	1972-2002	All-cause mortality	3692 (M)	9983† (M)	Using the survey of a national sample, Russian; Drinking frequency
[34]	Emberson, et al. 2005		UK	40-59	1980-2000	All-cause mortality Stroke	1552 352	6544 6544	The British Regional Heart Study, UK; Drinking quantity per day
[35]	Britton, et al. 2003		UK	35-55	1985-1999	All-cause mortality CHD	240; 111 775; 434	6840† (M); 3374† (F)	The Whitehall II Cohort Study, UK; Drinking quantity per week

[36]	Arndt, et al. 2004	German	25-64	1986-2000	All-cause mortality	693	17135†	A cohort study was set up with male employees from the German construction industry who underwent routine occupational health exams; Drinking quantity per day
[37]	Odegaard, et al. 2011	Singapore	45-74	1993-2009	Total Cardiovascular mortality	1971	593118	The Singapore Chinese Health Study, Singapore; Drinking quantity per week

† number of cohort.

Table 16. Relative risk and its 95% confidence intervals in previous studies alcohol consumption and disease or mortality risk

Ref	Author	No. of cases	No. of controls (cohort)	Stratification (amount or frequency)	No. of cases	No. of controls (cohort)	RR (95%CI)	Adjusted variables
Cohort study								
[31]	Hansen, et al. 2011	860; 271	195493 (M); 226678 (F)	Male				
				<1	80	9328	1.47 (1.14-1.89)	Age, smoking, school education, BMI, waist circumference, physical activity, intake of fruit, vegetables, fish, fat and saturated fat, hypercholesterolemia, diabetes, and for women: menopausal status and use of HRT
				1-6	251	49911	1.0	
				7-13	197	52456	0.82 (0.68-0.99)	
				14-20	107	23307	0.95 (0.76-1.20)	
				21-27	90	26685	0.71 (0.55-0.91)	
				≥28	135	33806	0.68 (0.53-0.91)	
				Female				
				<1	63	36071	0.99 (0.73-1.35)	
				1-6	130	102200	1.0	
				7-13	39	47453	0.73 (0.51-1.05)	

Ref	Author	No. of cases	No. of controls (cohort)	Stratification (amount or frequency)	No. of cases	No. of controls (cohort)	RR (95%CI)	Adjusted variables
				14-20	22	20660	0.92 (0.58-1.47)	
				≥21	17	20294	0.64 (0.38-1.09)	
[32]	Thygesen, et al. 2008	2686	12698§	<1			1.15 (1.07-1.23)	Smoking habits, physical activity, body mass index, years of education, sex and age (5-year categories) at wave 1 and marital status, job category, gross income, residence ownership and residence area per person the year before planned wave
				1-6			1.0	
				7-14			1.09 (1.01-1.18)	
				15-28			1.14 (1.04-1.26)	
				29-41			1.31 (1.13-1.52)	
				42-69			1.42 (1.17-1.72)	
				>69			1.27 (0.92-1.74)	
[33]	Nicholson, et al. 2005	3692	9983§ (M)	Never	443	1472	0.79 (0.71-0.88)	Relative, smoking behavior, decade of birth
				Occasional	1454	4288	1.0	
				Several times a month	654	1614	1.26 (1.15-1.38)	
				Weekly/more often	878	1990	1.37 (1.25-1.49)	
				Daily	263	619	1.52 (1.33-1.75)	

Ref	Author	No. of cases	No. of controls (cohort)	Stratification (amount or frequency)	No. of cases	No. of controls (cohort)	RR (95%CI)	Adjusted variables
[34]	Emberson, et al. 2005	All-cause death 1552 Stroke incidence 352	6544 6544	None		358	1.22 (0.98-1.52)† 1.58 (1.02-2.44)‡	Cigarette smoking, physical activity, BMI
				Occasional		1556	1.0 1.0	
				Light		2189	0.88 (0.77-1.01)† 0.97 (0.72-1.31)‡	
				Moderate		1745	1.12 (0.98-1.29)† 1.19 (0.88-1.61)‡	
				Heavy		696	1.44 (1.21-1.72)† 1.54 (1.06-2.22)‡	
[35]	Britton, et al. 2003	240; 111	6840§ (M); 3374§ (F)	**All-cause mortality**				Age, smoking (no/ex/light/moderate/ heavy), employment grade (high/medium/low), blood cholesterol, blood pressure, body mass index, general health questionnaire score.
		775; 434	6840§ (M); 3374§ (F)	Male				
				Never drink	16	219	2.09 (1.22-3.59)	
				None in past week	35	670	1.48 (0.98-2.23)	
				1-10 units	94	3119	1.0	
				11-20 units	24	862	0.86 (0.53-1.40)	
				21-30 units	42	1293	1.08 (0.74-1.58)	
				>30	29	670	1.40 (0.90-2.18)	

Ref	Author	No. of cases	No. of controls (cohort)	Stratification (amount or frequency)	No. of cases	No. of controls (cohort)	RR (95%CI)	Adjusted variables
				Female				
				Never drink	9	216	1.17 (0.52-2.63)	
				None in past week	34	766	1.28 (0.80-2.03)	
				1-10 units	42	1427	1.0	
				11-20 units	11	422	0.88 (0.44-1.77)	
				21-30 units	11	385	1.01 (0.51-2.00)	
				>30	4	159	0.90 (0.32-2.58)	
				CHD risk				
				Male	43	219		
				Never drink	77	670	1.82 (1.34-2.52)	
				None in past week	338	3119	1.01 (0.87-1.43)	
				1-10 units	94	862	1.0	
				11-20 units	148	1293	0.99 (0.82-1.30)	
				21-30 units	75	670	0.99 (0.93-1.37)	
				>30	43	219	0.94 (0.91-1.49)	
				Female				

Ref	Author	No. of cases	No. of controls (cohort)	Stratification (amount or frequency)	No. of cases	No. of controls (cohort)	RR (95%CI)	Adjusted variables
				Never drink	43	216	1.77 (1.23-2.50)	
				None in past week	104	766	1.06 (0.82-1.37)	
				1-10 units	173	1427	1.0	
				11-20 units	52	422	1.14 (0.83-1.57)	
				21-30 units	38	385	0.96 (0.67-1.38)	
				>30	24	159	1.57 (1.01-2.45)	
[36]	Arndt, et al. 2004	693	17135§	None	68	1793	1.52 (1.13-2.08)	Age, nationality, smoking
				Occasional	187	7454	1.0	
				1-30 g/day	43	1344	1.05 (0.75-1.46)	
				31-60 g/day	128	3210	1.13 (0.90-1.42)	
				61-90 g/day	105	1651	1.63 (1.28-2.08)	
				>90 g/day	162	1713	2.31 (1.86-2.87)	
[37]	Odegaard, et al. 2011	1971	593118	Light to moderate intake (1-14 drinks/wk)			1.0	Age, age at diagnoses of diabetes mellitus or cardiovascular disease, sex, dialect, year enrolled, education, marital
				None or >2drinks			0.82 (0.73-0.92)	

Ref	Author	No. of cases	No. of controls (cohort)	Stratification (amount or frequency)	No. of cases	No. of controls (cohort)	RR (95%CI)	Adjusted variables
								status, and energy intake.

† All-cause mortality
‡ Stroke relative risk
§ Number of cohort

Table 17. Summary of study results on smoking status for disease or mortality risk

Ref	Author	Control selection	Country	Age	Study period	Outcome	No. of cases	No. of control (cohort)	Comments
Cohort study									
[38]	Wen, et al. 2006.		China	40-70	1997-2004	All-cause death Overall cancer death	2464 1238	191375 191375	The Shanghai women's health study, China; Source of environmental smoking among never smoking women
[39]	Gupta, et al. 2005		India	≥35	1992-1999	All-cause death Overall cancer death	4119; 3412 234; 244	210129 (M); 323316 (F)	Cohort study conducted in the island city of Mumbai, India; Never smoking vs ever smoking (types of tobacco among smoker)
[40]	Ramadas, et al. 2010		India	≥34	1996-2004	All-cause death Overall cancer death	10131	1 060 067	A cluster randomized controlled oral cancer screening trial in Kerala, India; Never smoking vs ever smoking
[41]	Shankar, et al. 2008		Singapore	45–74	1993-2005	All-cause death Overall cancer death	4706; 3276 2741; 2512	27292 (M); 34028† (F)	The Singapore Chinese Health Study, Singapore; Never smoking vs ever smoking
[42]	Chao, et al. 2002		USA	≥30	1982-1996	Stomach cancer death	996; 509	5,980,051 (M); 7,913,543 (F)	The Cancer Prevention Study II (CPS II), USA; Never smoking vs ever smoking

[43]	Mozaffarian, et al. 2009	USA	≥65	1989-1998	DM incidence	337	34539	The Cardiovascular Health Study, USA ; Never smoking vs ever smoking

† No. of cohort

Table 18. Relative risk and its 95% confidence intervals in previous studies smoking status and disease or mortality risk

Ref	Author	No. of cases	No. of controls (cohort)	Stratification (amount or frequency)	No. of cases	No. of controls (cohort)	RR (95%CI)	Adjusted variables
Cohort study								
[38]	Wen, et al. 2006.	All-cause 2464 Overall cancer 1238	191375 191375	**All-cause mortality** Husband Workplace In early life All 3 sources **Overall cancer mortality** Husband Workplace In early life All 3 sources	1152 730† 582 586 358†	65180 66520† 59675 65180 66520†	1.11 (0.99-1.25) 1.08 (0.91-1.28) 0.98 (0.85-1.14) 1.15 (0.95-1.41) 1.08 (0.91-1.27) 1.19 (0.94-1.50) 0.79 (0.63-0.98) 1.06 (0.80-1.40)	Education, occupation, family income, physical activity, body mass index, and intake of meat, vegetables, fruit
[39]	Gupta, et al. 2005	4119; 3412	210129; 323316	**All-cause mortality** Never tobacco use Smokeless tobacco v never Fume-tobacco v never **Overall cancer mortality** Never tobacco use	M854 F 907 M1787 F 2470 M1478 F 35 M40 F 65	55717 130294 96884 191625 57528 1398 55717[M] 130294[F]	1.0 1.0 1.16 (1.06-1.26) 1.25 (1.15-1.35) 1.55 (1.42-1.69) 1.40 (0.99-1.97) 1.0 1.0	Age, education

Ref	Author	No. of cases	No. of controls (cohort)	Stratification (amount or frequency)	No. of cases	No. of controls (cohort)	RR (95%CI)	Adjusted variables
				Smokeless tobacco v never	M91 F 177	96884 191625	1.40 (0.95-2.06) 1.57 (1.16-2.13)	
				Fume-tobacco v never	M103 F 2	57528 1398	2.60 (1.78-3.80) 1.85 (0.45-7.60)	
[40]	Ramadas, et al. 2010	10131	1 060 067	All-cause mortality				
				Never	6370	823946	1.0	Sex, age, chewing habits, smoking habits, alcohol consumption, occupation, education level, vegetables intake, fruits intake, equipment, study group, religion.
				Ever	3751	236121	1.31 (1.24-1.39)	
				Overall cancer mortality				
				Never	622	809913	1.0	
				Ever	470	228307	1.63 (1.37-1.94)	
[41]	Shankar, et al. 2008	4706; 3276 2741; 2512	27292; 34028 27292; 34028	All-cause mortality			M1.50 (1.40-1.60) F 1.70 (1.50-1.80)	Age, dialect group, year of recruitment, level of education, daily ethanol intake, moderate physical activity
				Overall cancer mortality			M1.80 (1.60-2.00) F 1.90 (1.70-2.20)	
[42]	Chao, et al. 2002	996; 509	5,980,051 (M); 7,913,543 (F)	**Male**				
				Never	169	1,558,552	1.0	Age, race, education, family history of stomach cancer, consumption of high-fiber grain foods, vegetables, citrus fruits or juices, and use of vitamin C, multivitamins, and aspirin
				Ever	827	4,421,499	1.68 (1.42-1.98)	
				Female				
				Never	282	4,404,944	1.0	
				Ever	227	3,508,599	1.30 (1.15-1.65)	

Ref	Author	No. of cases	No. of controls (cohort)	Stratification (amount or frequency)	No. of cases	No. of controls (cohort)	RR (95%CI)	Adjusted variables
[43]	Mozaffarian, et al. 2009	337	34539	Never	135	16139	1.0	Age, sex, race, educational level, annual income, physical activity score, dietary score, alcohol use, waist circumference
				Ever	202	18400	0.77 (0.61-0.97)	

† Number of case and number of cohort was summed value for workplace and in early life.

Table 19. Summary of study results on BMI for mortality risk

Ref	Author	Control selection	Country	Age	Study period	Outcome	No. of cases	No. of control (cohort)	Comments
Cohort study									
[4]	Wei, et al. 2011		East Asians and Indian and Bangladesh		9.2 yr†	All-cause mortality	120758	1141609‡	In the cohorts of East Asians, including Chinese, Japanese, and Koreans; The lowest risk of death seen among persons with a BMI in the range of 22.6 to 27.5.
[44]	Matsuo, et al. 2008		Japan	40-79	1993-2003	All-cause mortality	3164(F)	615089 (F)	A total of 38 communities out of 85 in Ibaraki prefecture, in Japanese general population, Japan; The lowest risk of death seen among older female(60-79y) with a BMI in the range of 23.0 to 26.9.
[45]	Tsai, et al. 2011		Taiwan	≥53	1996-2007	All-cause mortality	2462	4440‡	Survey of Health and Living Status of the Elderly in Taiwan (SHLSET), Taiwan; The reference group was person with a BMI in the range or 21.0 to 27.0.
[46]	Manson, et al. 1995		USA	30-55	1976-1992	All-cause mortality	4726	1798993	The Nurses' Health Study cohort, USA; The lowest risk of death seen among persons with a BMI in the range of 22.0 to 24.9 and 25.0 to 26.9.

[47]	Singh, et al. 1999	USA	25-84	1976-1988	All-cause mortality	2364	231173	The Adventist Health Study (AHS), USA; The reference group was person with a BMI in the range or 22.4 to 27.3.

† This means mean follow-up period.
‡ Number of cohort participants

Table 20. Relative risk and its 95% confidence intervals in previous studies BMI and mortality risk

Ref	Author	No. of cases	No. of controls (cohort)	Stratification (BMI, kg/m^2)	No. of cases	No. of controls (cohort)	RR (95%CI)	Adjusted variables
Cohort study								
[4]	Wei, et al. 2011	East Asian†		**East Asians**				
		78467	779537	<15	456		2.76 (1.88-4.07)	Age, sex, educational level, urban or rural residence, marital status, and status with respect to baseline illnesses
		Indian‡		15.1-17.5	3795		1.84 (1.65-2.05)	
		14212	265036	17.6-20	13547		1.35 (1.25-1.45)	
				20.1-22.5	21200		1.09 (1.05-1.14)	
				22.6-25	21391		1.0	
				25.1-27.5	11009		0.98 (0.95-1.01)	
				27.6-30	4679		1.07 (1.02-1.12)	
				30.1-32.5	1623		1.20 (1.10-1.32)	
				32.6-35	484		1.50 (1.31-1.71)	
				35.1-50	283		1.49 (1.31-1.69)	
				Indian and Bangladesh				
				<15	755		2.14 (1.78-2.57)	
				15.1-17.5	2412		1.59 (1.40-1.81)	
				17.6-20	3340		1.26 (1.12-1.41)	

Ref	Author	No. of cases	No. of controls (cohort)	Stratification (BMI, kg/m^2)	No. of cases	No. of controls (cohort)	RR (95%CI)	Adjusted variables
				20.1-22.5	3196		1.09 (0.97-1.23)	
				22.6-25	2349		1.0	
				25.1-27.5	1269		0.98 (0.84-1.13)	
				27.6-30	537		0.94 (0.77-1.16)	
				30.1-32.5	233		1.03 (0.77-1.39)	
				32.6-35	64		0.86 (0.50-1.49)	
				35.1-50	57		1.27 (0.71-2.26)	
[44]	Matsuo, et al. 2008	3164 (F)	615089 (F)	**40-59 y**				Age, alcohol intake, smoking status, alcohol intake (≥66 g/day, <66 g/day), and smoking status (never, former, current <20 cigarettes/day, current ≥20 cigarettes/day)
				<18.5	20	10534	1.77 (1.09-2.88)	
				18.5-20.9	68	58689	1.13 (0.82-1.55)	
				21.0-22.9	88	82259	1.0	
				23.0-24.9	104	77466	1.18 (0.89-1.56)	
				25.0-26.9	72	49348	1.23 (0.90-1.68)	
				27.0-29.9	53	30202	1.46 (1.04-2.05)	
				≥30.0	28	10488	2.23 (1.46-3.42)	
				60-79 y				
				<18.5	226	13154	1.70 (1.46-1.99)	
				18.5-20.9	46	44811	1.17 (1.04-1.33)	

Ref	Author	No. of cases	No. of controls (cohort)	Stratification (BMI, kg/m^2)	No. of cases	No. of controls (cohort)	RR (95%CI)	Adjusted variables
				21.0-22.9	557	65241	1.0	
				23.0-24.9	559	71166	0.97 (0.87-1.10)	
				25.0-26.9	450	53701	1.03 (0.91-1.17)	
				27.0-29.9	357	37784	1.17 (1.02-1.33)	
				≥30.0	116	10246	1.39 (1.14-1.69)	
[45]	Tsai, et al. 2011	2462	4440‡	**53-64 y**				Age, smoking, drinking, exercise, hypertension, diabetes, heart disease, stroke, cancer and kidney disease in ≥53 year-old Taiwanese
				<21			M2.29 (1.11-4.75) F 4.05 (1.59-10.34)	
				21-27			M1.0 F 1.0	
				>27			M1.01(0.37-2.74) F 1.53 (0.50-4.64)	
				65-74 y				
				<21			M2.06 (1.39-3.04) F 1.76 (1.00-3.13)	
				21-27			M1.0 F 1.0	
				>27			M0.60 (0.27-1.31) F 0.62 (0.26-1.49)	
				≥75 y				
				<21			M1.54 (1.15-2.06) F 2.05 (1.44-2.91)	
				21-27			M1.0 F 1.0	
				>27			M0.57 (0.29-1.12) F 0.83 (0.46-1.52)	

Ref	Author	No. of cases	No. of controls (cohort)	Stratification (BMI, kg/m^2)	No. of cases	No. of controls (cohort)	RR (95%CI)	Adjusted variables
[46]	Manson, et al. 1995	4726	1798993	<19	577	230899	1.0	Age in five-year categories, smoking, menopausal status, oral-contraceptive and postmenopausal hormone use, parental history of myocardial infarction before the age of 60
				19-21.9	1054	501081	0.80 (0.70-0.90)	
				22-24.9	1392	565551	0.80 (0.70-0.90)	
				25-26.9	512	196254	0.80 (0.70-0.90)	
				27-28.9	385	114883	1.00 (0.90-1.10)	
				29-31.9	413	105803	1.20 (1.00-1.30)	
				≥32	393	84522	1.50 (1.30-1.70)	
[47]	Singh, et al. 1999	2364	231173	**Male (25-54 y)**				Age
				15.0-22.3			2.00 (0.90-4.20)§	
							0.90 (0.50-1.90)‖	
				22.4-27.3			1.0§	
							1.0‖	
				≥27.4			1.60 (0.70-3.60)§	
							1.50 (0.80-2.60)‖	
				Female (25-54 y)				
				15.0-22.3			1.20 (0.60-2.60)§	
							0.60 (0.20-1.20)‖	
				22.4-27.3			1.0§	
							1.0‖	
				≥27.4			2.00 (1.00-3.70)§	
							1.90 (1.20-3.00)‖	

† Including Chinese, Japanese, and Korean ‡ Indian and Bangladesh § After 1-6 years of follow-up ‖ After 7-12 years of follow-up

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초록

한국인 사망과 관련된 건강행태요인의 통합위험도에 관한 코호트 연구

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연구목적: 한국인에서 비만이나 음주 및 흡연은 암 발생은 물론 사망과도 관련되어 있다고 알려져 있다. 그러나 이들 위험요인의 복합적인 사망 영향에 대해서는 아직 연구된 바가 없다. 본 코호트 연구는 한국인을 대상으로 체질량지수, 흡연, 음주행태의 복합적 조합이 사망률에 미치는 영향을 파악하기 위해 한국 다기관 암 코호트 연구(KMCC)를 이용하여 수행되었다.

방법: 1993 년부터 일반 지역주민을 대상으로 구축되어 장기간 추적되어오고 있는 한국인 다기관 암 코호트의 연구대상자 20,059 명 중 20 세 이상 남녀로 연구가설상의 모든 정보를 가지고 있는 15,740 명을 분석대상으로 하여 건강행태와 사망률과의 관련성을 분석하였다. 체질량지수와 음주 및 흡연의 세 가지의 변수는 기존의 코호트 연구를 통해 얻어진 결과를 기반으로 선정하였다, 복합위험도를 산출하기 위하여 개별 위험요인은 이분화하였는데 위험도가 높은 집단의 기준은 기존의 코호트 연구 결과에 따라 체질량지수 22.6 이하 혹은 27.5 이상인 사람, 흡연자 및 과거 흡연자, 그리고 90gram/week 이상의 음주자로 고위험군을 정의하였다. 복합 위험도는 개별 위험요인 위험도의 합으로 산출하였는데 그 범위는 0 점에서 14 점이었다. 연구대상자 중 사망자의 확인은 2008 년 12 월을 기준으로 통계청 사망자료를 이용하였으며, 동 자료원을 통해 사망의 원인도 입수

하여 ICD-10 으로 분류하였다. 콕스 비례위험모형을 사용하여 건강행태 개별 위험요인과 복합 위험요인의 통합점수에 따른 사망률의 통합위험도를 사망위험비와 95%신뢰구간으로 평가하였다.

결과: 총 145,218.4 인년의 추적기간 중 사망한 사람은 모두 1,094 명이었으며 이 중 암 사망자는 474 명, 순환기계 질환에 의한 사망자는 229 명이었다.

전반적으로 비만한 경우 사망할 확률이 1.47 배(95% 신뢰구간 1.27-1.69) 높았으며, 흡연자의 경우 1.50 배(95% 신뢰구간 1.25-1.79), 그리고 음주자에서 1.36 배(95% 신뢰구간 1.08-1.72) 높았다. 여자에서 음주자가 사망에 영향을 주지 않는 것을 제외하고는 이러한 관련성은 남녀간에 크게 다르지 않았다. 암으로 인해 사망할 확률은 비만한 군에서 1.35 배 (95%신뢰구간 1,10-1.66) 높았으며, 흡연자

에서 비흡연자에 비해 1.75 배(95%신뢰구간 1.32-2.33) 높았으나 음주는 암 사망을 유의하게 높이지 않았다. 남자에서는 비만과 흡연이 암 사망을 유의하게 높였으나, 여성에서는 흡연만이 암 사망을 유의하게 높였다. 비만한 남성의 경우를 제외하고는 모든 경우에서 심혈관계질환에 의한 사망을 높이지 못했다.

이들 개별 위험요인의 다양한 조합에 따라 사망위험도를 분석한 결과, 개별 위험요인의 수가 많아지면 많아질수록 총 사망률은 물론 암 사망률도 유의하게 높아지는 양상을 보였다 (p for trend < 0.01). 즉, 위험요인을 하나도 가지지 않은 사람에 비해 세가지 위험요인을 모두 가진 사람의 경우 사망할 확률은 3.42 배 (95%신뢰구간 1.87-6.26) 높았으며, 암에 의해 사망할 확률은 2.70 배 (95%신뢰구간 1.19-6.15) 높았으나, 심혈관계 질환에 의한 사망은 유의하지 않았다. 통합 위험도를 통합점수로 산출한 결과에서도

통합점수가 높으면 높을수록 사망위험이 증가하는 같은 양상을 보였다.

결론: 한국인의 사망 및 암으로 인한 사망은 과도한 비만, 흡연 그리고 과도한 음주와 같은 건강행태에 의해 기인됨을 재 확인하였으며, 특히 이들 세 가지 위험요인을 모두 가지는 사람의 경우 복합적인 사망 위험이나 암 사망위험은 개별 위험도의 2 배에 달하는 것으로 추정되었다. 질병의 일차예방을 위해 건강행태의 변화를 유발하기 위한 보건교육 및 홍보 캠페인을 수행함에 있어 보다 포괄적인 접근이 필요하다 하겠다.

주요어 : 건강행태, 위험요인, 사망율, 암 사망율, 심혈관계질환 사망율, 통합 위험도, 한국 다기관 암 코호트 연구, 한국인

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