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Atherosclerotic Cardiovascular Disease Risk in Middle-aged according to Health Behavior in Young Adult Period

: Korean Life Course Health Study

청년기 건강행태에 따른 중년기 심뇌혈관질환 위험

: Korean Life Course Health Study를 이용하여

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Abstract

Atherosclerotic Cardiovascular Disease Risk in Middle-aged according to Health Behavior in Young Adult Period : Korean Life Course Health Study

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Life course research has focused on birth, pediatric, adolescent, middle-aged, and elderly people. However, there are few studies on the health of young adults. One of the reasons for the lack of research is that young people are at the healthiest time in human life with a low risk for developing various chronic diseases. However, the importance of health in the younger age, which was relatively less interested, is

increasing. The importance of healthy young people is significant in the following two contexts.

First, many studies in life course perspective has revealed that the health of early life in childhood and adolescence influences the health of the elderly. However, due to the increase in life expectancy, there is a lack of rationale as to whether the health of young adults in their twenties can affect their middle-aged or later health by expanding the perspective of childhood or adolescence as an early life. Prospective cohort studies that follow-up the effects of these behaviors on middle-aged health are needed.

Second, the health of the youth also has important implications in terms of healthcare spending. As a result of the rapid aging of Korea, the number of elderly people who spend a lot of healthcare costs increases. Therefore, healthcare of young adults before middle-age will have a significant impact on reducing future healthcare expenditure in Korea.

Given the fact that smoking and obesity is the most popular un-healthy factors in young adults, prospective cohort studies examining the effect of smoking and obesity in young adults on cardiovascular diseases in middle-age are needed.

The first study was a life course health study that investigated 307,041 participants aged 20-29 who received general health examinations provided by National Health Insurance Corporation for civil servants and private school teachers. Of these, 142,461 men were included in our analysis to investigate whether blood cholesterol at baseline act as an effect modifier in the association between baseline

smoking status and cardiovascular diseases occurred during 1993 and 2015. The results of this study showed that smoking in young adults increased the risk of ischemic heart disease, and stroke, regardless of their cholesterol levels at baseline.

The second study examined the patterns of tobacco use patterns during 10 years, and confirmed what kind of group they formed. I wanted to see how the risk varies. From 1992 to 2004, 60,709 men aged 20-29 years who participated in a screening survey were analyzed. The first smoking status in 1992 was non-smoking, ex- smoking, current smoking (1-9 cig. per day, 10-19 cig. per day, 20 cig. per day or more). The group based trajectory model (GBTM) was classified into five groups according to the change of smoking status after the first smoking status. Compared to baseline smoking-only models, the model considering the change of smoking status according to the trajectory group and mediator measured at the intermediate period showed the best explanation for the risk of cerebrovascular disease. The risk of most cardiovascular diseases was significantly higher in 'Very high steady' group.

The third study investigated the association between baseline body mass index (BMI) of the young adults and the risk of cardiovascular disease. In other words, the study aimed to show how BMI levels measured in 1992-1994 influenced the risk of cardiovascular disease occurred in 2005-2016 through the elevation of blood pressure, cholesterol, and fasting blood glucose measured after 10 years (2002-2004). We found that high BMI of young adults significantly increased blood pressure, cholesterol, and fasting blood glucose after 10 years, which also increased the risk of

cardiovascular disease in their middle-age. Moreover, the effect of BMI of young adults on cardiovascular disease in middle-age was more direct rather than indirect.

Each study confirmed that the smoking habit, one of the high prevalent unhealthy behaviors during youth, has changed in various forms over the past decades, and future studies will need to consider changes in smoking status when analyzing the effect of smoking cessation using longitudinal data.

The high smoking rate and BMI of adolescents were directly related to the occurrence of atherosclerotic cardiovascular disease risk. This study suggests that young adult is an early life of middle-aged health from a life-course perspective. Therefore, it can be said that healthcare is meaningful because it suggests that aggressive lifestyle management of youth is needed for mid-aged health.

Keywords: Young adult, Life Course approach, Cigarette smoking, Body mass index, Obesity, Mediation analysis, Trajectory analysis

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Contents

Acronyms

BMI Body Mass Index

ASCVD Atherosclerotic cardiovascular diseases

TOSTR Total stroke

TRSTR Thrombotic stroke

HRSTR Hemorrhagic stroke

AMI acute myocardial infarction

IHD Ischaemic Heart Disease

SBP Systolic Blood Pressure

FBS Fasting Blood Sugar

GBTM Group Based Trajectory Model

APC Age-Period-Cohort

TE Total effect

DE Direct effect

IE Indirect effect

NDE Natural direct effect

NIE Natural indirect effect

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Chapter I.

Overall introduction:

Significance of young adult health in human life course.

1.1. Life course approach

Life course approach is a framework that views health status of later life as an ultimate outcome affected not only by exposure to risk factors of later life, but also by the entire life course including fetal life, early childhood, adolescence and adulthood (Ben-Shlomo & Kuh, 2002; Chittleborough, Baum, Taylor, & Hiller, 2006; D. Kuh, Ben-Shlomo, Lunch, Hallqvist, & Power, 2003). A life course research is a study design that investigates long-term effects of various exposures throughout life on health (D. Kuh & Ben-Shlomo, 1997), aiming to find the cause of different health outcomes occur in later life as depicted in figure 1.1 (Kalache & Kickbusch, 1997).

Two major conceptual models of life course approach include the critical period model and the accumulation of risk model – explain the association between health exposures in early life and health outcomes in later life (Ben-Shlomo & Kuh, 2002).

The critical period model emphasizes the timing of exposure with two sub-models: 'the model with or without later life risk factors' and 'the model with later life effect modifiers'. Critical period is when an exposure during a specific period of development has lifelong effects on the structure or function of organs, tissues and later life factors may modify this early risk (Frankel et al, 1996).

The accumulation of risk model focuses on the significance of during life course and the sequence of exposure, which is divided into 'the model with independent and uncorrelated insults' and 'the model with correlated insults' (Rosvall, Chaix, Lynch, Lindström, & Merlo, 2006).

1.1.1. Population aging

Globally, population aging becomes an important demographic and policy issue. Nearly two-thirds of the Organization for Economic Co-operation and Development (OECD) member countries have predicted that the aged over 65 elderlies will account for 25% of the overall population by 2050 (OECD, 2015). Especially, Korea is one of the fastest-aging countries in the world.

Population aging is associated with multi-level issues in terms of health. At national level, heavy burden of social welfare services, cost of public pension, and healthcare costs for seniors will lead to an increase in national health expenditures.

Due to the current trends in aging, policy makers focus on health and social issues facing the elderly such as long-term care service, health care and welfare. From a life course perspective, health status in elderly is an outcome of the health accumulated throughout the entire life, especially during the critical period in early life and adult life.

1.1.2 Significance of young adult health in the context of life course approach

The critical period model in life course approach usually consider fetal life, early childhood, or adolescence as an early life period when growth and development process is ongoing.

Despite the lack of interest in the health of young adults, we may need to explore the significance of young adult health given the extended life expectancy. Therefore, this study hypothesized that young adult period can be an another critical period in life course

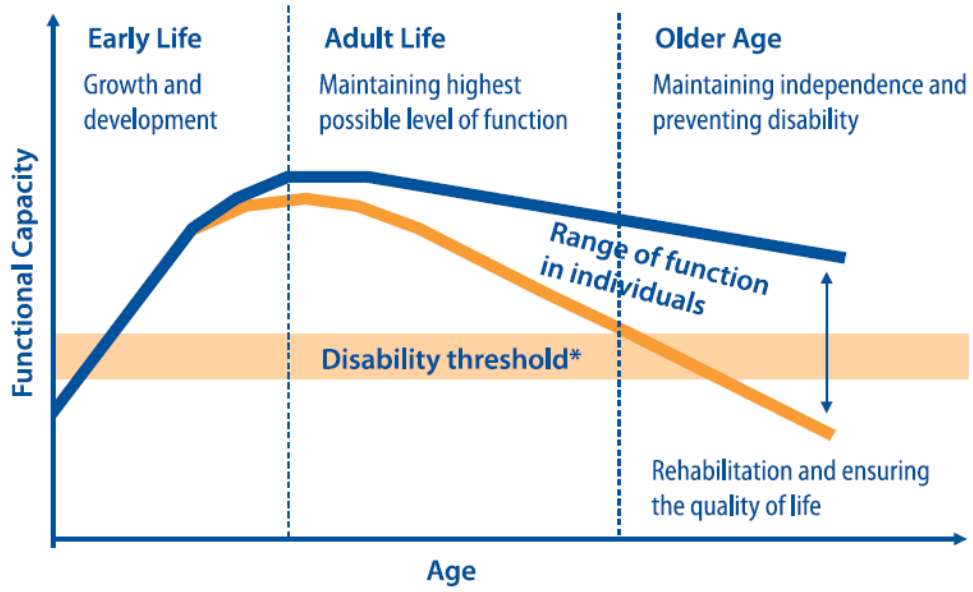


Figure 1-1. A life-course perspective to maintain the highest possible level of functional capacity (*Source*: Kalache and Kickbusch, 1997**;** Quoted and modified in WHO (2002), Active aging: a policy framework)

1.2. Needs of ecological understanding on young adult's health

Since young adults are generally regarded as the healthiest age group in human life course, young adults have a low risk perception of various chronic illness. The health of young adult years has received less attention, while there were many previous studies on health of the middle-aged adults or elderly, and adolescents. Young adults are often grouped together with adolescents. However young adults should be distinguished with adolescents in terms of risky behaviors, health outcomes and access to care. The key health issues among young adults are in the extension line from the adolescence such as injury, homicide, substance use in risky behaviors.

1.2.1. Contextual Framework for Young adult health

Two main social context influences the shape of young adult health include a prolonged transition to adult roles and enhanced responsibilities and the weakening of the safety net that protects adolescents or younger children. In Korea, the age of 19 can legally gain adult privileges. In reality, however, many young adults do not carry out adult roles and responsibilities for first few years while seeking for exploration and stepping toward independence. These periodical features in young adulthood have significant implications for risky behaviors.

Arnett described the characteristics of young adult period in the following way. "Young adult is the period for exploring significant identity with greater freedom and fewer constraints in the context of diminished parental surveillance. Therefore, risk behaviors in young adult period can be understood as a reflection to the desire to obtain a wide range of behavior before settling down. (Arnett., 2000)."

Schulenberg et al reviewed various events and paths to adulthood in young adult period involving college entrance/graduation, military service, parenthood, and marriage. Each event gives different significance for health in the sense of constraints and role expectations. In the context of substance use, risky behaviors can either increase by diminished parental surveillance, or decline by marriage, parenthood and employment (Schulenberg., et al 2005).

Transition to adulthood in young adult period is often influenced by periodical events such as major socio-economic transformations. For instance, transitions to postindustrial economy and changes in women's social participation have changed the timing of young adult transitions including leaving home by economic independence, entering or graduating school, entering the workforce, and forming a family (Arnett JJ., 2000; Settersten et al., 2005; Mortimer & Larson., 2002; Kerckhoff., 2002; Brown., 2004). In fact, this period of transition is related to weaken safety net or supportive institutions, organizations and networks that used to supervise them in adolescent period.

Unlike adolescents who are mostly under parental protection and enrolled in school, young adults begin to have various social economic status. While three-quarters of young adults have continue their academic work in colleges, some young adults start economic activities or enter the military [Rumbaut., 2005; Jekielek ., 2005]. Young adults who did not engage in college education without any socio-economical or parental support are more likely to exposed to unhealthy lifestyle or risky behaviors [Halperin., 1998]. Rapid transition to adulthood make some young adults suffer with diminished parental and institutional support, often resulting in mental health problems or offer special health care needs [Osgood et al., 2005].

Definitions of young adult age period was varied by different studies. In order to view previous studies and definitions regarding young adults, scoping review of electronic databases such as PubMed, Cochrane library and Embase was conducted using search terms including "young adult, "early adult". "emerging adult" and "age". Throughout the scoping review, several studies were selected as a main reference papers to help decision making on defining young adult age.

Park and her colleagues defined young adulthood as ages 19-24 years, since age 18 is the year of high school and regarded as age which most young people begin steps to achieve independence until age 24 in United States society. Park categorized late 20s differ from early 20s on several social indicators, such as employments and school enrollment (Park et al., 2006). In reality, United States census data in year 2000 counted 27.1 million young adults aged 18-24 years.

However, social context in Asian society was differed from western context.

Soga and his colleagues conducted a study using data from the Kobe City Young Adult Health Examination. They defined young adulthood as ages 30-39 years. Alden and his colleagues conducted a study comparing the preferences for physician decision-making style in Japan and the United States, defining the age range of young adults on age 18-30 [Alden et a., 2012].

Based on previous literature review and considering the uniqueness of young adults in Korean society, features of the cohort that majority of participants are private school staff and civil servants, I defined young adults as ages 29 to 29 in baseline period 1992 to 1994. Since age 18 to 24 in Korea is too young in Korean society that most of them are students. And in the context of sensitivity analysis, several additional analyses were conducted by extending the age range as 20 to 39.

1.2.2. Tobacco use among young adults

Smoking is a well-known risk factor for various noncommunicable diseases (NCD) including cancer, cardiovascular and respiratory disease (Centers for Disease Control and Prevention, 2004). The majority of tobacco users start smoking during young adulthood. Tobacco contains more than 4,000 chemicals, at least 250 hazardous substances, and approximately 50 carcinogens, highly addictive ingredients such as nicotine, caused many young people to progress from occasionally smoking to daily or heavy smoking (CDC, 2006; WHO, 2014). Annually, 6 million smoking-related deaths are reported, and the projected number of smoking-

related death until 2030 will increase to more than 8 million per year (WHO, 2014).

Smoking habits initiated in young adulthood is closely associated not only with subsequent smoking intensity including the amount and frequency of tobacco smoking, difficulties in smoking cessation, and high nicotine dependency (Breslau & Pererson, 1996; Chen & Millar., 1998; Fernandez et al., 1999; Khuder et al., 1994; Lando et al., 1999; Park et al., 2004), but also with other risk behaviors and negative health/social consequences such as alcohol and/or illicit drug use, academic problems, mental health problems, violence, and risky sexual behaviors (Ellickson et al., 2001; Mathers et al., 2006; Park et al., 2004).

Jee and Cho identified the contributions of age, period, and birth cohort effects on smoking prevalence in Korean young adults aged 20 to 30 (Jee and Cho, 2016). For men, subjects aged 19-22 showed rapid increase in smoking prevalence and the increase slowed down around the age of 23-30. Smoking prevalence among young adults during 2008 to 2010, while it was stabilized during 2011 to 2013. Smoking prevalence declined among birth cohorts prior to 1988 but stabilized in those who were born after 1988. In Age-Period-Cohort (APC) model, smoking prevalence increased with age in the 1988 to 1991 birth cohort. Specifically in this cohort, smoking prevalence at age 19 to 20 years was approximately 24% and increased to 40% when the subjects turned 23 to 24 years.

Previous studies reported clinical evidence that harmfulness of smoking in young adults in later life. A report from the Surgeon General revealed that smoking in young adulthood for a few years can also show signs of narrowing this artery since

one breath of smoking cause immediate damage to blood vessels throughout the body (Surgeon General Report, 2012; WHO Fact sheet, 2017).

Since young adults tend to have relatively low risk in metabolic risk factors for chronic disease such as hypertension, diabetes, and hyperlipidemia, modifiable lifestyle factors such as cigarette smoking may be the most important for various chronic disease.

1.2.3. Obesity in Young adults

The prevalence of overweight and obesity rapidly increased in both developed and developing countries in recent decades (WHO, 1998; Finucane et al., 2011; Stevens et al., 2012).

Although, the prevalence of obesity in Asian populations is lower than that of Western populations, obesity have been reported to occur at a lower body mass index (BMI) in Asian people (International Obesity Task Force, 1999).

South Korea has experienced rapid socioeconomic growth over the last few decades, which led to prominent nutrition transition and greatly increased burden of chronic diseases, such as obesity (Park et al., 2008) and type 2 diabetes (Yoon et al., 2006). Kwon and his colleagues reported that the prevalence of obesity (BMI≥30 kg m^2) increased 2.5-fold in men and 2.3-fold in women between 1992 and 2000 (Kwon et al., 2007). According to the study conducted by Park et al, the prevalence of men with BMI of 30 kg m^2 or over increased from 1.8% to 2.8% between 1998 and 2001

(Park et al., 2008).

The association between high BMI and increased risk of cardiovascular disease (CVD) have been reported in several prospective cohort studies (Wormser et al., 2011; Whitlock et al., 2009; Ni Mhurchu et al., 2004). A growing body of evidence showed that adipose tissue acts as an active endocrine organ and releases pro-inflammatory cytokines, which may have a critical impact on endothelial dysfunction, induce low-grade systemic inflammation, and effect fibrinolysis (Van Gaal et al., 2006; Poirier et al., 2006).

A high BMI also leads to increase of intermediate risk factors of cardiovascular disease (CVD) such as hypertension, diabetes and hyperlipidemia (Kim et al., 2014; Kim., 2016; Deurenberg et al., 1998; Rhee et al., 2018). Since increased level of fasting blood glucose and cholesterol is a previous stage before the actual incidence of CVD, management of these intermediate risk factors in early life is important in the terms of prevention for CVDs. Studies reported the association between high BMI in young adulthood period and increased risk of CVD in middle age (Murray et al., 2015; Gooding et al., 2016; Berry et al., 2012; Lloyd-Jones et al., 2006; WHO., 2000; Parsons et al., 1999; Must & Strauss, 1999).

1.3. Methodological approaches to reflect the changes in exposure in longitudinal data

According to Twisk's classification, epidemiological studies are generally divided into observational and experimental studies (Twisk, 2013). While observational cohort studies can be further divided into prospective, retrospective and cross sectional cohort studies, Twisk classified prospective cohort study as an only cohort study that can be characterized as a longitudinal study.

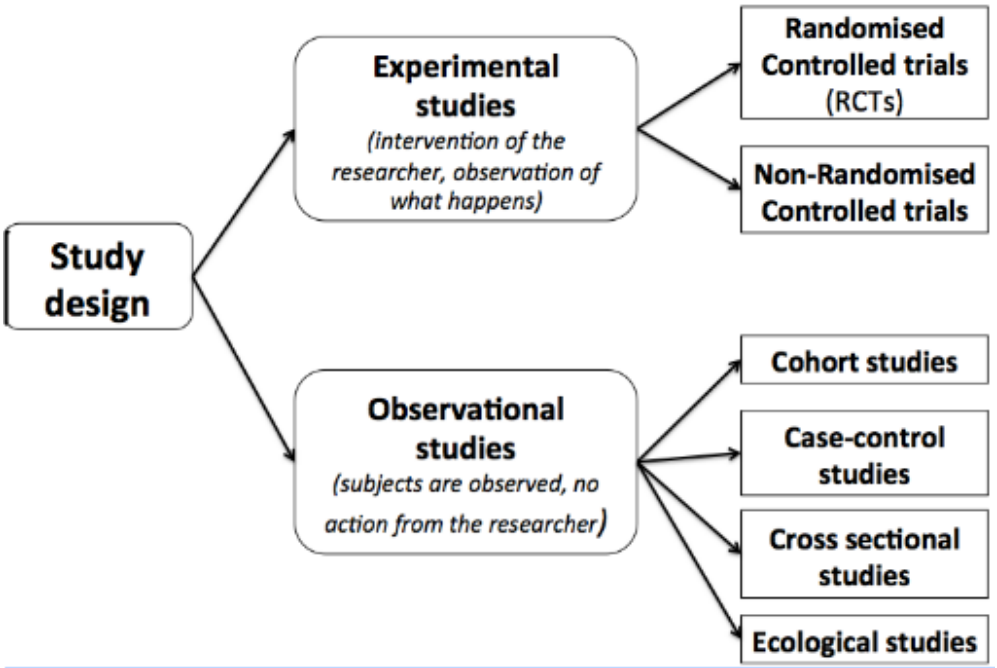


Figure 1-2. Schematic illustration of different epidemiological study designs.

Prospective cohort studies were usually designed to analyze the longitudinal development of a certain exposure throughout the follow up period. In prospective longitudinal studies following individual development, each variable measured at a particular time-point is influenced by three main factors.

(1) age (time from date of birth to date of enroll, measurement)

(2) period (time or moment at which the measurement was taken)

(3) birth cohort (group of participants born in the same year)

Extensive amount of previous studies using cross sectional data used classical age-period-cohort model to problem of identification caused by co-linearity among age, period, and cohort (age+cohort=period) (Clayton et al., 1987; Clayton et al., 1987) was solved by using intrinsic estimator (IE) method.

The data collected through a longitudinal study also face challenges in the health status or exposures during life course. Longitudinal studies should be designed to reflect the changes in time varying exposure over time, in order to empirically demonstrate a causal association.

Therefore, throughout the studies in my thesis I will compare three different methodologies to reflect the changes in exposures: Group Based Trajectory analysis (Chapter III) and Mediation analysis (Chapter IV).

1.3.1 Time dependent analysis

In longitudinal studies like survival analysis, time-dependent factors that are immeasurable in baseline cannot be recorded at baseline, and change in value occurs during follow up time. Such variables are called "time-dependent value" since their value change over time (Walraven et al., 2004). Time dependent variables can be divided to two categories; "baseline measurable" time dependent variables and "baseline immeasurable" time variables.

"Baseline measurable" time dependent variables are variables that can change over time but are measurable at baseline like systolic blood pressure or body mass index. Researchers usually give fixed value on these baseline measurable time dependent variables.

"Baseline immeasurable" time dependent variables are variables cannot be measured in at baseline and occur during observation. Biased estimates can occur when fixed value on baseline immeasurable is given. Glesby and Hoover named this bias as a "survivor treatment selection bias (Glesby & Hoover, 1996)." "Time dependent bias" or "immortal time bias" is used more generally since survivor treatment selection bias is not limited to treatment variables (Levesque et al., 2010). Since participants in longitudinal observational studies can choose to when to get treatment or to get exposed to certain exposure, participants who survive are more likely to select treatment. Bias from time dependent bias has been previously reported in the context of disease screening and prevalent longitudinal cohort analysis (Cole & Morrison, 1980; Brookmeyer et al., 1987).

One approach for handling time dependent bias is to classify patients in the baseline and then to ignore subsequent changes in treatment status. Although this approach can partly solve the problem of time dependent bias, conservatively biased estimate or treatment effect still remains (Glesby & Hoover, 1996).

Another approach is using multivariate regression techniques to adjust or control simultaneously the effects of multiple factors on the outcome of interest. Using proportional hazards model enables eliminating the time dependent bias by adjusting time-dependent covariate; value in the model is allowed to change with the time component in the model (Lundgren et al., 1994; Kopec-Schrader et al., 1993; Gallant et al., 1996).

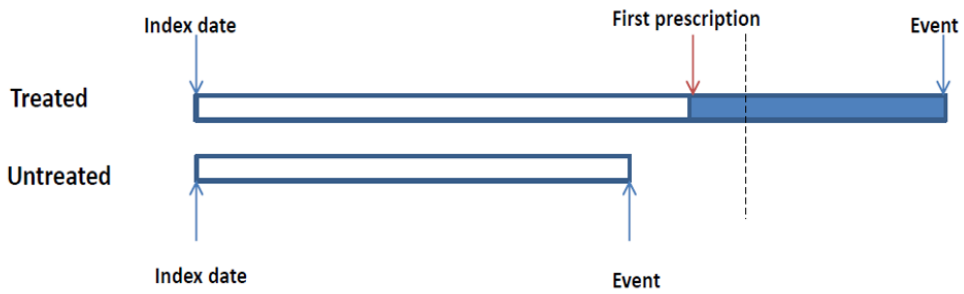


Figure 1-3. Schematic illustration of time dependent bias (Levesque et al., 2010)

1.3.2 Group Based Trajectory Analysis (GBTM)

Trajectory analysis is one of popular method to handle the repeatedly

measured data in longitudinal prospective cohort. Although longitudinal studies are conducted to depict and explain the changes in the outcome over time, conventional cohort studies that merely explained the outcome by exposure once measured in the baseline has certain limitations to explain the exposure or health status during life course.

Developmental trajectory describes the course of such outcome over age or time. In the perspective of analyzing developmental trajectories, most statistical approaches focused on explaining individual changes about population trend represented by the mean value. However longitudinal analysis faced challenges to eligibly divide the meaningful sub-groups that show the distinctive trajectories which reflect the individual characteristics (Nagin, 2005).

In order to create inevitably subjective meaningful sub groups, researchers used a mixture of analysis, however merely mixing several analysis methods still had remaining statistical risk such as producing the sub-groups which reflect only the random variation, and neglecting significant but uncommon trajectories (Nagin, 2005). Rather than blending analytical methods, two major analytical methods; multilevel model and latent curve model (MacCallum, Kim, Malarkey, & Kiecolt-Glaser, 1997) were used to analyze the developmental trajectories within individual level. Those two models both are based on continuous distribution functions like mean and covariance matrix used for population distribution of dependent variable in unconditional models.

Over the past decade studies of developmental trajectories in psychology,

medicine that applied a alternative method called group-based trajectory modeling (GBTM) by (Nagin, 2005, 1999) or growth mixture modeling (GMM) by Muthen (Muthen., 2001). GBTM is conducted to investigate similar patterns of change in developmental trajectories with multinomial modeling strategy (Nagin, 1999).

In epidemiological studies, trajectory analysis were used to understand the etiology and developmental change of disorders (Dekker et al., 2007; Mora et al., 2009), post-traumatic stress disorder (Orcutt et al. 2004) and substance use (Hu et al., 2008).

1.3.3 Mediation analysis

Mediation analysis is another analysis which a researcher can consider when exposures and mediators vary over time. How the cause and certain initial states lead to particular outcome through a process or a series of process involving set of mediator and intermediate stages is the basic conceptual mechanism of causal mediation analysis (VanderWeele, 2015). The use of mediations analysis has become quite common in social sciences to explain biological and social mechanisms and inform how to make policy by intervention.

Casual mediation analysis yield allow valid inferences for natural direct effect and natural indirect effect under assumptions that the covariates between (1) exposure-outcome, (2) mediator-outcome, and (3) exposure-mediator relations, and (4) none of the mediator-outcome confounders affected by the exposure.

Baron and Kenny (1986) were those who advocated the traditional (classic) mediation analysis approach based on regression analysis. More recently, causal mediation analysis became popular to supplement the limitations from regression based analysis. Assuming certain identification conditions, approach based on causal inference yields to define direct and indirect effects and decomposition of total effect into a direct and indirect effect even when interaction and non-linearities exist.

1.3.3.1 Classic approach to mediation analysis

Two different method exists to estimate the indirect effect in the classical approach to mediation analysis which are known as difference method and product method. Figure 1-3 depicts the concept of these two methods by using the example used in Chapter IV. BMI is defined as a continuous exposure variable and obesity as a binary exposure variable. Two kinds of mediator variables are also used in this example there as SBP, FBS, and TC are defined as continuous mediator variables, while hypertension, diabetes and dyslipidemia are defined as binary mediator variables. ASCVD was defined as a binary outcome. Total effect from the exposure to outcome is named as θ_0. θ_0 can be decomposed to direct effect and indirect effect.

As mentioned above, difference method and product method are the two different methods used to estimate the indirect effect. On the other hand, there is only one method exists to estimate the direct effect. That is, direct effect is estimated as the effect of exposure when the mediators are adjusted in the model. Direct effect is

named as θ_1. The process of estimating the indirect effect is described as follows (figure 1-3).

Difference method: Indirect effect using difference method estimates the indirect effect by subtracting the direct effect θ_1 from the total effect θ_0. This method seems to look very simple, but can only be used under special assumptions when there is no interaction between exposure and mediator, and when both variables are continuous. In other words, if interaction exists between binary exposure variable and binary outcome variable, the indirect effect estimated by difference method and product method does not match.

Product method: Product method estimates the indirect effect by multiplying the $\beta 1$ and θ_2. Here $\beta 1$ is estimated by regression analysis when mediator is the dependent variable. As mentioned above, there are limitations in using the product method when exposure and mediator are binary variables.

Overall, the classic approach has limitation when two or more mediators are included in parallel or in series. An approach aiming to improving this limitation is the counterfactual approach.

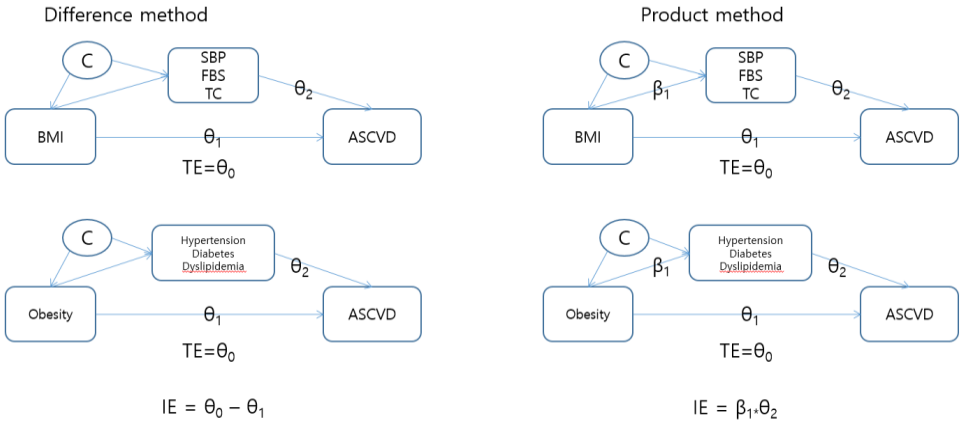


Figure 1-4. Classic approach to mediation analysis

1.3.3.2 Counterfactual approach to mediation analysis

Conceptualization of counterfactual variable is required for appropriate understanding of direct effect. “Counterfactual outcome” or “potential outcome” *Y*, which denotes the outcome that is possibly contrary to fact have observed for that subject had the exposure A been set to the value a through some intervention or manipulation (Rubin, 1978; Hernan 2004). If the exposure A is dichotomous, the causal effect of the exposure on the outcome can be defined as the expected difference between both counterfactual outcomes. In other words, we define conditional casual effect of exposure level 1 versus 0 on the outcome, when pre-exposure covariates C are given.

Total effect requires following 2 assumptions to be made. First, consistency assumption states that the observed exposure level is equal to the potential outcome.

The next assumptions needed to state is referred as “no unmeasured confounders assumption”. When we have three random variables A, B and C, let A ⊥ B|C, when A is conditionally independent of B, given C. We can assume that different exposure level A, but the same pre-exposure characteristics C, are comparable

$$Yam \perp A|C$$

$$Yam \perp M|C$$

NIE and NDE requires following 2 assumptions to be made.

$$Ma \perp A|C$$

$$Yam \perp M^*|C$$

This assumption states that exposure level A is possibly associated with pre-exposure characteristics C, and has no residual dependence with pre-exposure characteristics. In other words, variable C are the only confounders of the association between exposure and outcome.

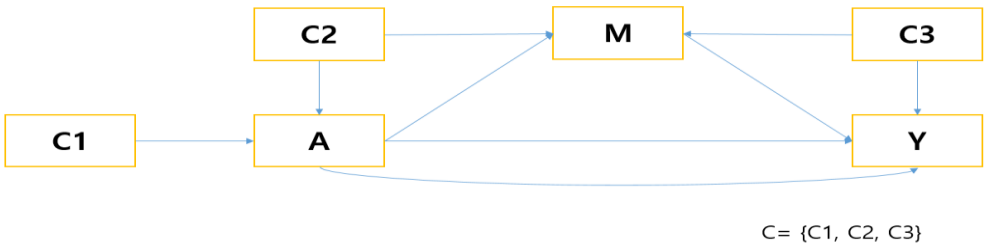


Figure 1-5. Assumptions needed to estimate total effect.

1.4. Study framework and main objectives

The main research objective is to provide evidence that health in young adult period may be a significant period and its importance was relatively underestimated in previous studies.

The thesis consists of three sub-studies. All sub-studies used prospective cohort data, investigating the association between smoking behavior, BMI and the incidence of ASCVD.

The specific research objectives are listed below:

Hypothesis 1. *Smoking in young adult period affects the risk of ASCVD.*

I aimed to examine the effect of smoking on risk of ASCVD in Korean young adults with relatively low serum cholesterol levels. I also investigated whether the effect of smoking can be modified by serum levels of cholesterol.

Hypothesis 2. *Trajectory of smoking status would change throughout 10 years and the change of smoking status would be associated with the incidence of ASCVD among Korean young adult men.*

My aim was to analyze the trajectory of smoking in young adults and analyze the effects of the trajectory group on incident ASCVD.

Hypothesis 3. *High BMI in young adults increases not only the risk of metabolic mediators in the middle age but also the risk of ASCVD.*

A growing concern is that for young adults, cigarette smoking and obesity may be the leading cause of ASCVD, given their high prevalence of cigarette smoking and low levels of metabolic risk factors, including hypertension, diabetes, and hypercholesterolemia. Therefore, the study aimed to examine the effect of smoking and BMI on the risk of ASCVD in Korean young adults using life course health approach (figure 1-5).

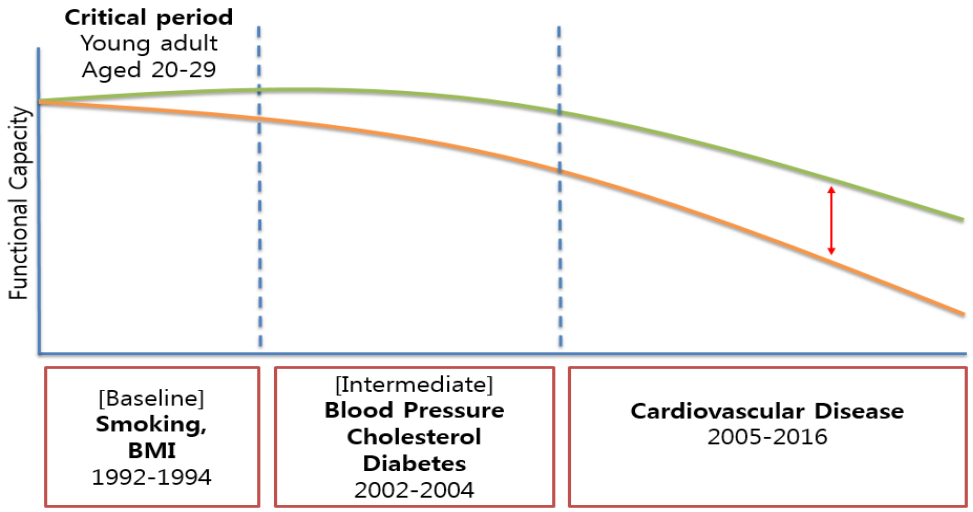


Figure 1-6. Conceptual framework of chapter 3 and 4 using life course health approach

Chapter II.

Smoking and atherosclerotic cardiovascular disease risk in young men: The Korean life course health study

2.1. Introduction

Atherosclerotic cardiovascular diseases (ASCVD) are the leading cause of death globally, with more people dying from ASCVD than any other causes of death annually. A total of 17.7 million people died as a result of ASCVDs in 2015 globally, comprising 31% of all deaths. Of these deaths, 7.4 million are estimated to have been the result of coronary heart disease, whilst 6.7 million were due to stroke (WHO Report., 2018). According to previous studies published in the western countries, tobacco use has been reported to be a major risk factor for ASCVD following hypertension (WHO Report., 2018).

A growing concern is that for young adults, cigarette smoking may be the first leading cause of ASCVD, owing to the high prevalence of cigarette smoking in comparison to lower levels of alternate risk factors, including hypertension, diabetes, and high cholesterol levels. However, despite these observations, there remain only a small number of studies considering the relationship between smoking and ASCVD in Korea and other countries in East Asia (Jee et al., 2004; Yuan et al., 1996; Liu et al., 1998; Niu et al., 1998).

Further, comparisons with Western populations may be less informative owing to the relatively lower levels of cholesterol commonly present in Asian countries. Biological studies have explored the interaction between smoking and serum cholesterol levels (Robertson et al., 1977; Lawlor et al., 2008; Hozawa et al., 2007; Nakamura et al., 2009). Nevertheless, very few studies have analyzed the interaction effects of smoking and serum cholesterol on ASCVD in young adults.

'World No Tobacco Day 2018' is a campaign, with the primary objective of raising awareness of the link between tobacco use and negative health outcomes, predominantly heart and other cardiovascular diseases (CVD) including stroke. It will also seek to expand the range of potential strategies key public actors such as governmental and public bodies can take to reduce the health risks of tobacco use. If there is an established link between tobacco smoking in young adults and CVD, the campaign will further increase awareness on smoking in young adults. The government and the public can then subsequently take actions to reduce risks of smoking at earlier stage. Unfortunately, however, the association between smoking and CVD in young adults has not received much attention because at least a long term (over 20 years) follow-up study is needed. This serves as motivation for this study, in which we aimed to examine the effect of smoking on risk of ASCVD in Korean young adults with relatively low serum cholesterol levels. We also investigated whether the effect of smoking can be modified by serum levels of cholesterol.

2.2. Materials and methods

2.2.1. Study participants

In Korea, the Korean Medical Insurance Corporation (KMIC) provided health insurance for private school staff and civil servants prior to the current insurance system, under which it was integrated as National Health Insurance (Jee et al., 2004). A total of 4,862,438 (10.7%) of the Korean population were covered by KMIC insurance, of which 1,297,833 were employees, and 3,364,605 were dependents. All insured participants are required to participate in a biennial health checkup (Jee et al., 2004). Approximately 94% of the insured participants in 1992 and 1994 were examined biennially. We established a prospective cohort for participants (aged 20-29) who routinely responded to the questionnaire on disease risk factors and chronic diseases, naming this study the Korean Life Course Health Study (KLCHS). The KLCHS cohort included 307,041 Koreans (142,461 males, 164,580 females) who were screened by KMIC in 1992 and 1994. Of these participants, 205,840 (67.0%) were registered in 1992 and 101,201 (33.0%) were registered in 1994 (figure 2.1).

Of these 307,041 participants, 71,760 (23.4%) who had incomplete data height, blood pressure, fasting glucose, total cholesterol, or body mass index were excluded. We also excluded 6,170 people from our analysis who reported a past history of cancer and ASCVD, as well as 2,091 people who had missing information on smoking, exercise, or alcohol drinking, and 65 people who died before start of follow-up. Female participants were excluded, because of the low prevalence of

smoking for females in Korea, resulting in a total of 118,531 eligible participants for the analysis. The study proposal obtained an approval by the Institutional Review Board of Human Research, Yonsei University (4-2001-0029). This study was a retrospective cohort using past routine laboratory data and did not receive consent.

2.2.2. Data collection

The biennial KMIC screening was provided at local hospitals by medical practitioners according to standard protocols. During the two-year interval examination from 1992 to 2008, we examined the variables related to the lifestyle of participants, such as daily smoking amount, duration of smoking, and variables related to drinking. From data collected at baseline, participants were defined as 'current smokers' if they were smoking currently, 'never smokers' if they had no prior history of smoking, and 'ex-smokers' if they had previously smoked but at the time of measurement did not smoke. Current smokers were further categorized by amount of cigarettes consumed on average per day (1–9, 10–19, and 20 or greater) as well as duration of smoking (1–9, 10–19, and 20 or more years) following the example of previous studies (Jee et al., 2004; Jee et al., 1999; Jee et al., 2007).

The definition of hypertension was a systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg.12 Body mass index (BMI) was measured as weight (kg) / height (m)2. Serum total cholesterol was grouped as desirable (<200 mg/dl), borderline-high (200-239 mg/dl), and high (≥240 mg/dl).13 Definition of diabetes was fasting blood glucose ≥ 126 mg / dl.14

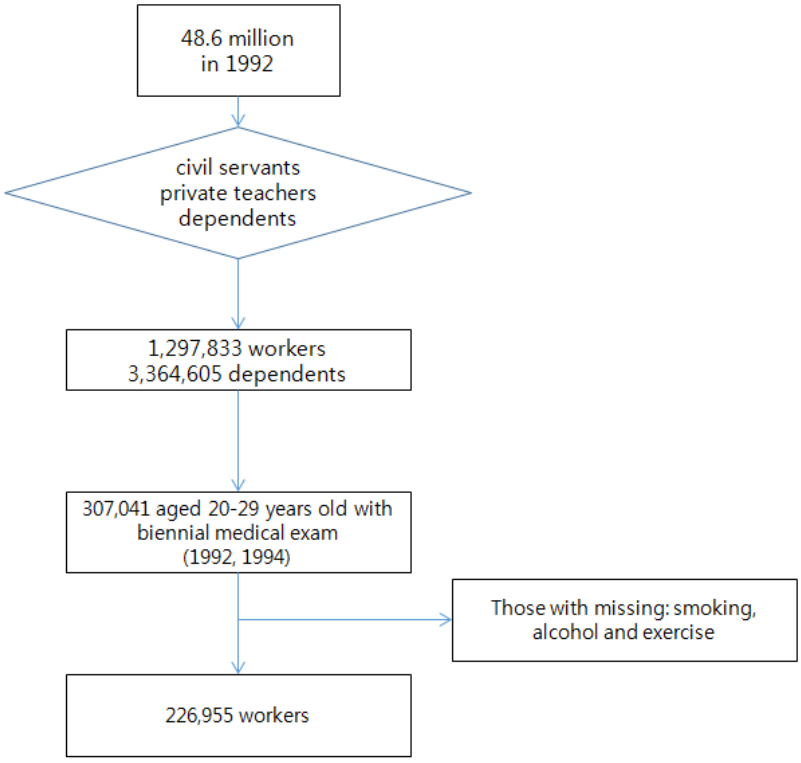


Figure 2.1. Flow chart of Korean Life Course Health Study

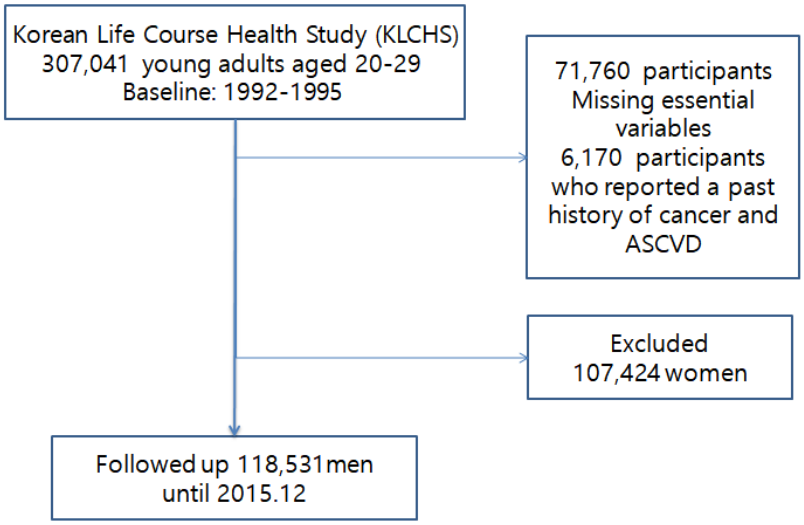


Figure 2.2. Inclusion/exclusion criteria of the participants from Korean Life Course Health Study

2.2.3. Follow-up and outcomes

The main outcome variables used in the analysis were morbidity and mortality categorized by IHD, stroke, and ASCVD. For IHD, alone (ICD 10 codes, I20–I25), acute myocardial infarction (AMI) alone (I21), and angina pectoris (AP) alone (ICD 10 codes, I20) are used. For stroke, stroke alone (I60-I69) was used. Finally, with regard to ASCVD, we used total ASCVD, including disease of hypertensive (I10–I15), ischemic heart disease (I20–I25), all stroke (I60–I69), other heart disease (I44–I51), sudden death (R96), and other vascular disease (I70–I74).

The study outcomes were identified through diagnosis information recorded in hospital admission, and from causes of death using death certificates. The study follow-up was nearly 100% complete, as we were able to search ASCVD event data electronically by KMIC registrants regarding the morbidity information of ASCVD. The period of follow-up was 23 years from January 1st, 1993 to December 31st, 2015. Data on causes of death were available during years 1993–2015, and incidence could be tracked during years 1995–2015. The time frames over which these outcomes could be assessed varied with data availability (Figure 2.3).

A validation study was conducted by 20 internists from the Korean Society of Cardiology in 2009 (Kimm et al., 2012) For the participants who provided written permission for the use of their personal information, 673 CHD events between 1994 and 2007 were confirmed with individual hospital medical records, showing that 73% of designated myocardial infarctions were valid. The validation study was updated in

2013 with a value of 93% (Kimm et al., 2013). The validation study on mortality data has not been conducted.

2.2.4. Statistical analysis

First, I examined relationships between smoking status and established ASCVD risk factors at baseline. In considering continuous ASCVD risk factors, we used ordinary least squares regression and coded smoking quantity as an ordinal variable. In this study, the Mantel Haenszel method was applied for dichotomous variables (Breslow., Day., 1980).

To assess the independent effects of smoking on the risk of IHD, stroke, and ASCVD, Cox proportional hazards models were used, controlling for age and the confounding variables such as hypertension, diabetes, high cholesterol, and alcohol drinking. The proportional assumption was also tested utilizing Schoenfeld residuals, and the survival curve according to smoking status was plotted using the life-table method. I used Levins formula for calculating population attributable risk (PAR) (Levin., 1953). In additional analyses, we excluded all events that had occurred in the first 4 years of follow-up. These analyses ensured sensitivity in our results. In all analyses, a two-sided significance level of 0.05 was used.

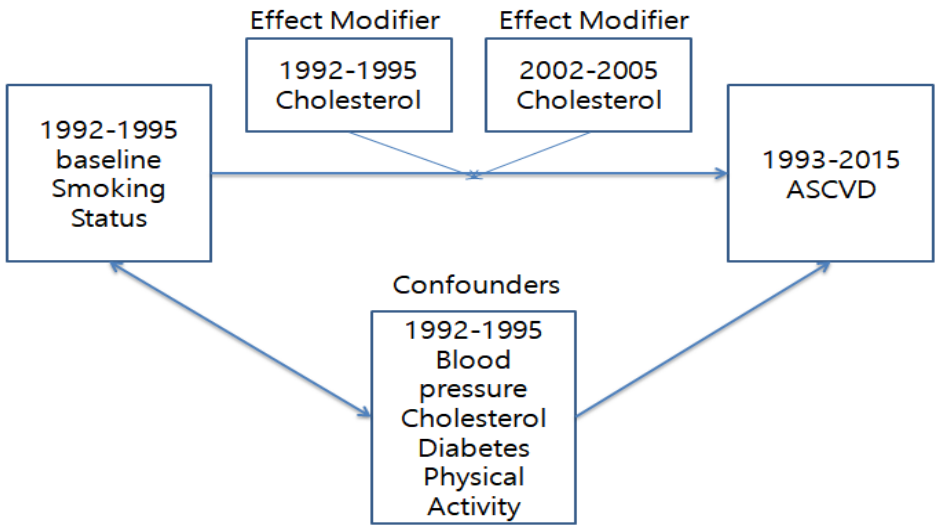


Figure 2.3. Study design: time frame of the study

2.3. Results

The average age of the study participants was 26.7 ± 2.0 (SD) years. Among the 118,531 men, 78,455 (66.2%) were current smokers, 15,126 (12.8%) were ex-smokers, and 92,403 (15.4%) had hypertension. For total cholesterol, 94,413 (79.7%) had a total serum cholesterol level < 200 mg/dL, 19,764 (16.6%) had a borderline level of 200-240 mg/dL, and 4,444 (3.8%) had a level of 240 mg/dL or higher. In terms of amount of smoking, 28.9% smoked more than 20 cigarettes per day while 45.5% and 25.6% of current smokers smoked 1 to 9 and 10 to 19 cigarettes per day, respectively. Among current smokers, 92.0% smoked for less than 10 years while 7.6% and 0.4% of current smokers smoked for 10 to 19 years and more than 20 years, respectively.

Population characteristics by smoking status are presented in Table 4-1. After adjusting for age, current smokers had a significantly higher body mass index (P for trend = 0.0056), higher consumption of alcohol drinking (P for trend <.0001), and higher prevalence of diabetes (P for trend = 0.0060) than nonsmokers.

During 23 years of follow up for average (5,191,823 person-years), 2,786 (90 fatal) IHD cases (53/100,000 person year), stroke cases 2,368 (126 fatal) (45.4/100,000 person year), and 6,368 ASCVD cases (306 fatal) (122.7/100,000 person year) occurred.

The independent effects of smoking on IHD, stroke, and ASCVD were analyzed controlling for confounding factors through Cox proportional hazards

models, as shown in Table 2-2. The hazard ratios (HR) relating to IHD for current smokers were 1.5 (P <.0001), and those of ex-smokers were 1.0 (P=0.8567). The HR of stroke was 1.4 (P <.0001) for current smokers and 1.1 (P = 0.5008) on ex-smokers.

Compared to nonsmokers, the HR for any ASCVD event was 1.4 (P < 0.0001) in current smokers and 1.1 in ex-smokers (P = 0.1406). Figure 2-5 shows the survival probability by smoking history (never, former, 1-9, 10-19, ≥20 cigarette per day among current smokers) and the corresponding unadjusted association with ASCVD. The overall results demonstrated that smoking among young men increased the risk for ASCVD relative to nonsmokers. After adjusting for age and traditional ASCVD risk factors, the HRs for IHD and stroke were estimated for groups classified by amount of smoking (A and B in Figure 2-6) and duration of smoking (C and D in Figure 2-6). For IHD and stroke, the risk of events increased linearly with higher amount of cigarette per day (P for trend, <.0001 and <.0001, respectively) and longer duration of smoking (P for trend, <.0001 and <.0001, respectively).

To examine whether serum total cholesterol levels could modify the effect of smoking on ASCVD, we divided the cohort participants into quartile of total cholesterol. The risks above were also found throughout the range of serum levels of cholesterol demonstrating that serum total cholesterol levels did not modify the effect of smoking on ASCVD (A to C in Figure 2-7).

Estimated risk factor prevalence in current studies of smoking and other additional risk factors were used to estimate the PARs for IHD alone, stroke alone and total ASVCD (Table 2-3). For IHD, current smoking accounts for about 24.9%

of events, and hypertension accounts for 8.1% of events. In the case of stroke, smoking was estimated to account for 20.9%, whilst hypertension was estimated to be responsible for 13.3% of stroke cases.

Table 2-4 depicts the difference in ASCVD risks according to different smoking initiation age in young adult ex-smokers and current smokers. Compare to non-smokers, ASCVD risks elevated in early initiated smokers those who started smoking before age 20 (Figure 2-8, 2-9).

Table 2-1. Baseline Characteristics of the Korean Life Course Health Study, 1992-1994, According to Smoking Status*

Characteristic	Nonsmokers (n=24,950)	Ex-smokers (n=15,126)	No. of cigarettes per day among current smokers			
			1-9 (n=22,642)	10-19 (n=35,690)	≥20 (n=20,123)	*P* for Trend¶
Age, year	26.6 (2.1)	26.9 (1.9)	26.6 (2.0)	26.8 (1.9)	26.8 (1.9)	0.1622
Systolic Blood Pressure, mmHg	120.4 (11.6)	120.0 (11.8)	119.8 (11.6)	120.1 (11.6)	120.3 (11.6)	0.2558
Diastolic Blood Pressure mmHg	78.0 (9.0)	77.7 (9.1)	77.5 (9.0)	77.8 (9.0)	78.0 (9.0)	0.1122
Total cholesterol, mg/dL	173.4 (32.9)	173.4 (32.6)	172.9 (33.1)	174.5 (33.4)	177.2 (34.4)	0.9543
Body mass index, kg/m^2	22.3 (2.4)	22.4 (2.4)	22.3 (2.4)	22.5 (2.5)	22.9 (2.6)	0.0056
Fasting serum glucose, mg/dL	86.7 (13.3)	86.6 (13.5)	86.2 (14.1)	86.4 (14.1)	86.6 (15.3)	0.4821
Alcohol consumption, g per day	7.3 (17.7)	9.7 (19.7)	12.2 (22.6)	14.5 (25.1)	20.4 (36.1)	<.0001
Conditions, %						
Hypertension†	15.7	15.1	14.5	15.6	15.7	0.7987
Hypercholesterolemia‡	3.4	3.3	3.3	3.9	4.7	0.0743
Diabetes§	0.7	0.8	0.9	0.9	1.0	0.0060
Alcohol use‖	61.2	81.3	88.2	88.3	86.9	0.1035
Physical activity	24.9	26.8	22.9	17.5	13.0	<.0001

*Data are expressed as means (SD) unless otherwise indicated; †Systolic blood pressure of at least 140 mmHg and/or diastolic blood pressure of at least 90 mmHg; ‡Total cholesterol level of at least 6.21 mmol/L (240 mg/dL); § Fasting serum glucose value of at least 6.99 mmol/L (126 mg/L); ‖ Consumption of Soju which is a colorless distilled beverage of Korean origin; ¶Testing for trend across nonsmokers and current smokers; ex-smokers were excluded.

Table 2-2. Risk of Morbidity from Ischemic Heart Disease, Cerebrovascular Disease, and Atherosclerotic Cardiovascular Disease in Korean Men in the Korean Life Course Health Study, 1992-2015*

	Ischemic Heart Disease		Cerebrovascular Disease		Atherosclerotic Cardiovascular Disease	
Variables and Categories	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age (5-year age group)	1.4 (1.2 – 1.6)	<.0001	1.4 (1.3 – 1.6)	<.0001	1.3 (1.2 – 1.4)	<.0001
Cigarette smoking						
Ex-smoker	1.0 (0.9 – 1.2)	0.8567	1.1 (0.9 – 1.3)	0.5008	1.1 (1.0 – 1.2)	0.1406
Current smoker	1.5 (1.3 – 1.6)	<.0001	1.4 (1.2 – 1.6)	<.0001	1.4 (1.3 – 1.5)	<.0001
Blood Pressure†						
High normal	1.2 (1.1 – 1.4)	<.0001	1.2 (1.0 – 1.3)	0.0152	1.2 (1.1 – 1.3)	<.0001
Stage 1 hypertension	1.6 (1.4 – 1.8)	<.0001	1.7 (1.5 – 2.0)	<.0001	1.7 (1.5 – 1.8)	<.0001
Stage 2 hypertension	2.0 (1.6 – 2.5)	<.0001	3.2 (2.5 – 4.0)	<.0001	2.9 (2.5 – 3.3)	<.0001
Total cholesterol‡						
Borderline-high cholesterol	1.4 (1.3 – 1.6)	<.0001	1.4 (1.3 – 1.6)	<.0001	1.4 (1.3 – 1.5)	<.0001
High cholesterol	2.5 (2.1 – 2.8)	<.0001	1.7 (1.4 – 2.1)	<.0001	2.1 (1.8 – 2.3)	<.0001
Fasting blood sugar§						
Diabetes	1.3 (0.9 – 1.9)	0.1375	1.6 (1.1 – 2.3)	0.0222	1.5 (1.2 – 1.9)	0.0008
Physical activity						
No exercise	1.1 (1.0 – 1.3)	0.0122	1.1 (1.0 – 1.3)	0.2156	1.1 (1.0 – 1.3)	0.0075

*Hazard ratio (HRs) and 95% confidence intervals (Cls) from multivariable Cox proportional hazards models. †The reference category is normal (systolic blood pressure<140 mmHg and diastolic blood pressure<90mm Hg). ‡ The reference category is desirable (serum cholesterol level, < 5.17 mmol/L [200 mg/dL]). §The reference category is a fasting serum glucose level of less than 6.99 mmol/L (126 mg/dL).

Table 2-3. Population Attributable Risks (PARs) and 95% Confidence Intervals (CIs) From Smoking and Other Risk Factors of Ischemic Heart Disease, Cerebrovascular Disease, and Atherosclerotic Cardiovascular Disease in Korean Men: The Korean Life Course Health Study

Variables and Categories	Prevalence %	Ischemic Heart Disease PAR (95% CI)	Cerebrovascular Disease PAR (95% CI)	Atherosclerotic Cardiovascular Disease PAR (95% CI)
Smoking				
Current smoker	66.2	24.9 (16.6 – 28.4)	20.9 (11.7 -28.4)	20.9 (16.5 – 24.9)
Blood Pressure*				
Hypertension	22.0	8.1 (6.2 – 9.9)	13.3 (9.9 – 14.9)	9.9 (9.9 – 11.7)
Total cholesterol†				
Borderline	16.6	6.2 (4.7 – 9.1)	6.2 (4.7 – 7.7)	6.2 (4.7 – 7.6)
High	3.8	5.4 (4.0 – 6.4)	4.0 (2.9 – 4.7)	4.0 (2.9 – 4.7)
Fasting blood sugar‡				
Diabetes	0.9	0.3 (-0.9 – 0.8)	0.5 (0.08 – 1.1)	0.4 (0.2 – 0.8)
Physical activity				
No exercise	0.8	7.4 (0 – 19.3)	7.4 (0 – 19.3)	7.4 (0 – 19.3)

*The reference category is normal (systolic blood pressure < 140 mmHg and diastolic blood pressure < 90mm Hg). †The reference category is desirable (serum cholesterol level < 5.17 mmol/L [200 mg/dL]). ‡ The reference category is a fasting serum glucose level of less than 6.99 mmol/L (126 mg/dL).

Table 2-4. Effect of smoking initiation groups and covariates on ASCVD events, using Cox proportional hazard model

Variables and Categories		HR (95% CI)
Age, year		1.058 (1.057-1.059)
Body mass index, kg/m^2		1.19 (1.18-1.21)
Smoking status (1992-1994)	Smoking initiation age (mean)	
Non-smoker		1.00
Ex-smoker	≥30 (32.9)	1.02 (0.98-1.04)
	20-29 (24.9)	1.16 (1.13-1.19)
	<20 (17.3)	**1.37 (1.28-1.47)**
Current-smoker	≥30 (32.9)	1.29 (1.27-1.32)
	20-29 (24.9)	1.43 (1.41-1.46)
	<20 (17.3)	**1.55 (1.52-1.59)**
Systolic BP, per 10 mmHg		1.205 (1.200-1.209)
Serum glucose, per 10 mg/dL		1.059 (1.056-1.061)
Total cholesterol, per 10 mg/dL		1.042 (1.040-1.044)
N		783,949
Number ASCVD event		111,329
AIC		2,913,063.5 (DF=12)

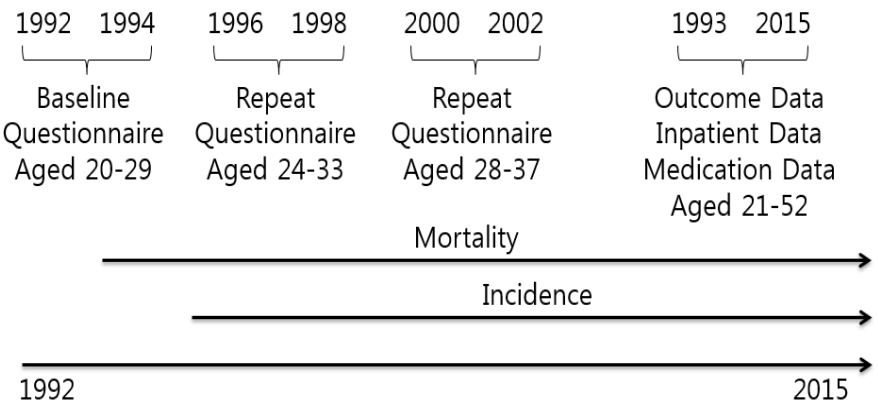


Figure 2-4. Timeline for data collection in the Korean Life Course Health Study

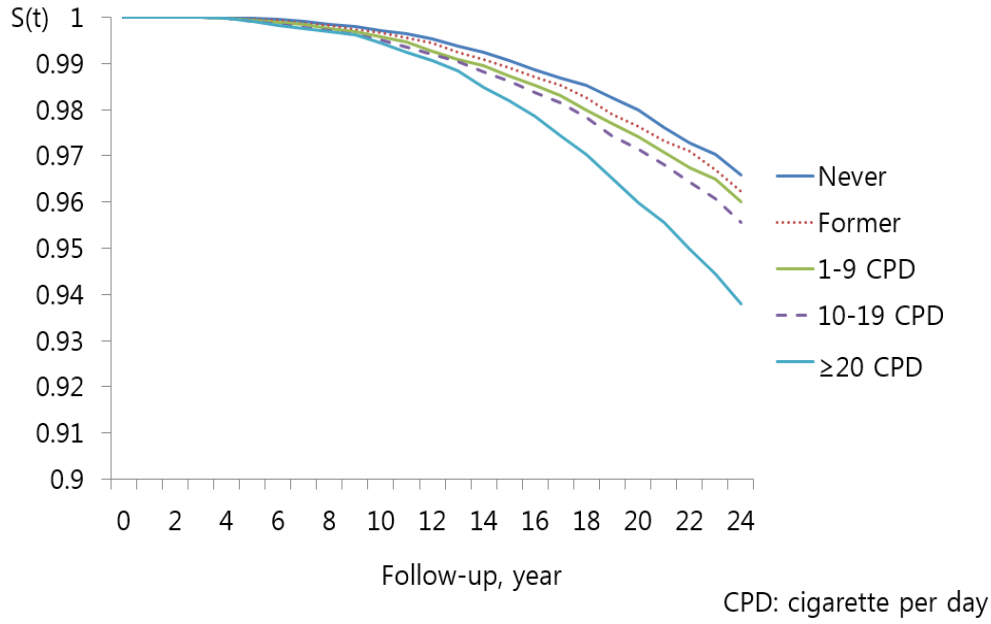


Figure 2-5. Survival of atherosclerotic cardiovascular disease event by smoking history in Korean young adult men, 1992-2015

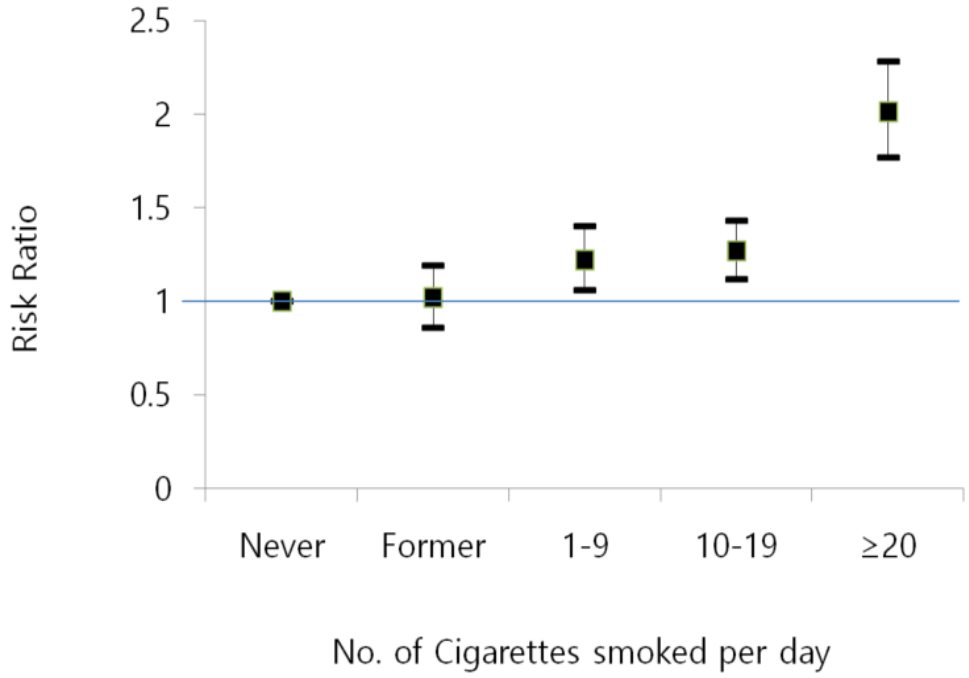


Figure 2-6-A. Hazard ratios with 95% confidence intervals for from ischemic heart disease by cigarette per day

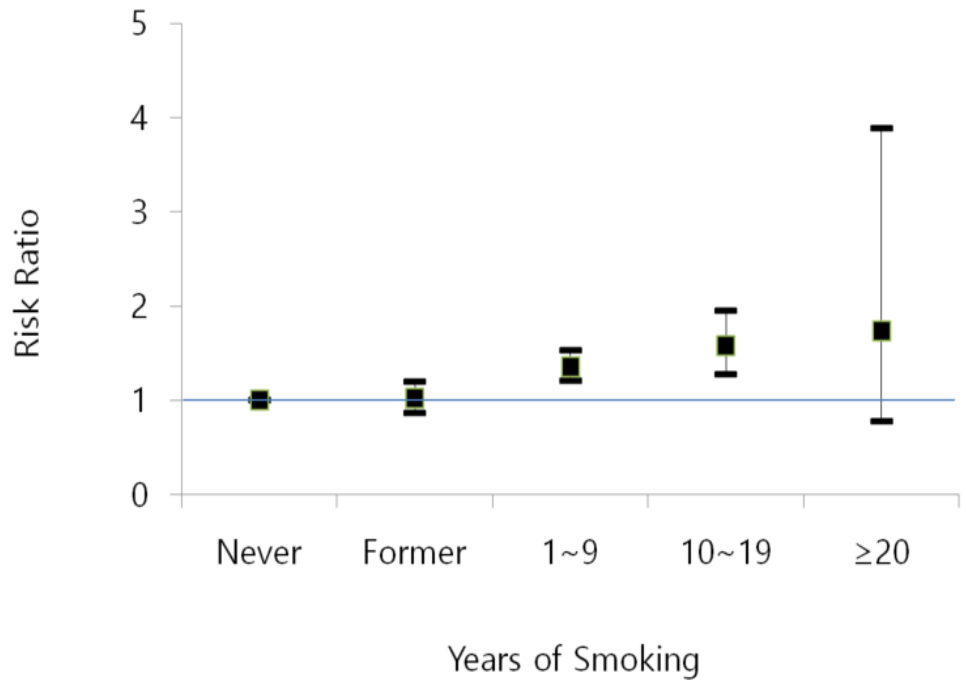


Figure 2-6-B. Hazard ratios with 95% confidence intervals for from ischemic heart disease by duration of smoking

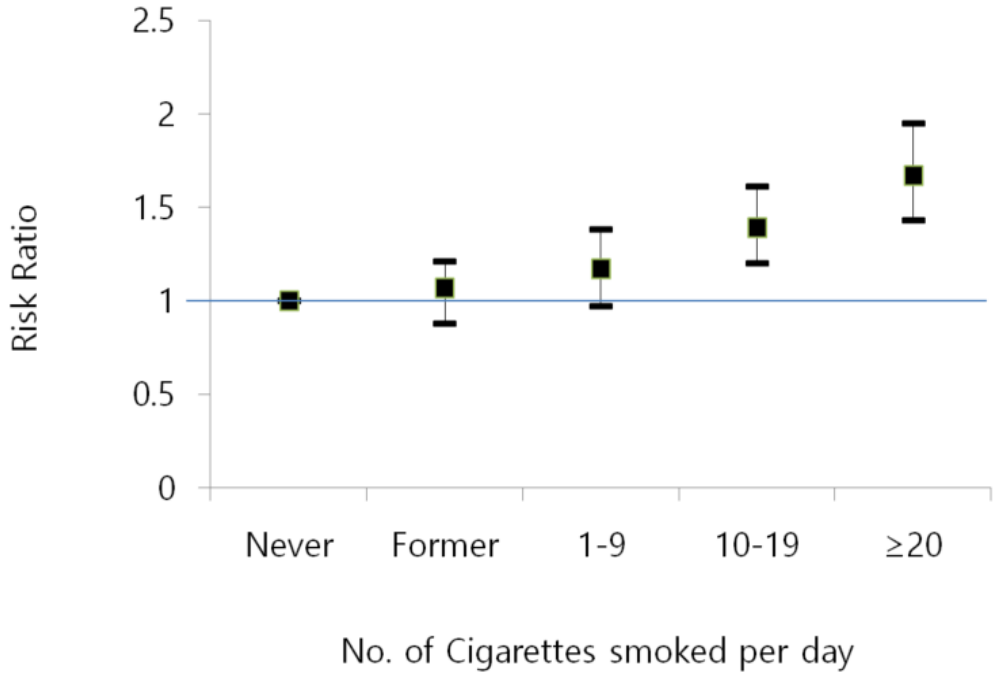


Figure 2-6-C. Hazard ratios with 95% confidence intervals for from stroke by cigarette per day

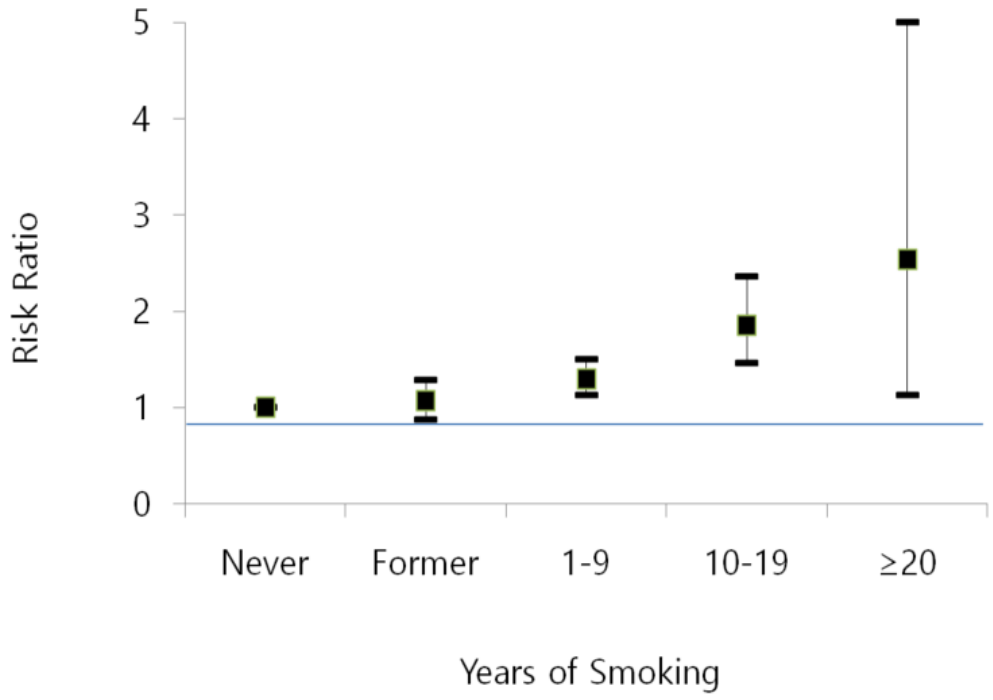


Figure 2-6-D. Hazard ratios with 95% confidence intervals for from stroke by duration of smoking

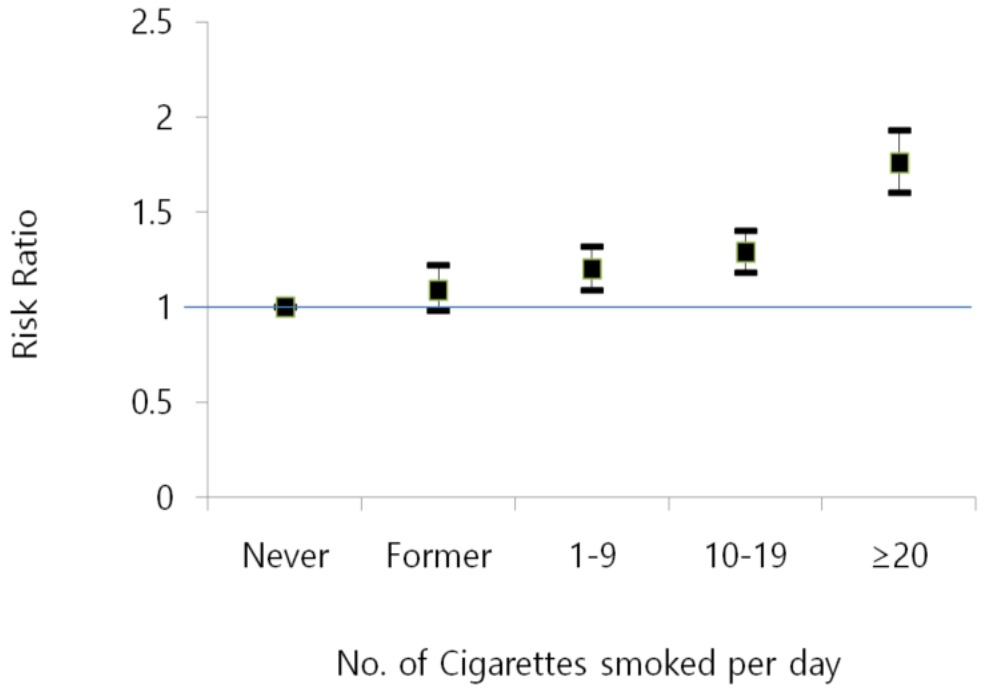


Figure 2-6-E. Hazard ratios with 95% confidence intervals for from ASCVD by cigarette per day

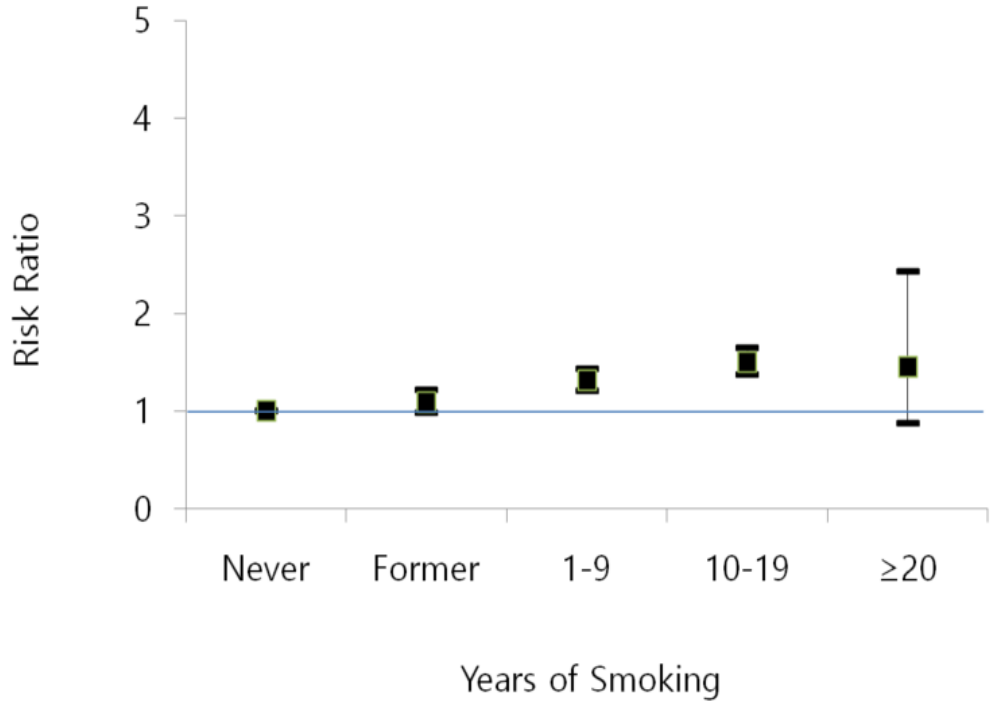


Figure 2-6-F. Hazard ratios with 95% confidence intervals for from ASCVD by duration of smoking

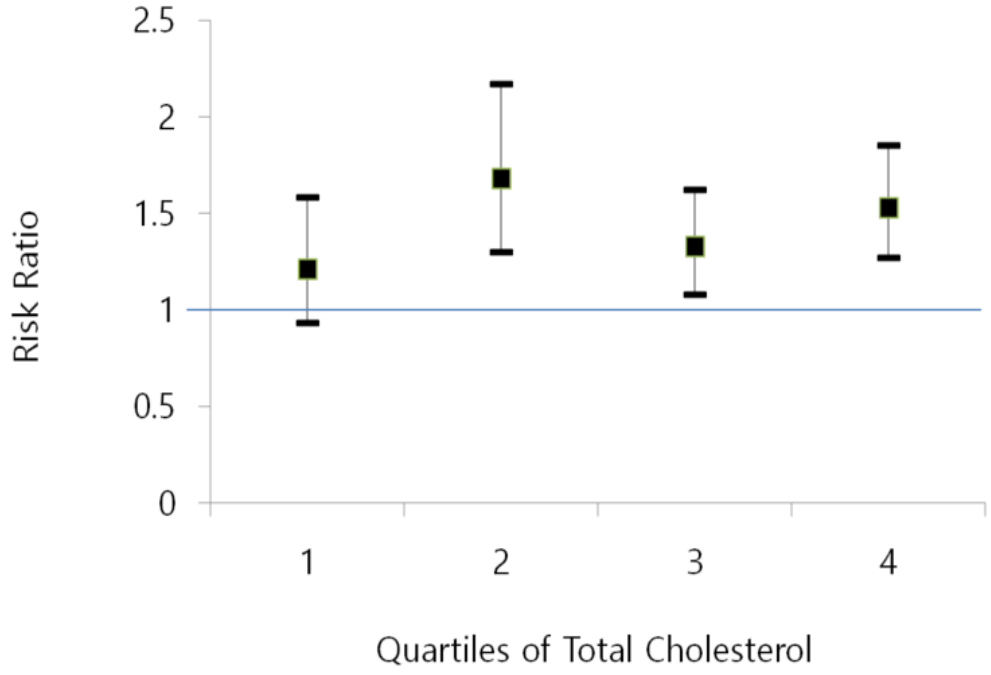


Figure 2-7-A. Hazard ratios with 95% confidence intervals for ischemic heart disease by total cholesterol groups of smokers compared with non-smokers: Each group of total cholesterol levels are as follows: first, 149 mg/dl; second, 150-169 mg/dL; third, 170-194 mg/dL; fourth, ≥195 mg/dL. The reference group is non-smokers in each quartile of total cholesterol.

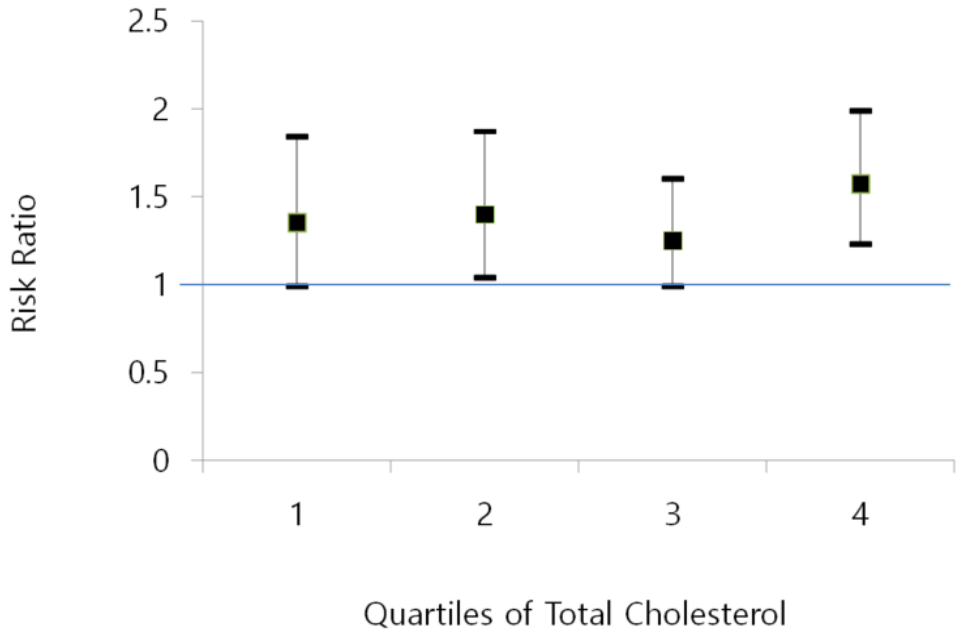


Figure 2-7-B. Hazard ratios with 95% confidence intervals for stroke by total cholesterol groups of smokers compared with non-smokers: Each group of total cholesterol levels are as follows: first, 149 mg/dl; second, 150-169 mg/dL; third, 170-194 mg/dL; fourth, ≥195 mg/dL. The reference group is non-smokers in each quartile of total cholesterol.

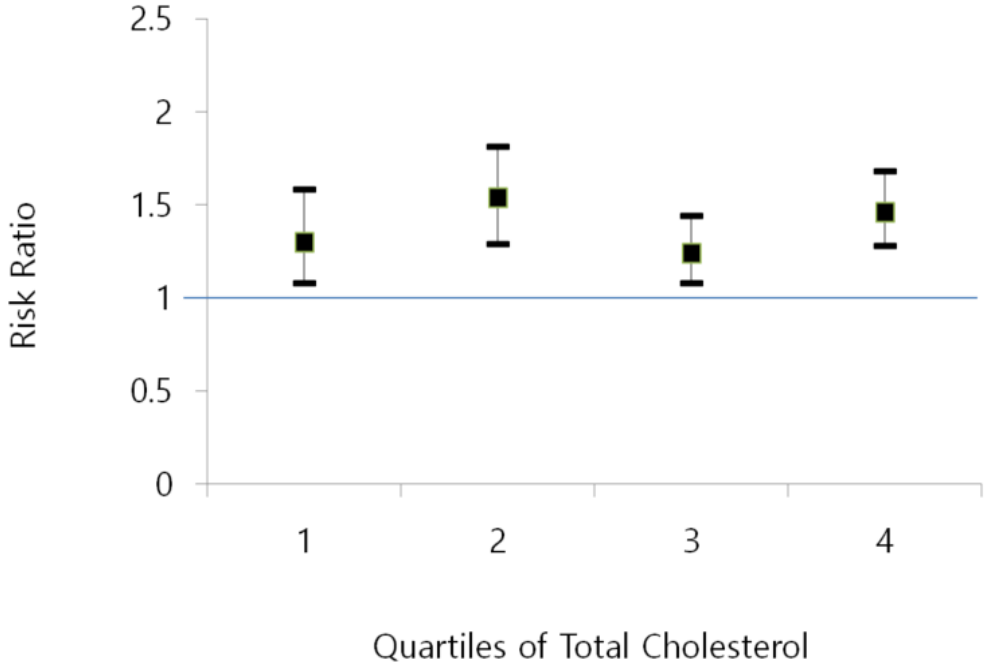


Figure 2-7-C. Hazard ratios with 95% confidence intervals for ASCVD by total cholesterol groups of smokers compared with non-smokers: Each group of total cholesterol levels are as follows: first, 149 mg/dl; second, 150-169 mg/dL; third, 170-194 mg/dL; fourth, ≥195 mg/dL. The reference group is non-smokers in each quartile of total cholesterol.

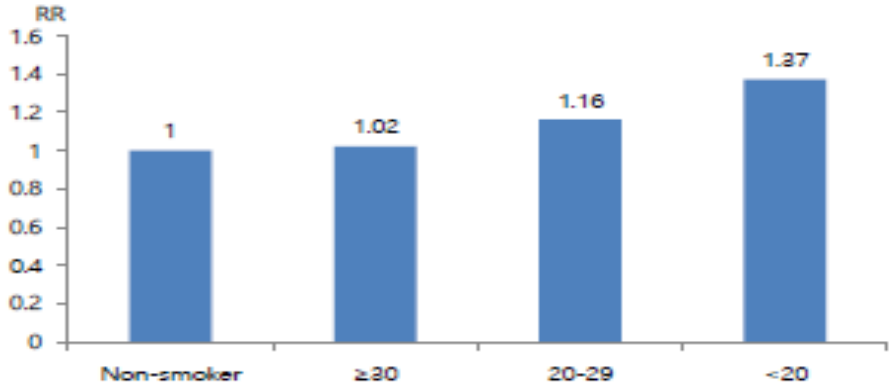


Figure 2-8. Hazard ratios with 95% confidence intervals for ASCVD by smoking initiation age in young adult ex-smokers.

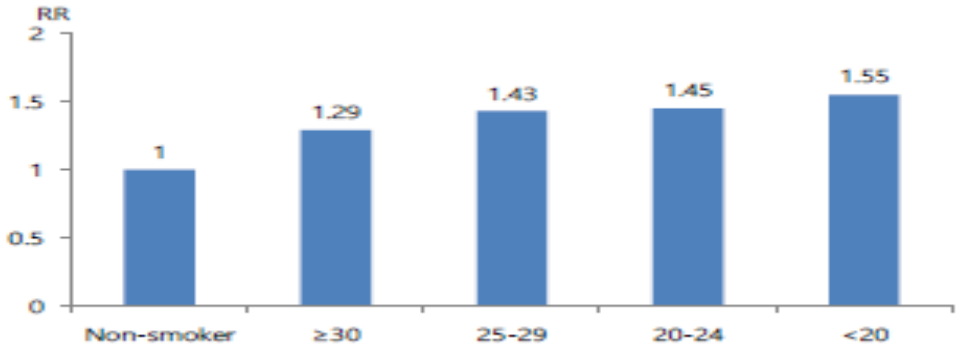


Figure 2-9. Hazard ratios with 95% confidence intervals for ASCVD by smoking initiation age in young adult current-smokers.

2.4. Discussion

In this chapter, I investigated the association between smoking and risk of ASCVD among Korean young men within a cohort study with a 23 year of follow-up. To our knowledge, this is the first study focusing on Korean young adults. In our study, smoking was the most crucial risk factor attributing to 20% of ASCVD mortality in middle age.

Diabetes, hypertension, and hyperlipidemia are well known risk factors for ASCVD (Jee et al., 2010). However, for young adults with relatively low incidence of diabetes, hypertension and hyperlipidemia, smoking is the most important and an independent risk factor for predicting ASCVD in the present study. Furthermore, the high smoking rate among young people is important with respect to the development of middle-aged hypertension and transition to ASCVD (Thut et al., 2010; Kim et al., 2018). Thus, middle-aged ASCVD morbidity is likely predominantly predicted by smoking in young adulthood.

The body of research centered upon the health effects of smoking is steadily increasing, with findings reported from many countries around the world. However, few studies have examined the effect of smoking on ASCVD in young adults (Morotti et al., 2014). Here, I presented the evidence that current smoking is an independent risk factor affecting the incidence of IHD, stroke and ASCVD.

These risk associations have been estimated across total serum cholesterol groups. A cohort study in Hasayama Japan found that smoking showed positive

association with coronary heart disease in people with high levels of serum cholesterol above 180 mg / dl, but not with people with low level of cholesterol less than 180 mg / dl (Kiyohara et al., 1990; Fujishima et al., 1992).

Afterward, several epidemiological studies were conducted. Among them, one study from Puerto Rico Heart Health Program (Gordon et al., 1974) showed similar results, but not all (Lawlor et al., 2008; Hozawa et al., 2007; Nakamura et al., 2009; Jee et al., 1999; Jee et al., 2007). Of course, all studies were conducted among adult populations. To the best of our knowledge, no study has been done on young adults with much lower levels of serum cholesterol. In addition, the high smoking rate among young adults is likely to be, even directly, linked to high blood pressure among the adult population who developed ASCVD as a major health problem.

In this study, the non-significant risk of ASCVD among ex-smokers can be interpreted in two ways. First, this result may simply reflect the effect of smoking cessation. Most previous studies have shown that the effects of smoking cessation are immediate in CVD (most of the excess risk of vascular mortality due to smoking may be eliminated rapidly upon cessation), while lung cancer occurs within 20 years (Thun et al., 1992; Kenfield et al., 2008).

Second, even if a number of young adult ex-smokers, aged 20-29 years, may have smoked continuously from adolescence, it is still a short term of smoking, compared to adults. Previous study shown that reducing adult smoking pays more immediate dividends, both in terms of health improvements and cost savings (Lightwood & Glantz., 1997). While present study lacks information on smoking

duration of ex-smokers, current smokers who continued to smoke seem to have increased risk of CVD by 40%. Therefore, while the smoking duration of ex-smokers is unknown, it may be reasonable to consider the results were mainly affected by the smoking cessation. Further research on the effects of smoking cessation among young adults is necessary.

There are several studies regarding cardiovascular risk among young people. According to a study conducted by Bernaards et al (Bernaards et al., 2008), blood pressure and waist circumference were decreased by lowering weekly tobacco consumption in younger participants. However, they did not report the risk of developing cardiovascular disease events due to changes in smoking. This seems to be another significant topic relating to the health of young adults

Morotti and his collegaues reported that on young women with polycystic ovary syndrome (PCOS) reported an association between smoking habitude in lean PCOS patients, and the increase of soft markers of cardiovascular risk (Morotti et al., 2014). For young adult African Americans, the association between cigarette smoking and carotid intima assuming the genetic variation of smokers was reported and the -930A/G polymorphism modified the association among young healthy adults (Murtaugh et al., 2002). The study on association between second hand smoking among childhood and cardiovascular event in adulthood was conducted and found that the carotid plaque risk in adulthood is increased in children whose parents had smoked (West et al., 2015; Roy et al., 1994)

This LCHS study has several strengths, such as high follow-up rates and a

large, national sample. The large sample size of cohort allowed us to investigate the association of smoking with various levels of serum cholesterol. The civil servants and private school teachers who participated in this study accounted for about 11% of the total population in 1992. We did not compare the characteristics of the 89% population not included in the study. Therefore, this study will not represent the whole population. Moreover, selection bias may be a potential issue, since the final sample contains a subset of over 118,531 young male adults (38.6%) out of 307,041 subjects initially selected for our study. In the context of methodological issues, smoking variables used in this study are category variables, thus it has limitation to examine the PAR increase per 1 unit. We therefore urge conservative interpretations of our study results with regard to the general population.

Low PAR of cholesterol in young adult men may be associated with low variation cholesterol in young adults. Therefore, smoking initiation data showing the difference in ASCVD incidence is required to stress that smoking behavior in young adult period itself is risky. Early smokers those who initiated smoking before age 20 showed higher ASCVD incidence. Therefore, my study showed that smoking was an independent risk factor of ASCVD without interaction with traditional ASCVD risk factors such as cholesterol. And regardless of cholesterol and other risk factors, early smoking initiation itself elevated the risk of ASCVD, which could be an evidence to manage smoking in early adult period.

Chapter III. Trajectory of smoking and incidence of atherosclerotic cardiovascular disease among Korean young adult men

3.1 Introduction

Smoking is the most potent preventable risk factor for nearly all chronic diseases and causes of death. Smoking habits vary by individual and country, but can change almost every year (Mazur et al., 2016). In Korea, the rate of male smokers in 1980 was 79.3% (Jee et al., 2004), but in 2017 it was 38.1 percent (KNHANES, 2017). For the last 30 years in Korea, there has been a nearly 40% decrease in smoking, which has been reduced further by about 1.2% per year. In this context, information gained from smoking prevalence measured at one-time point is very limited. Possible applications of these measurements, however would be a time varying exposure or a trajectory analysis of smoking (Lenk et al., 2000; Selya et al., 2016; Dziak et al., 2015). Trajectory analysis of cigarette smoking is especially useful for visualizing the various smoking trends for a certain period.

Recent studies have shown that smoking in young adults is the greatest risk factor for developing middle-aged heart disease in the future (Thut et al., 2010; Kim et al., 2018; Morotti et al., 2014). This is because smoking rates are relatively high in young adults, but the prevalence of diabetes, hypertension, and dyslipidemia is low (Bucholz et al., 2018). In addition, analysis of the trajectory using multiple measured smoking rates, rather than the one-time smoking rate in young adults would better reflect the characteristics of youth smoking.

This study analyzed the trajectory of smoking in young adults for 12 years, and analyzed the effects of the trajectory group on future cardiovascular outcomes in a prospective cohort during another 11 years.

3.2 Methods

3.2.1 Study participants

The participants were young adult men aged 20 to 29 years-old in the Korean Life Course Health Study (KLCHS), which consisted of government employees and private school staff members who were covered by medical insurance between 1992 and 1994. The characteristics of this study can be referenced in the previously reported Korean Cancer Prevention Study (KCPS) (Jee et al., 2004). The KLCHS cohort included 307,041 Koreans (142,461 males, 164,580 females) who were screened by the Korean Medical Insurance Corporation in 1992 and 1994. Of these participants, 205,840 (67.0%) were registered in 1992 and 101,201 (33.0%) were registered in 1994. For this study, 60,709 male youth participated in the smoking questionnaire from 1992 to 2004.

3.2.2 Smoking history and other covariate data

All participants were given the opportunity to have a medical examination every two years since 1992. The smoking history data were obtained by self-administered questionnaire. Cigarette smoking history was coded from 1 to 5. In the cigarette smoking variables, 1 means non-smoker, 2 means former smoker, 3 means 1 to 9 cigarettes per day among current smokers, 4 means 10 to 19 cigarettes per day, and 5 means more than 20 or above cigarettes per day. These smoking amounts surveys were conducted every two years from 1992 to 2004.

Among 142,461 male participants, 60,709 (42.6%) had their height, systolic blood pressure (SBP), fasting blood glucose (FBG), total cholesterol (TC), or body mass index (BMI) measured and were included in the study. Female participants were excluded, because of the low prevalence of smoking for females in Korea. The study proposal obtained an approval by the Institutional Review Board of Human Research, Yonsei University (4-2001-0029) and the Seoul National University (E1812/001-010). This study was a retrospective cohort using past routine laboratory data and did not receive consent.

3.2.3 Outcome

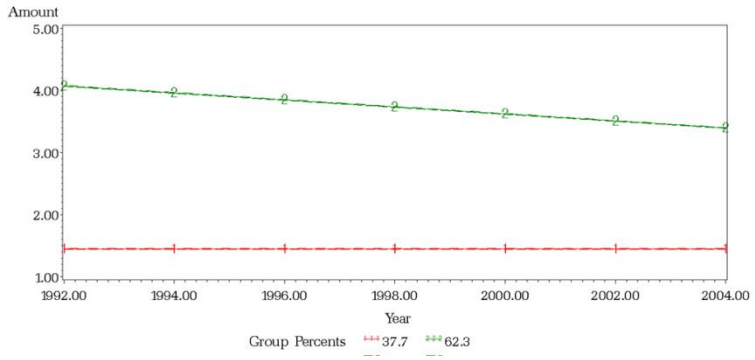
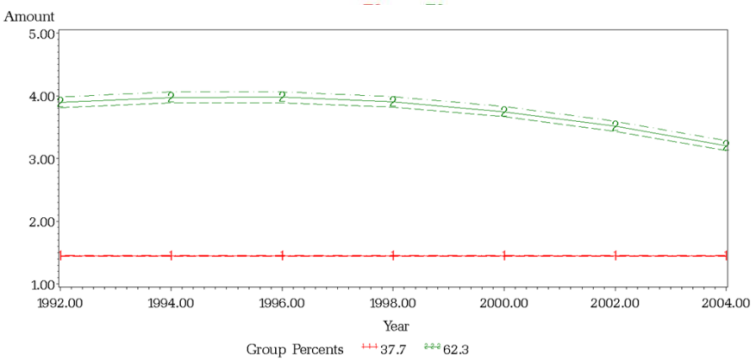
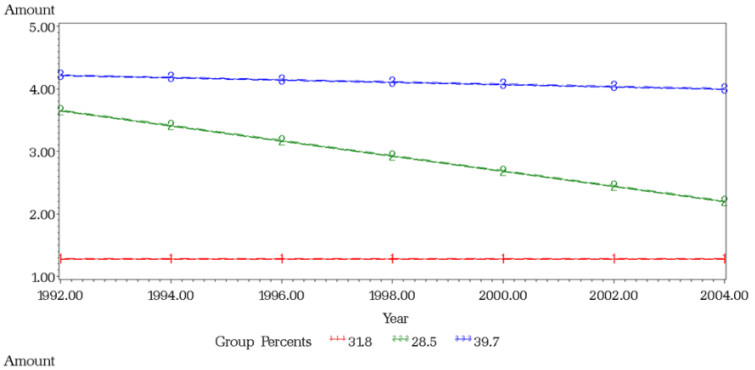
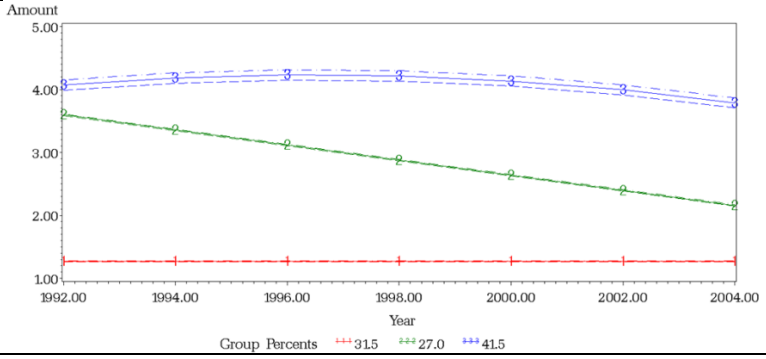
The main outcome in this study was the occurrence of atherosclerotic cardiovascular disease (ASCVD). It was classified into ischemic heart disease (IHD) (ICD 10 codes I20–I25), total stroke (ICD codes I60-I69), ischemic stroke (I63), and hemorrhagic stroke (I60–I62) (Jee et al., 1999). Regardless of what hospital in the country study participants used, the disease ICD-10 code was reported to the National Health Insurance System. The first admission record of ASCVD in this study was defined as the onset of ASCVD event. A validity of the diagnosis of ASCVD was verified by 20 internists from the Korean Society of Cardiology in 2009 (Kimm et al., 2012). From 1994 to 2007, 673 cases of coronary heart disease were identified by private hospital records and 73% of the cases identified as myocardial infarction were valid.

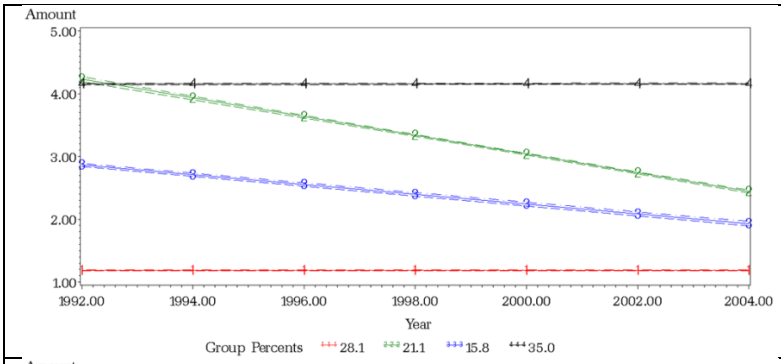
3.2.4 Statistical analysis

In the first analysis, 12-year smoking survey data obtained every 2 years from 1992 to 2004, were used for trajectory analysis using the PROC TRAJ command in SAS (Conklin et al., 2005). Trajectory analysis uses semi-parametric group-based modeling strategies to identify potential patterns of end-to-end data. Each model represents an individual with a similar trajectory (Nagin & Odgers., 2010). We limited the number of trajectory groups to less than five, using the Bayesian Information Criterion (BIC) to assess best model fit (Raftery., 1995; Schwartz., 1978). In the second analysis, general characteristics of selected trajectory groups were compared. In a third analysis, the risk of developing heart disease, according to the selected trajectory group was compared. At that time, the group with the lowest smoking rate, the almost non-smoking group was selected as the reference group. The independent effects of the trajectory groups on ASCVD were analyzed through the Cox proportional hazard model, controlling for confounding variables. Various ASCVD models, including smoking rates measured once, smoking rate trajectory, and mediators in smoking and heart disease, were evaluated as Akaike information criterion (AIC) values.

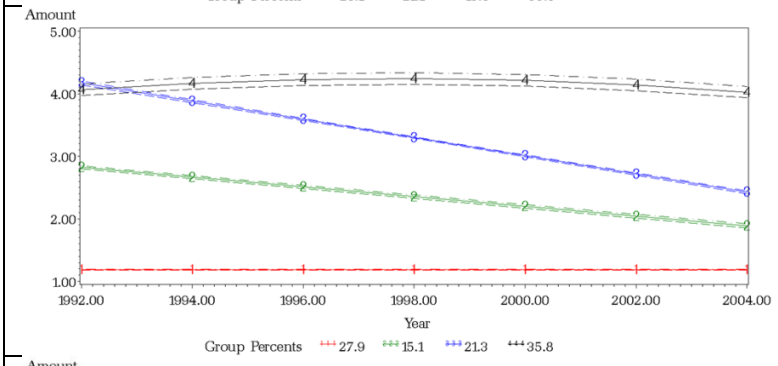
3.3 Results

The study included 8 smoking trajectory models. Among the 8 models, the model with 5 trajectory groups (1 1 1 2 2) showed the smallest BIC, and was selected as the final model (Supplementary Table 2-1 and Figure 2-2). Therefore, trajectory analysis showed that smoking categorized into five groups (Figure 1). According to the characteristics of the five groups shown in the figure 1, the groups were named as follows: Group 1 (28.3%), low steady; Group 2 (14.7%), lowering; Group 3 (17.3%), high steady; Group 4 (15.6%), rise and fall; and Group 5 (24.2%), very high steady.

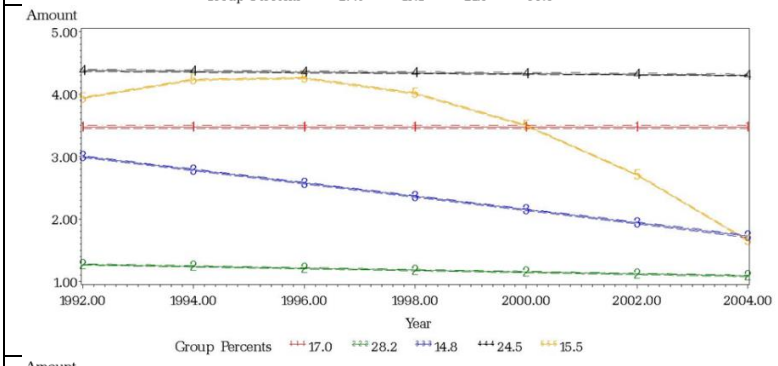
Trajectory model	Model parameter
	1) order 0 1 BIC=-537422.2 (N=60711)
	2) order 0 2 BIC=-534935.8 (N=60711)
	3) order 0 1 1 BIC=-508340.2 (N=60711)
	4) order 0 1 2 BIC=-507160.4 (N=60711)



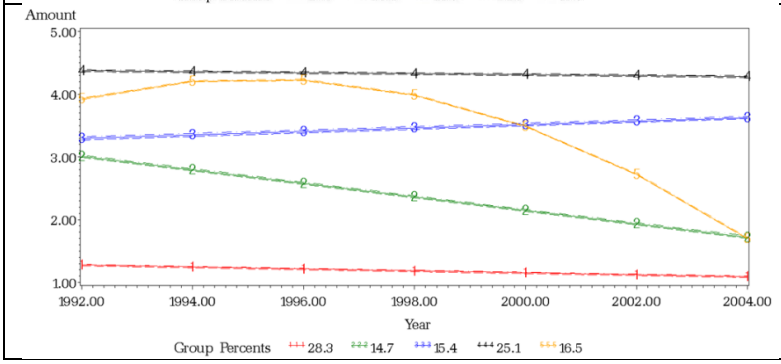
5) order 0 1 1 1
BIC=-501189.4
(N=60711)



6) order 0 1 1 2
BIC=-500673.8
(N=60711)



7) order 0 1 1 1 2
BIC=-485860.7
(N=60711)



8) order 1 1 1 1 2
BIC=-485471.7
(N=60711)

Figure 3-1. Trajectory group of smoking amount for 8 models

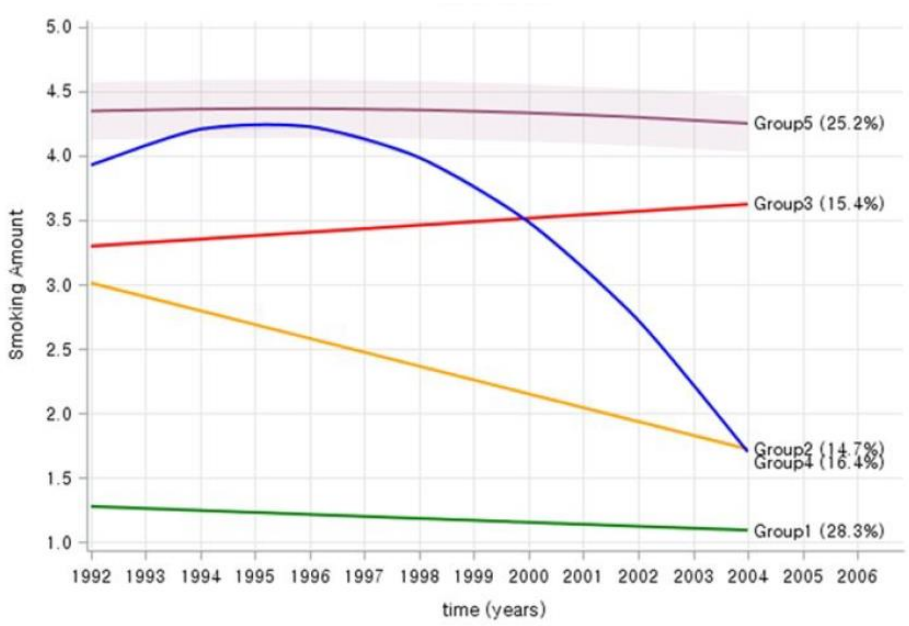


Figure 3-2. Trajectory group of smoking amount in Korean young adult men.

Table 3-1 shows general characteristics among the trajectory groups. There was no difference in age, BMI, SBP, FBG, or TC between trajectory groups in either 1992 or 2004. However, the percentage of exercise was 22.1% in group 1, 19.1% group 2, and 20.0% group 3, but only about 15% in groups 4 and 5. The characteristics of group 1 (low steady) were mostly non-smokers in 1992 and 2004. Group 2 (lowering) had the highest ex-smokers in 2004 (47.5%), compared to 1992. The characteristics of group 3 (high steady) were higher in the 1-9 cigarette per day in 2004 (59.4%), then in 1992 (46.3%). Groups 4 (rise and fall) and 5 (very high steady) were mostly current smokers in 1992. Of these, the group that was still smoking in 2004 became group 5, and the group whose smoking rate decreased sharply for any reason became group 4.

Table 3-2 is a traditional model showing the relationship between smoking history at baseline and ASCVD, after controlling for confounding variables. In model 1, current smokers had a 1.22-fold higher risk of developing ASCVD than non-smokers. In Model 2, among current smokers, smokers who smoked more than 20 cigarettes per day had a 1.52-fold greater risk of developing ASCVD.

Table 3-3 shows the effect of the trajectory group estimated from 7 smoking data collections between 1992 and 2004, on ASCVD. The performance of model 1 (AIC=51847.85) with trajectory group in table 3 was similar with model 2 in table 2 (AIC=51846.84) without trajectory group. However, the performance of trajectory model 2 (AIC=51670.78) with mediators in table 3 was better than the model (AIC=51847.85) without mediators. The trajectory model showed that the heavy smokers seemed to be divided into two trajectory groups (group 4 and 5). In other

words, the group with heavy smoking was divided into two groups: those who maintained heavy smoking (group 5), and those who maintained heavy smoking and sharply decreased their smoking amount for any reason (group 4). In group 4, 15.6% of heavy smokers sharply decreased the amount of smoking, and there was no difference in the risk of developing ASCVD, compared to group 1 (reference group). Group 5, on the other hand, maintained 24.2% of its heavy smokers, and their risk of ASCVD increased by 49%, compared to group 1.

Table 3-4 shows the trajectory effects of smoking on IHD and stroke risk. The risk of IHD was 1.63 times higher for group 5 and 1.31 times higher for group 4, compared to group 1, after adjusted for confounding variables and mediators simultaneously. Compared to group 1, group 5 had 1.36 and 1.58 times higher risk of total stroke and ischemic stroke, respectively. As of 1992, group 4, which had a sudden decrease in the amount of smoking of current smokers, had a higher risk of IHD (HR=1.31, 95% CI=1.09-1.57), but was not associated with the risk of stroke risk (HR=1.01, 95% CI=0.81-1.26).

Aiming to clarify whether the results from this study has life course perspective implications, I compared the model performance between group-based trajectory model and conventional model with cumulative amount of smoking (Table 3-5, 3-6). Conventional model using cumulative amount of smoking showed better model performance then the group-based trajectory model. Although The trajectory analysis model has the advantage of showing differences in health outcomes according to changes in the amount of smoking over a period of time, model performance was

better in the conventional cumulative amount of smoking. This may be due to different range of smoking amount, which is the cumulative cigarette amount has higher range then the trajectory model. When I cross-checked the correlation of cigarette amount between trajectory and conventional model, several groups had difference in cigarette amounts.

Table 3-1. General characteristic of study participants, according to trajectory group

Detailed smoking status between 1992 and 2004, attached as supplementary table.

	Trajectory group				
	Group 1 Low steady	Group 2 Lowering	Group 3 High steady	Group 4 Rise and fall	Group 5 Very high steady
N (%)	17,158 (28.3)	8,934 (14.7)	10,479 (17.3)	9,461 (15.6)	14,679 (24.2)
Age, mean, y (1992-94)	26.9	27.0	26.9	27.1	26.9
BMI, kg/m2 (1992-94)	22.3	22.3	22.2	22.6	22.7
BMI, kg/m2 (2002-04)	24.1	24.2	24.1	24.7	24.5
SBP, mmHg (1992-94)	120.2	119.4	119.2	120.1	120.0
SBP, mmHg (2002-04)	122.6	122.6	122.5	124.2	123.7
FBG, mg/dL (1992-94)	86.5	86.1	85.8	86.3	86.2
FBG, mg/dL (2002-04)	90.7	91.4	91.8	93.1	93.3
TC, mg/dL (1992-94)	174.0	173.5	174.0	176.1	176.4
TC, mg/dL (2002-04)	192.7	193.8	194.7	199.2	197.7
Alcohol drinking, %	67.5	83.8	83.6	84.5	85.3
Exercise, %	22.1	19.1	20.0	15.1	13.4
Smoking status (1992)					
Non-smoker	72.6	2.4	3.8	0.7	0.3
Ex-smoker	24.7	24.8	8.5	2.7	0.7
1-9 cig/day	2.3	43.1	46.3	16.6	4.9
10-19 cig/day	0.3	23.8	36.2	50.1	49.5
≥20 cig/day	0.1	6.1	5.3	29.9	44.7
Smoking status (2004)					
Non-smoker	91.6	38.3	0.2	43.8	0.0
Ex-smoker	6.2	47.5	6.5	51.6	2.1
1-9 cig/day	1.7	11.9	28.5	3.5	2.6
10-19 cig/day	0.4	2.2	59.4	1.1	55.2
≥20 cig/day	0.1	0.1	5.3	0.0	40.1

BMI, body mass index; SBP, systolic blood pressure; FBG, fasting blood glucose; TC, serum total cholesterol; cig, cigarettes.

Table 3-2. Basic model with effect of smoking status and amount of smoking on ASCVD events, using Cox proportional hazard model

Baseline variables (1992-1994)	HR (95% CI) in model 1	HR (95% CI) in model 2
Age, year	1.03 (1.01-1.06)	1.03 (1.01-1.06)
Body mass index, kg/m^2	1.09 (1.07-1.11)	1.09 (1.07-1.11)
Smoking status		
Non-smoker	1.00	1.00
Former smokers	1.13 (0.97-1.31)	1.12 (0.97-1.30)
Current smokers	1.22 (1.09-1.36)	
1-9 cig/day		1.07 (0.94-1.23)
10-19 cig/day		1.12 (0.99-1.27)
≥20 cig/day		1.52 (1.34-1.73)
Alcohol drinking (yes)	1.00 (0.90-1.11)	1.01 (0.91-1.12)
Exercise (yes)	0.93 (0.83-1.03)	0.95 (0.85-1.05)
Systolic BP, per 10 mmHg	1.17 (1.13-1.21)	1.17 (1.13-1.21)
Serum glucose, per 10 mg/dL	0.99 (0.96-1.02)	0.99 (0.96 to 1.02)
Total cholesterol, per 10 mg/dL	1.06 (1.04-1.07)	1.05 (1.04-1.07)
N	60,709	60,709
Number ASCVD event	2,392	2,392
AIC	51880.44 (DF=9)	51846.84 (DF=11)
Difference in AIC		33.6 (DF=2), p<0.0001

AIC: Akaike information criterion; HR, hazard ratio; CI, confidence interval: cig, cigarettes.

Table 3-3. Basic model with effect of trajectory groups and mediators on ASCVD events, using Cox proportional hazard model

	HR (95% CI) in model 1	HR (95% CI) in model 2
Trajectory group (1992-2004)		
Group 1 (Low steady)	1.0	1.0
Group 2 (Lowering)	1.05 (0.92-1.20)	1.05 (0.92-1.20)
Group 3 (High steady)	1.11 (0.98-1.25)	1.09 (0.97-1.23)
Group 4 (Rise and fall)	1.13 (0.99- 1.29)	1.10 (0.96-1.25)
Group 5 (Very high steady)	1.49 (1.33-1.68)	1.46 (1.30-1.64)
Baseline variables (1992-1994)		
Age, year	1.04 (1.02-1.06)	1.04 (1.02-1.06)
Body mass index, kg/m^2	1.09 (1.07-1.11)	1.07 (1.05-1.08)
Alcohol drinking	1.01 (0.91-1.12)	0.98 (0.88-1.09)
Exercise	0.94 (0.85-1.05)	0.96 (0.86-1.07)
Systolic BP, per 10 mmHg	1.17 (1.13-1.21)	1.10 (1.06-1.14)
Serum glucose, per 10 mg/dL	0.99 (0.96-1.02)	0.98 (0.95-1.01)
Total cholesterol, per 10 mg/dL	1.05 (1.04-1.07)	1.04 (1.02-1.05)
Mediators (2002-2004)		
Systolic BP, per 10 mmHg		1.19 (1.15 to 1.22)
Serum glucose, per 10 mg/dL		1.03 (1.01 to 1.04)
Total cholesterol, per 10 mg/dL		1.05 (1.02 to 1.04)
N	60,709	60,709
Number ASCVD event	2,392	2,392
AIC	51847.85 (DF=11)	51670.78 (DF=14)
Difference in AIC		177.07 (DF=3), p<0.0001

AIC: Akaike information criterion; HR, hazard ratio; CI, confidence interval

Table 3-4. Basic model with effect of trajectory groups and mediators on ASCVD events, using Cox proportional hazard model

	Ischemic heart disease HR (95% CI)	Total stroke HR (95% CI)	Ischemic stroke HR (95% CI)	Hemorrhagic stroke HR (95% CI)
Trajectory group (1992-2004)				
Group 1 (Low steady)	1.0	1.0	1.0	1.0
Group2 (Lowering)	1.18 (0.99-1.39)	0.99 (0.81-1.22)	1.03 (0.74-1.44)	0.79 (0.54-1.16)
Group 3 (High steady)	1.14 (0.94-1.38)	0.95 (0.75-1.21)	0.96 (0.66-1.42)	0.68 (0.43-1.09)
Group 4 (Rise and fall)	1.31 (1.09-1.57)	1.01 (0.81-1.26)	1.00 (0.69-1.44)	1.05 (0.71-1.56)
Group 5 (Very high steady)	1.63 (1.39-1.92)	1.36 (1.11-1.66)	1.58 (1.16-2.16)	1.07 (0.75-1.59)
Baseline variables (1992-1994)				
Age, year	1.05 (1.02-1.09)	1.05 (1.01-1.09)	1.07 (1.01-1.14)	1.02 (0.95-1.09)
Body mass index, kg/m^2	1.07 (1.05-1.10)	1.03 (1.00-1.06)	1.07 (1.02-1.11)	0.96 (0.91-1.02)
Alcohol drinking	0.89 (0.77-1.02)	1.10 (0.91-1.32)	1.03 (0.77-1.38)	1.39 (0.95-2.02)
Exercise	0.92 (0.79-1.02)	0.96 (0.80-1.16)	0.94 (0.70-1.27)	1.19 (0.85-1.66)
Systolic BP, per 10 mmHg	1.09 (1.06-1.14)	1.10 (1.03-1.16)	1.09 (0.99-1.20)	1.11 (1.00-1.25)
Serum glucose, per 10 mg/dL	0.98 (0.94-1.02)	0.95 (0.91-1.01)	0.90 (0.83-0.96)	1.05 (0.96-1.14)
Total cholesterol, per 10 mg/dL	1.04 (1.02-1.06)	1.03 (1.01-1.06)	1.06 (1.02-1.10)	1.00 (0.96-1.05)
Mediators (2002-2004)				
Systolic BP, per 10 mmHg	1.10 (1.05-1.14)	1.29 (1.23-1.36)	1.20 (1.20-1.39)	1.45 (1.33-1.58)
Serum glucose, per 10 mg/dL	1.04 (1.02-1.06)	1.03 (1.00-1.06)	1.04 (1.01-1.06)	1.01 (0.96-1.07)
Total	1.04	1.01	1.04	0.98

cholesterol, per 10 mg/dL	(1.02-1.06)	(0.96-1.04)	(1.01-1.07)	(0.94-1.02)
N	60,709	60,709	60,709	60,709
Number ASCVD event	2,392	2,392	2,392	2,392
AIC	51670.78 (DF=14)	51670.78 (DF=14)	51670.78 (DF=14)	

AIC: Akaike information criterion; HR, hazard ratio; CI, confidence interval

Table 3-5. Comparison of model performance between trajectory model and convention model with cumulative amount of smoking.

Baseline	Trajectory model	Conventional model
Age	1.08 (1.07-1.08)	1.08 (1.07-1.08)
Alcohol	0.91 (0.87-0.95)	0.91 (0.87-0.95)
Exercise	0.89 (0.85-0.93)	0.90 (0.86-0.94)
SBP	1.22 (1.20-1.24)	1.22 (1.20-1.24)
FBS	1.06 (1.05-1.07)	1.06 (1.05-1.07)
TC	1.06 (1.06-1.07)	1.06 (1.06-1.07)
Trajectory group (1992-2005)		
Low steady	1.0	
Lowering	1.16 (1.10-1.23)	
High steady	1.29 (1.21-1.36)	
Rise and fall	1.35 (1.28-1.43)	
Very high steady	1.64 (1.56-1.73)	
Cumulative amount, cig year (1992-2005)		
0		1.0
1-99		1.16 (1.10-1.23)
100-199		1.30 (1.24-1.37)
200-299		1.56 (1.49-1.65)
≥300		1.91 (1.79-2.05
N (case)	159,805 (12,839)	159,805 (12,839)
AIC (DF)	302,750.14 (10)	302,675.50 (10)

Table 3-6. Comparison between trajectory model and convention model with cumulative amount of smoking.

	Trajectory group (1992-2005)				
	Group 1 Low steady	Group 2 Lowering	Group 3 High steady	Group 4 Rise and fall	Group 5 Very high steady
N (%)	46,623 (28.9)	29,542 (18.3)	24,576 (15.3)	26,436 (16.4)	33,921 (21.1)
Cumulative amount (1992-2005)					
0	90.9	12.1	0	0	0
1-99	9.1	83.0	12.8	3.3	0
100-199	0	5.0	80.2	70.7	0.2
200-299	0	0	7.1	24.2	73.3
≥150	0	0	0	1.3	26.6

3.4 Discussion

This study showed the trajectory of cigarette smoking and association with the risk of ASCVD, measured 7 times every two years between 1992 and 2004 in young adults. The main results were that the heavy smokers at baseline were divided into two groups: those who maintained heavy smoking; and those who maintained heavy smoking, but sharply decreased their smoking amount for any reason. As expected, reduction in the number of cigarettes smoked reduced the risk of ASCVD. The best explanatory model for the risk of ASCVD was a model with both trajectory and mediators.

In this study, group 4 (rise and fall), which had a sudden decrease in cigarette smoking, had a higher risk of IHD, but was not associated with an increased risk of stroke. This can be explained in two ways. First, this can be explained as an effect of smoking cigarettes on IHD before smoking amount decreased. This is because this group showed a high smoking rate at baseline. Second, this may be due to a feeling of symptoms in the heart and a decrease in smoking. If so, this can be the result of reverse causation (Stokes & Preston., 1978). However, in order to determine the likelihood of reverse causation, we have excluded the initial follow-up of two years as an additional analysis. However, the results were similar.

In group 2 (lowering), there was a steady decline in smoking between 1992 and 2004. This group actually contained many participants who had quit smoking. Although group 2 had a high level of smoking in 1992, they quit smoking over time. As a result, there was no difference in risk of group 1 (low steady), which also had the lowest CVD risk. This agrees with previous studies showing that smoking cessation immediately lowers the risk of heart disease (Shields & Wilkins., 2013; Kawachi et al., 1994). The effect of smoking on ASCVD in this study was 1.22-fold (model 1 in Table 2), which was lower than other previous studies. This study included the subjects who participated in the smoking rate survey from 1992 to 2004, so we think that only the subjects who were alive until 2004 were included in the study, and out data can be explained as a kind of survival bias (Weuve et al., 2012).

In this study, young adults decreased the risk of developing ASCVD to the same level as non-smokers when they steadily reduced the number of cigarettes smoked (group 2), or when they smoked a lot of cigarettes and then steadily reduced the number of cigarettes smoked (group 4). This meant that convincing young adult smokers to quit smoking can be a strategy to reduce the incidence of middle-aged heart disease.

A recent study on college students found smoking-related beliefs and norms recognized in individual social networks were important factors among smokers in Bangladesh (Kamimura et al., 2018). Nonetheless, the reason many young people continue to smoke and cannot stop smoking is due to nicotine addiction. In other words, smokers are smoking cigarettes despite knowing that tobacco may not only claim many lives, but also their own (Kamimura et al., 2018).

3.4.1 Strengths

The strengths of this study were that it was large-scale study of over 60,000 subjects, and that there were 7 collections of smoking data made every two years for 12 years. Through analysis of this data, we found five distinct smoking trajectories. Then, during the next 11 years, the incidences of ASCVD, including heart disease and stroke were investigated. It is the first study to see the effect of smoking trajectories on ASCVD events in young adults.

3.4.2 Limitations

The biggest limitation of this study is that the amount of cigarette smoking is not a continuous variable, but a categorical variable. Cigarette smoking variables were coded from 1 to 5. In the cigarette smoking variables, 1 means non-smoker, 2 means former smoker, 3 means 1 to 9 cigarettes per day among current smokers, 4 means 10 to 19 cigarettes per day, and 5 means more than 20 cigarettes per day. The smoking amounts surveys were conducted every two years from 1992 to 2004. These limitations could be difficult to analyze by trajectory itself because cigarette smoking variables are categorical. Nonetheless, we used the Cnorm model of trajectory analysis (Nemeth et al., 2018; Kim et al., 2018). This model was originally used for continuous variables. Fortunately, the performance of the trajectory model was excellent. More importantly, although the smoking variable is composed of categorical variables, trajectory analysis using this result shows consistent results in relation to ASCVD outcome.

Conclusion and recommendation

In conclusion, the trajectory model with mediators was far more informative to the relationship between smoking and ASCVD risk. In other words, the group who maintained steady smoking over time increased their risk of heart disease, and those who decreased smoking continuously lowered the risk of heart disease, eventually to the level of nonsmokers. It is necessary create to policies to lower the smoking rate in young adults through consistent smoking education or smoker treatment.

Chapter IV.

Mediators of the Effect of Body Mass Index on Stroke and Heart Disease Risk: Decomposing Direct and Indirect Effects

4.1. Introduction

Although Asian populations, in general, have lower BMI than non-Asian populations, the demographic and nutrition transition accompanied by rapid economic growth has inevitably generated marked changes in dietary habits and lifestyles of Asian populations. For example, South Korea's economy grew at a rapid pace during the past three decades, the economy has improved, people's incomes have increased, and westernized dietary habits become popular, just like other developing countries that experienced nutrition and health transition which during industrialization period. Since then, unfavorable shifts in lifestyles leading to weight gain among Korean population have been reported in several cross sectional studies (Kim et al., 2000; Kim et al., 2014).

The World Health Organization proposed that the definition of obesity should be different for Asians from that for Europeans. The suggested categories are as follows: 18.5-22.9 kg/m2 normal weight; 23-24.9 kg/m2 overweight; 25-29.9 kg/m2 moderate obesity; and over 30 kg/m2 severe obesity (WHO., 2016). High BMI is an important risk factor for intermediate risk factors such as hypertension, diabetes, and dyslipidemia, which also increase the risk of cardiovascular disease (CVD) (Kim et al., 2014; Kim., 2016; Deurenberg et al., 1998; Rhee et al., 2018). High BMI in young adults is also associated with increased risk of CVD in their middle age (Murray et al., 2015; Gooding et al., 2016; Berry et al., 2012; Lloyd-Jones et al., 2006; WHO., 2000; Parsons et al., 1999; Must & Strauss., 1999).

Several mechanisms for the association of BMI with heart disease have been suggested in western countries. However, the mechanisms might be different in Asian populations where the average BMI is lower than that of populations. Previous studies on metabolic mediators including blood pressure, fasting glucose, and total cholesterol on CVD used baseline measurements of mediators without accounting for the time-varying nature of these variables and did not consider the subtypes of atherosclerotic cardiovascular disease (ASCVD).

In this study, we examined the association between BMI and ASCVD over a 23-year follow-up in young adults. Specifically, we investigated whether the participants with high BMI in their 20s increased the risk of ASCVD including stroke and ischemic heart disease (IHD) later in their 40s. We also decomposed the effects of BMI on ASCVD into total effect, direct effect, and indirect effect through metabolic mediators in their 30s.

4.2. Methods

4.2.1. Study participants

The Korean Life Course Health Study (KLCHS) is a cohort from the Korean Medical Insurance Corporation (KMIC) on beneficiaries who were government employees as well as private school teachers. Among the entire Korean population (approximately 43.7 million in 1992), 4,662,438 (10.7%) were insured by KMIC, 1,297,833 workers and their 3,364,605 dependents. All participants were required to participate in biennial medical examinations, and approximately 94% of these participants completed their examinations either in 1992 and 1994 (Jee et al., 2004). The KLCHS cohort consists of 307,041 young Korean adults (142,461 men and 164,580 women) between the ages of 20 and 29 who received health insurance from the KMIC with biennial medical evaluations in 1992 and 1994. Among these young adults, 205,840 (67.0%) were enrolled in 1992, and 101,201 (33.0%) were enrolled in 1994. The exclusion criteria among 307,041 participants were as follows: those who had missing data on height, systolic blood pressure (SBP), fasting serum glucose (FSG), total cholesterol (TC), BMI (71,760); those who had missing data on smoking status, exercise, and alcohol drinking (2,091); those who had a history of cancer or ASCVD before recruitment (6,170); and those who died in the period of time between their questionnaire completion and the follow-up initiation on 1st of January in the subsequent year. Therefore, we analyzed 169,429 participants for this study. We received approval for our study proposal from the Institutional Review Board of Human Research, Yonsei University (4-2001-0029), and the Seoul National

University (E1812/001-010). This was a retrospective cohort study using past routine laboratory data, and thus consent was waived.

4.2.2. Data collection

The KMIC biennial examinations were conducted by medical staffs at local hospitals based on a standardized procedure between 1992 and 2004, and participants were asked to describe their lifestyles including smoking habits and alcohol consumption. General checkups provided by National Health Insurance Service were provided on a biennial basis for insured in even years, dependents of insured in odd years. Between 1992 and 1999, before Korean health insurance service was nationally unified, civil servants insurant were examined in even years, and dependents of civil servants were examined in odds years. Since 2000, when the National health insurance was unified, health check-ups were provided by birth year (odds year, even year). Thus, the current health insurance system enables to measure the whole participants during two years. In this study, the first measurement contains the data in 1992 and 1993, which was denoted as 1992. Likewise, the second measurement contained the data in 1994 and 1995, which was denoted as 1994. Aiming to reduce the measurement error, the mean value of the first and second measured values were used as the baseline exposure value. Baseline confounding variables are summarized in the same way (table 4-1).

In the study, participants were classified as current smokers if they reported to be a smoker at baseline for at least one year, never smokers if they had never smoked, and ex-smokers if they used to smoke but not anymore. BMI was calculated as weight/height2 (kg/m2) and was categorized into six groups (less than 18.5, 18.5 to 21.4, 21.5 to 24.9, 25.0 to 27.9, 28.0 to 31.9, or 32.0 or more) (Jee et al., 1999; Jee et al., 2006).

Table 4-1. Exposure and mediator data structures: weight as an example

	Data structure											
		Baseline, Exposure						Mediator				
ID		**1992**	1993	**1994**	1995	Mean		**2002**	2003	**2004**	2005	Mean
1	Insured	75		77		76	Even birth year	77		79		78
2	Insured	66	67		69	67.8	Even birth year	66		69		67.5
3	Dependant		76		77	76.5	Odd birth year		80		82	81
4	Dependant		78	79	80	78.8	Odd birth year		78		80	79

A. Body mass index as an exposure variable

As mentioned above, the mean value of BMI measured in 1992 and 1994 was used as the baseline exposure variable value. We used two types of exposure variable; BMI as a continuous variable and obesity defined as BMI 25kg/m^2 as a dichotomous variable.

B. SBP, FBS, TC as mediators

The mean values of the data measured in 2002 and 2004, respectively were sued as mediators. Two types of mediators were used in this study; SBP, FBS, and TC were used as continuous variables, while hypertension (SBP>=140 or DBP>-90mmHg),

diabetes (FBS>=125mg/dl), dyslipidemia (TC>=240mg/dl) were used as dichotomous variables.

4.2.3. Morbidity and mortality follow-up

Our main outcome variables include morbidity from (1) IHD (ICD-10 codes I20–I25), (2) stroke (codes I60-I69), and (3) total ASCVD, including hypertensive diseases (codes I10–I15), IHD (I20–I25), hemorrhagic stroke (I60–I62), thrombotic stroke (I63), other types of stroke (I64–I69), other heart diseases related to ASCVD (I44–I51), sudden death (R96), and other vascular diseases (I70–I74). We used the first event in our analyses for those who had more than one events during the follow-up period of time. In our data, professionally trained and certified medical chart recorders organized charts and assigned discharge diagnoses. In terms of morbidity and mortality, follow-up was 100% complete because all participants were followed by electronic linkage to national databases for the first ASCVD events. The follow-up period was up to 23 years from January 1, 1993 to December 31, 2015.

4.2.4. Statistical analysis

I used Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of the associations between baseline BMI and ASCVD events in men and women adjusting for the following covariates: age at enrollment (continuous variable), alcohol intake (yes and no), and participation in regular exercise (yes or no). The Cox proportional model, which examined the effects

of young adults' BMI measured in 1992-1994 on ASCVD (Model 1), adjusted baseline covariates (Model 2) and additionally adjusted metabolic mediators including SBP, FSG, and TC examined in 2002-2004 (Model 3). The direct and indirect effects were estimated using the coefficients from the aforementioned models. We compared our mediation analyis results using the methodology reported by Valeri and VanderWeele (VanderWeele. 2015)

We also calculated the percentage of excess HR mediated based on the direct and indirect effect. All analyses were conducted using SAS software, version 9.3 (SAS Institute, Cary, North Carolina, USA).

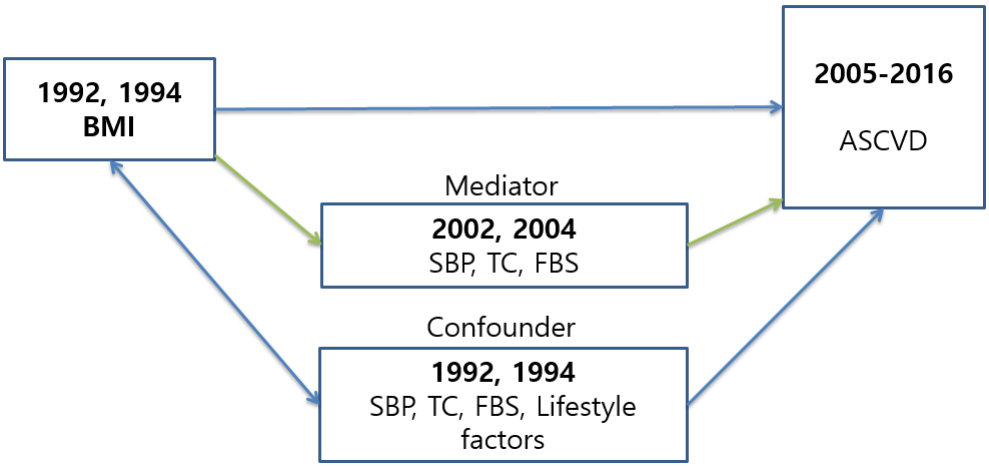


Figure 4.1 Study design

4.3. Results

The mean BMI at baseline (1992-1994) was 22.4 kg/m2 in men and 20.3 kg/m2 in women, which increased to 24.3 kg/m2 and 21.5 kg/m2, respectively, after 10 years of follow-up (2002-2004). During this period, SBP, FSG, and TC also increased in both men and women. In particular, TC increased by 20.8 mg/dl for men and 5.9 mg/dl for women. Baseline prevalence of current smoking and alcohol use in men decreased over the 10 years (65.1% to 47.4% and 83.3% to 75.6%, respectively), whereas prevalence of physical activity increased by 42.2% in men and 20.7% in women (Table 4-1).

For the entire follow-up period (1993-2015), there were 4,827 ASCVD events in men and 1,541 events in women. After 10 years of follow-up from baseline (2005-2015), there were 3,469 ASCVD events in men and 934 events in women (Table 4-13).

Table 4-2. Baseline and repeated measurements of study participants

Characteristic	Men			Women		
	1992-1994 N=98,117 (B)	2002-2004 N=98,117 (A)	A - B	1992-1994 N=71,312 (B)	2002-2004 N=71,312 (A)	A - B
Age, y	26.8 (2.0)	36.3 (2.4)		25.3 (2.6)	34.9 (3.1)	
Body mass index, kg/m^2	22.4 (2.4)	24.3 (2.9)	1.9	20.3 (2.0)	21.5 (2.5)	1.2
Systolic blood pressure, mm Hg	120.0 (11.6)	123.0 (13.7)	3.0	111.3 (10.3)	111.7 (12.1)	0.4
Fasting serum glucose, mm Hg	86.3 (13.6)	91.6 (20.6)	5.3	83.3 (11.7)	86.1 (12.5)	2.7
Total serum cholesterol, mg/dl	173.9 (33.0)	194.7 (36.0)	20.8	172.9 (33.0)	178.8 (32.3)	5.9
Alcoholic drinks – g per day	17.1 (23.6)	14.3 (21.0)	-2.8	1.05 (3.8)	0.9 (2.9)	0.06
Smoking status - %						
Former smoker	13.2	17.7	4.5	0.5	0.6	0.1
Current smoker	65.1	47.4	-17.7	0.1	0.2	0.1
Any alcohol use (yes) - %	83.3	75.6	-7.7	32.3	23.8	-8.5
Physical activity (yes) - %	20.4	62.6	42.2	8.7	29.4	20.7

*Data are expressed as mean (SD) unless otherwise indicated. All differences (A-B) were statistically significant (P for paired t test: < 0.001

In both men and women, compared to participants with <18.5 kg/m2 of BMI, participants in the highest BMI group (≥32.0 kg/m2) are at an elevated risk of ASCVD without adjusting for any covariates (HR=5.66 [3.33-9.60] in men, HR= 4.15 [0.58-29.60] in women) (Table 4-2). However, after adjustment for the covariates and mediators, the associations were attenuated, although they remained significant. In men, older age, current smokers, higher SBP, and higher TC were associated with significantly higher risk of ASCVD during outcome follow-up between 2005 and 2015 (Table 4-2). In women, current smokers and higher TC were not associated with higher risk of ASCVD.

Table 4-3. Hazard ratios for ASCVD during follow-up (2005-2015), according to BMI after adjusting for baseline covariates and intermediate variables

	Men (N=97,657)			Women (N=71,133)		
	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
Baseline (1992-1994)						
BMI						
<18.5	1.0	1.0	1.0	1.0	1.0	1.0
18.5-21.4	1.25 (0.94-1.66)	1.17 (0.87-1.55)	1.13 (0.85-1.51)	1.18 (0.97-1.43)	1.14 (0.94-1.38)	1.11 (0.92-1.35)
21.5-24.9	1.74 (1.31-2.31)	1.47 (1.10-1.95)	1.34 (1.01-1.79)	1.52 (1.23-1.88)	1.38 (1.11-1.71)	1.27 (1.03-1.58)
25.0-27.9	2.63 (1.97-3.52)	1.94 (1.45-2.60)	1.65 (1.23-2.22)	2.08 (1.39-3.11)	1.80 (1.20-2.70)	1.55 (1.03-2.33)
28.0-31.9	3.87 (2.81-5.33)	2.61 (1.89-3.60)	2.11 (1.53-2.92)	2.12 (0.78-5.72)	1.83 (0.67-4.96)	1.50 (0.55-4.06)
≥32.0	5.66 (3.33-9.60)	3.42 (2.00-5.82)	2.55 (1.49-4.36)	4.15 (0.58-29.60)	3.46 (0.48-24.68)	2.53 (0.35-18.10)
Age, year		1.05 (1.03-1.07)	1.05 (1.03-1.07)		1.14 (1.11-1.17)	1.13 (1.10-1.16)
Ex-smoker		1.08 (0.95-1.22)	1.09 (0.96-1.23)		0.94 (0.35-2.51)	0.97 (0.36-2.58)
Current smoker		1.27 (1.17-1.39)	1.25 (1.14-1.37)		0.76 (0.11-5.39)	0.70 (0.10-4.99)
Alcohol (yes)		0.95 (0.87-1.03)	0.92 (0.85-1.00)		1.04 (0.91-1.22)	1.04 (0.90-1.22)
Exercise (yes)		0.89 (0.82-0.97)	0.91 (0.83-0.99)		1.08 (0.86-1.35)	1.08 (0.86-1.35)
SBP x 10 mmHg		1.16 (1.13-1.20)	1.09 (1.06-1.12)		1.13 (1.06-1.20)	1.06 (1.00-1.13)
FBS x 10 mg/dL		0.99 (0.97-1.02)	0.98 (0.96-1.01)		1.00 (0.95-1.06)	0.99 (0.94-1.05)
TC x 10 mg/dL		1.06 (1.05-1.07)	1.04 (1.02-1.05)		1.00 (0.98-1.02)	0.99 (0.97-1.01)
Mediators (2002-2004)						
SBP x 10 mmHg			**1.19 (1.16-1.22)**			**1.23 (1.17-1.30)**
FBS x 10 mg/dL			1.03 (1.02-1.04)			1.04 (0.99-1.08)
TC x 10 mg/dL			1.03 (1.02-1.04)			1.02 (1.00-1.05)

4.3.1 Comparison between classic approach and counterfactual approach

(Example: BMI as an exposure; SBP as a mediator; stroke as an outcome)

Mediation analysis is one of the most popular methodology aiming to analyze the role of third variables involved in the causal association between an independent variable and outcome variable. Classic approach and counterfactual approach are the main two approaches for mediation analysis. Theoretical root of Classic approach goes up to Campbell's causation theory, and was the modern concept of classical mediation approach was developed in 1980s. (Judd & Kenny, 1981; Baron & Kenny, 1986). In my study, I compared the two mediation approach in the association between BMI and stroke when SBP is the single mediator in men.

Table 4-4. Total, direct, and indirect effects of BMI on stroke using **classic approach** in men: exposure in continuous and mediator in continuous

	Crude	Adjusted for age, smoking, alcohol, and exercise at baseline	Additional adjustment for SBP, FBS and TC at baseline
	Parameter (SE)	Parameter (SE)	Parameter (SE)
Total effect (TE) of BMI9294 (θ_0)	0.09485 (0.00433)	0.07667 (0.00444)	0.03896 (0.00472)
Direct effect (DE) of BMI9294 (θ_1)	0.05271 (0.00452)	0.04076 (0.00459)	0.02400 (0.00470)
θ_2 of SBP0204	0.27649 (0.00733)	0.25566 (0.00459)	0.21398 (0.00829)
β_1 of BMI9294	0.14356 (0.00095)	0.13357 (0.01907)	0.07270 (0.00093)
Indirect effect (IE)			
Difference method ($\theta_0 - \theta_1$)	0.04214	0.03591	0.01496
Product method ($\beta_1 * \theta_2$)	0.03969	0.03415	0.01556
% mediated by difference method	44.4	46.8	38.4
% mediated by product method	41.8	44.5	39.9

% mediated: IE / TE * 100;

Table 4-5. Total, direct, and indirect effects of obesity on stroke using **classic approach** in men: exposure in binary and mediator in binary

	Crude	Adjusted for age, smoking, alcohol, and exercise at baseline	Additional adjustment for systolic blood pressure, fasting glucose, and total cholesterol at baseline
	Parameter (SE)	Parameter (SE)	Parameter (SE)
Total effect (TE) of OB9294 (θ_0)	0.46596 (0.02467)	0.37578 (0.02492)	0.20411 (0.02584)
Direct effect (DE) of OB9294 (θ_1)	0.35014 (0.02507)	0.28317 (0.02522)	0.16817 (0.02591)
θ_2 of HTN0204	0.66865 (0.02507)	0.60287 (0,02367)	0.45348 (0.02512)
β_1 of OB9294	0.7763 (0.00953)	0.70980 (0.00966)	0.41040 (0.01040)
Indirect effect (IE)			
Difference method (θ_0 - θ_1)	0.11582	0.09261	0.03594
Product method ($\beta_1 * \theta_2$)	**0.51907**	**0.42792**	**0.186108**
% mediated by difference method	24.9	24.6	17.6
% mediated by product method	NE	NE	NE

% mediated: IE / TE * 100;

Table 4-6. Total, direct, and indirect effects of obesity on stroke using **counterfactual approach** in men: exposure (obesity) in binary and mediator (hypertension) in binary

	Crude	Adjusted for age, smoking, alcohol, and exercise at baseline	Additional adjustment for systolic blood pressure, fasting glucose, and total cholesterol at baseline
	Parameter (95% CI)	Parameter (95% CI)	Parameter (95% CI)
Natural total effect (NTE)	0.39862 (0.34086-0.45637)	0.32207 (0.26804-0.38028)	0.21847 (0.15814-0.27880)
Natural direct effect (NDE)	0.32758 (0.26804-0.38712)	0.26299 (0.20290-0.32310)	0.18455 (0.12260-0.24650)
Natural indirect effect (NIE)	0.07104 (0.05542-0.08665)	0.05907 (0.04502-0.07303)	0.03391 (0.02476-0.04307)
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Natural total effect (NTE)	1.48976 (1.40615-1.57834)	1.37998 (1.30194-1.46270)	1.24417 (1.17133-1.32154)
Natural direct effect (NDE)	1.38761 (1.30740-1.47273)	1.30082 (1.22495-1.38140)	1.20268 (1.13043-1.27955)
Natural indirect effect (NIE)	1.07362 (1.05698-1.09052)	1.06085 (1.04605-1.07576)	1.03449 (1.02507-1.04401)
% mediated	20.858	20.832	16.990

% mediated: IE / TE * 100;

4.3.2. **Mediation analysis using classic approach**: using three different mediators and various outcomes.

4.3.2.1 **Difference method**: using continuous exposure variable and continuous mediator variables.

Classical approach was used to estimate the direct and indirect effects of obesity on ASCVD. Beta coefficients presented in the table was estimated from the Cox proportional hazard model. As presented in the following table total effect is defined as the effect of BMI on ASCVD with controlled baseline confounding variables. Direct effect was then estimated by estimating the effect of BMI on ASCVD including the metabolic mediators (mean value measured twice).

In men, the total effect of BMI on ASCVD incidence was 0.05879 per BMI unit increase. If we exchange this beta coefficient to exponential value, the hazard ratio was 1.06533 times. In other words, as the BMI increased by 1 unit, risk of ASCVD incidence increased by 1.06533. This total effect was decomposed into direct and indirect effect.

Direct effect: Direct BMI effect on ASCVD was 0.04286 (HR=1.043792) when the continuous metabolic mediators SBP, FBS and TC were included in the model

Indirect effect: In the classic approach when mediators were continuous variables, indirect effect was 0.01593 (HR=1.016058) using difference method. In other words, incidence of ASCVD increased 1.016058 times per 1 BMI unit through mediator SBP, FBS and TC. If this value is exchanged to proportion of mediated, 27.1% was

mediated by mediators. In detail, the proportion mediated was largest in total stroke with 60.4%, while Ischemic heart disease was mediated by 21.5%. For the hemorrhagic stroke, the IE was not estimated since the direct effect was negative and statistically insignificant.

Also in women, direct effect and indirect effect was estimated by difference was estimated by difference method. Proportion of Indirect effect mediated by mediators was 33.3% in total ASCVD, and was highest in AMI which was 47.2%.

Since I used the difference method by combining the mediating effects of SBP, FBC, TC rather than separately estimating the mediating effects of each mediator, careful interpretation is required. Moreover, further research splitting the effect of each mediators is required.

Table 4-7. Direct and indirect effects of BMI on ASCVD using difference method in men and women: exposure in continuous and mediators in continuous

	ASCVD	Stroke			IHD		
		All	Ischemic	Hemorrhagic	All	AMI	Angina
	Parameter	Parameter	Parameter	Parameter	Parameter	Parameter	Parameter
Men							
Total effect (TE)	0.05879	0.03896	0.06036	0.00902	0.06389	0.05713	0.05989
Direct effect (DE)	0.04286	0.01541	0.03392	-0.02385	0.05524	0.04486	0.05234
Indirect effect (TE-DE)	0.01593	0.02355	0.02644	0.03287	0.00865	0.01227	0.00755
% mediated	27.1	60.4	43.8	NE	13.5	21.5	12.6
Women							
Total effect (TE)	0.06761	0.04380	0.08701	-0.00183	0.09315	0.03420	0.00986
Direct effect (DE)	0.04508	0.02828	0.06050	-0.02653	0.07408	0.01810	0.08153
Indirect effect (TE-DE)	0.02253	0.01552	0.02651	0.0247	0.01907	0.03239	-0.07167
% mediated	33.3	35.4	30.5	NE	20.4	47.2	NE

Total effect: adjusted for age, smoking, alcohol, exercise, systolic blood pressure (SBP), fasting glucose, and total cholesterol at baseline (’92 and ‘94); Direct effect: adjusted for age, smoking, alcohol, exercise, SBP, fasting glucose, and total cholesterol at baseline plus mediators (SBP, FBS, and TC) (’02 and ’04); % mediated: (TE-DE)/TE * 100; NE: not estimated due to small sample or insignificant results.

4.3.2.2 Difference method: using binary exposure variable and binary mediator variables.

Table 4-8 describes the results of mediation analysis using classic approach when exposure and mediator variables are both binary variables.

Total effect of obesity on ASCVD is 0.27732.

If we exchange this beta coefficient to exponential value, the hazard ratio was 1.31958 times. In other words, obese participants had 1.31958 times higher risk of ASCVD than normal weight participants.

Total effect was decomposed to direct and indirect effects.

In men, the direct effect of obesity on ASCVD was 0.15744 (HR=1.170511) and indirect effect was 0.06988 (HR=1.072379). Proportion of indirect effect was 30.7% among the total effect in ASCVD. Proportion of indirect effect was largest in total stroke which was 48.7% (Table 4-8).

In women, the total effect of Obesity on ASCVD was 0.36094 (HR=1.434677), direct effect with mediator adjusted was 0.20253 (HR=1.224497). Total effect minus direct effect was 0.15841 (HR-=1.171466)

Also in women, proportion mediated by the indirect effect was largest in stroke (66.5%)

Table 4-8. Direct and indirect effects of obesity on ASCVD using difference method in men and women: exposure in binary and mediators in binary

	ASCVD	Stroke			IHD		
		All	Ischemic	Hemorrhagic	All	AMI	Angina
	Parameter (B)	Parameter (B)	Parameter (B)	Parameter (B)	Parameter (B)	Parameter (B)	Parameter (B)
Men							
Total effect (TE)	0.22732	0.20411	0.28390	0.11768	0.21768	0.16530	0.20445
Direct effect (DE)	0.15744	0.10444	0.17171	-0.01886	0.17750	0.11143	0.16875
Indirect effect (TE-DE)	0.06988	0.09967	0.11219	0.13654	0.04018	0.05387	0.0357
% mediated	30.7	48.8	39.5	NE	18.5	32.6	17.5
Women							
Total effect (TE)	0.36094	0.16162	0.21469	0.09630	0.53391	0.68409	0.62364
Direct effect (DE)	0.20253	0.05409	0.07940	-0.02796	0.39392	0.47854	0.49259
Indirect effect (TE-DE)	0.15841	0.10753	0.13529	0.12426	0.13999	0.20555	0.13105
% mediated	43.9	66.5	63.1	NE	26.2	30.0	21.0

Total effect: adjusted for age, smoking, alcohol, exercise, systolic blood pressure (SBP), fasting glucose, and total cholesterol at baseline (’92 and ‘94); Direct effect: adjusted for age, smoking, alcohol, exercise, SBP, fasting glucose, and total cholesterol at baseline plus mediators (hypertension, diabetes, and dyslipidemia) (’02 and ’04); % mediated: (TE-DE)/TE * 100; NE: not estimated due to small sample or insignificant results

4-3-2-3. Product method: exposure in continuous and mediators in continuous

Table 4-9. Total and indirect effects of BMI on ASCVD using product method in men: exposure in continuous and SBP as mediator in continuous.

	ASCVD	Stroke			IHD		
		All	Ischemic	Hemorrhagic	All	AMI	Angina
	Parameter (B)	Parameter (B)	Parameter (B)	Parameter (B)	Parameter (B)	Parameter (B)	Parameter (B)
Total effect	0.05879	0.03896	0.06036	0.00902	0.06389	0.05713	0.05989
β_1 : BMI-> SBP	0.0727	0.0727	0.0727	0.0727	0.0727	0.0727	0.0727
θ_2 : SBP-> ASCVD	0.14940	0.20826	0.20068	0.33957	0.06061	0.08504	0.05284
IE: β_1* θ_2	0.01086	0.01514	0.01459	0.02469	0.00441	0.00618	0.00384
β_1 : BMI-> FBS	0.12262	0.12262	0.12262	0.12262	0.12262	0.12262	0.12262
θ_2 : FBS-> ASCVD	0.03966	0.05274	0.06888	0.04132	0.03476	0.05118	0.03024
IE: β_1* θ_2	0.00486	0.00647	0.00845	0.00507	0.00426	0.00628	0.00371
β_1 : BMI-> TC	-0.01355	-0.01355	-0.01355	-0.01355	-0.01355	-0.01355	-0.01355
θ_2 : TC-> ASCVD	0.01899	0.00147	0.01803	-0.03595	0.03476	0.07299	0.02382
IE: β_1* θ_2	NE	NE	NE	NE	NE	NE	NE

Total effect: adjusted for age, smoking, alcohol, exercise, systolic blood pressure (SBP), fasting glucose, and total cholesterol at baseline (’92 and ‘94); % mediated: (TE-DE)/TE * 100; NE: not estimated due to small sample or insignificant results

Table 4-10. Total and indirect effects of BMI on ASCVD using product method in women: exposure in continuous and SBP as mediator in continuous.

	ASCVD	Stroke			IHD		
		All	Ischemic	Hemorrhagic	All	AMI	Angina
	Parameter (B)	Parameter (B)	Parameter (B)	Parameter (B)	Parameter (B)	Parameter (B)	Parameter (B)
Total effect	0.06761	0.04380	0.08701	-0.00183	0.09315	0.03420	0.00986
β_1 : BMI-> SBP	0.07753	0.07753	0.07753	0.07753	0.07753	0.07753	0.07753
θ_2 : SBP-> ASCVD	0.20004	0.16896	0.16600	0.03141	0.12780	0.18821	0.12716
IE: β_1* θ_2	0.01551	0.01310	0.01287	0.00244	0.00991	0.01459	0.00986
β_1 : BMI-> FBS	0.06455	0.06455	0.06455	0.06455	0.06455	0.06455	0.06455
θ_2 : FBS-> ASCVD	0.05531	0.02216	0.09521	-0.07145	0.06602	0.11797	0.06353
IE: β_1* θ_2	0.00357	0.00143	0.00615	NE	0.00426	0.00762	0.00762
β_1 : BMI-> TC	0.04556	0.04556	0.04556	0.04556	0.04556	0.04556	0.04556
θ_2 : TC-> ASCVD	0.00543	-0.01441	0.00348	-0.03478	0.03647	0.01471	0.02674
IE: β_1* θ_2	0.00025	NE	0.00016	NE	0.00166	0.00067	0.00122

Total effect: adjusted for age, smoking, alcohol, exercise, systolic blood pressure (SBP), fasting glucose, and total cholesterol at baseline ('92 and '94); % mediated: (TE-DE)/TE * 100; NE: not estimated due to small sample or insignificant results

4.3.3 Mediation analysis using counterfactual approach.

Table 4-11 and Table 4-12 describe the relationships between baseline characteristics and mediators and their associations with total and subtypes of ASCVD development in men and women. In both men and women, the direct effect of high BMI on the development of ASCVD was greater than the indirect effect. The percentage of excess HR of BMI mediated by SBP, FSG, and TC was 22.22% in men and 33.33% in women.

I explored the mediators of BMI on stroke and IHD risk by decomposing the direct and indirect effects in men (Table 4-11) and women (Table 4-12). The total effect of BMI was greater with ischemic stroke than with hemorrhagic stroke in men, with a total effect HR of 1.11 (1.07-1.14) for ischemic stroke and 1.02 (0.98-1.06) for hemorrhagic stroke. The similar results were shown in women (ischemic stroke: HR=1.10 [1.02-1.18], hemorrhagic stroke: HR=1.05 [0.97-1.14]). The percentage of excess HR of BMI mediated by SBP, FSG, and TC was 45.67% for stroke and 18.7% for IHD in men and 27.5% for stroke and 17.63% for IHD in women.

Table 4-11. Mediators of the obesity on stroke and IHD risk among men: decomposing the direct and indirect effects

Decomposing effect of mediators	ASCVD HR (95% CI)	Total stroke HR (95% CI)	Ischemic HR (95% CI)	Hemorrhagic HR (95% CI)	IHD HR (95% CI)
Hypertension					
Crude effect	1.36 (1.31-1.42)	1.31 (1.22-1.41)	1.45 (1.31-1.61)	1.21 (1.02-1.44)	1.35 (1.28-1.43)
Natural direct effect	1.33 (1.28-1.38)	1.27 (1.20-1.35)	1.41 (1.29-1.53)	1.12 (0.98-1.27)	1.32 (1.26-1.39)
Natural indirect effect	1.04 (1.04-1.05)	1.06 (1.05-1.08)	1.06 (1.04-1.08)	1.09 (1.06-1.13)	1.02 (1.01-1.03)
Total effect	1.39 (1.34-1.44)	1.35 (1.27-1.43)	1.49 (1.38-1.62)	1.22 (1.07-1.39)	1.35 (1.29-1.41)
% of mediated (SE)	15.2	22.0	18.0	47.6	6.9
Diabetes					
Crude effect	1.33 (1.28-1.37)	1.28 (1.20-1.35)	1.38 (1.27-1.50)	1.16 (1.03-1.32)	1.29 (1.23-1.35)
Natural direct effect	1.30 (1.26-1.34)	1.27 (1.20-1.34)	1.38 (1.28-1.49)	1.15 (1.02-1.29)	1.27 (1.22-1.32)
Natural indirect effect	1.05 (1.04-1.05)	1.05 (1.03-1.06)	1.06 (1.04-1.07)	1.04 (1.02-1.06)	1.05 (1.04-1.05)
Total effect	1.36 (1.32-1.40)	1.32 (1.26-1.39)	1.45 (1.35-1.56)	1.19 (1.06-1.33)	1.33 (1.28-1.38)
% of mediated (SE)	17.0	17.6	16.7	22.2	18.0
Dyslipidemia					
Crude effect	1.41 (1.34-1.48)	1.31 (1.20-1.42)	1.46 (1.30-1.64)	1.19 (1.01-1.41)	1.39 (1.30-1.49)
Natural direct effect	1.39 (1.33-1.44)	1.32 (1.24-1.41)	1.46 (1.33-1.60)	1.25 (1.09-1.43)	1.37 (1.30-1.44)
Natural indirect effect	1.00 (1.00-1.01)	1.00 (1.00-1.01)	1.01 (1.00-1.01)	1.00 (0.99-1.01)	1.01 (1.00-1.01)
Total effect	1.39 (1.34-1.45)	1.33 (1.24-1.42)	1.47 (1.34-1.61)	1.25 (1.09-1.43)	1.38 (1.31-1.45)
% of mediated (SE)	1.7	1.3	1.7	0.3	2.6

HR: hazard ratio, CI: confidence interval, adjusted for age, smoking, alcohol, and exercise.

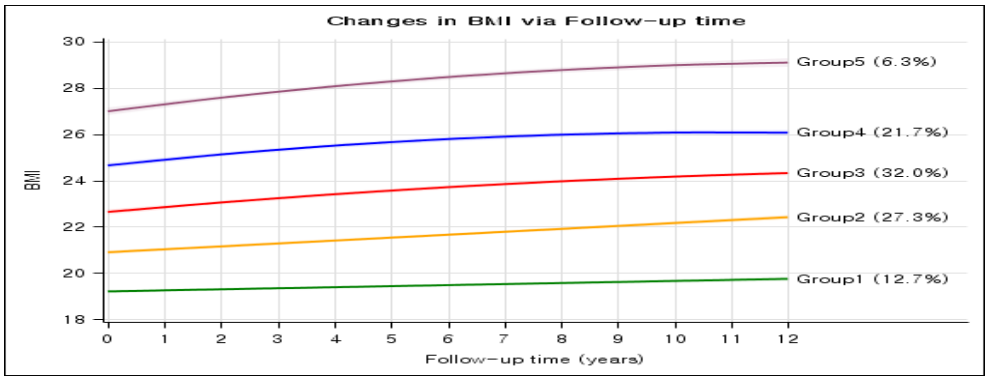
Table 4-12. Mediators of the obesity on stroke and IHD risk among women: decomposing the direct and indirect effects

Decomposing effect of mediators	ASCVD HR (95% CI)	Total stroke HR (95% CI)	Ischemic HR (95% CI)	Hemorrhagic HR (95% CI)	IHD HR (95% CI)
Hypertension					
Crude effect	1.63 (1.39-1.91)	1.31 (1.02-1.68)	1.12 (0.66-1.92)	1.12 (0.61-2.05)	2.03 (1.63-2.54)
Natural direct effect	1.61 (1.39-1.86)	1.30 (1.03-1.64)	1.20 (0.76-1.90)	1.23 (0.76-2.00)	1.95 (1.58-2.41)
Natural indirect effect	1.05 (1.02-1.09)	1.06 (1.00-1.12)	1.15 (1.00-1.33)	1.25 (1.06-1.48)	1.00 (0.96-1.04)
Total effect	1.69 (1.47-1.94)	1.38 (1.11-1.71)	1.38 (0.91-2.10)	1.54 (1.00-2.37)	1.96 (1.60-2.40)
% of mediated (SE)	12.4	19.9	4.83	57.4	0.5
Diabetes					
Crude effect	1.51 (1.30-1.76)	1.20 (0.94-1.52)	1.21 (0.75-1.94)	1.50 (0.96-2.34)	1.73 (1.38-2.17)
Natural direct effect	1.49 (1.29-1.72)	1.19 (0.95-1.50)	1.21 (0.77-1.90)	1.46 (0.94-2.26)	1.70 (1.37-2.12)
Natural indirect effect	1.03 (1.01-1.06)	1.03 (1.00-1.07)	1.10 (1.00-1.20)	0.99 (0.95-1.04)	1.04 (1.00-1.07)
Total effect	1.54 (1.34-1.77)	1.23 (0.99-1.54)	1.33 (0.88-2.00)	1.45 (0.95-2.22)	1.77 (1.44-2.17)
% of mediated (SE)	9.5	17.6	35.2	-2.0	8.4
Dyslipidemia					
Crude effect	1.40 (1.13-1.75)	1.03 (0.73-1.46)	0.98 (0.48-1.99)	1.11 (0.57-2.18)	1.85 (1.35-2.55)
Natural direct effect	1.51 (1.27-1.79)	1.19 (0.91-1.54)	1.27 (0.78-2.07)	1.17 (0.68-2.00)	1.83 (1.42-2.37)
Natural indirect effect	1.03 (1.00-1.06)	1.05 (1.00-1.09)	1.08 (0.99-1.18)	1.02 (0.94-1.10)	1.01 (0.97-1.05)
Total effect	1.55 (1.32-1.83)	1.24 (0.97-1.60)	1.37 (0.86-2.18)	1.19 (0.71-2.00)	1.85 (1.44-2.37)
% of mediated (SE)	7.9	22.5	27.1	10.8	2.5

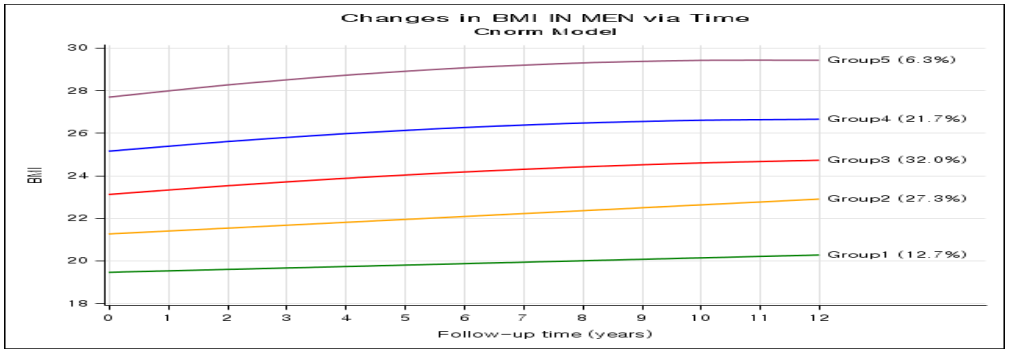
HR: hazard ratio, CI: confidence interval, adjusted for age, smoking, alcohol, and exercise.

Table 4-13. Mediators of the smoking on stroke and IHD risk among: decomposing the direct and indirect effects

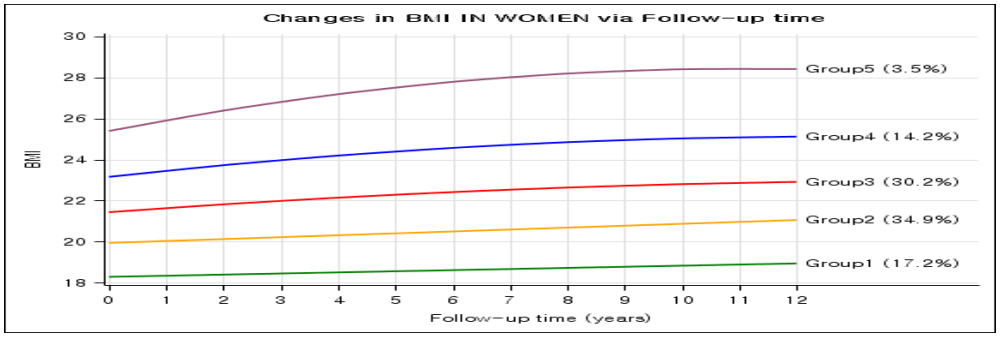
Decomposing effect of mediators	ASCVD HR (95% CI)	Total stroke HR (95% CI)	Ischemic HR (95% CI)	Hemorrhagic HR (95% CI)	IHD HR (95% CI)
Hypertension					
Crude effect	1.41 (1.35-1.48)	1.35 (1.24-1.46)	1.58 (1.40-1.78)	1.25 (1.05-1.48)	1.44 (1.35-1.53)
Natural direct effect	1.38 (1.32-1.44)	1.35 (1.25-1.45)	1.60 (1.43-1.78)	1.15 (1.00-1.33)	1.43 (1.36-1.51)
Natural indirect effect	0.999 (0.998-1.002)	0.999 (0.997-1.002)	0.999 (0.996-1.002)	0.999 (0.995-1.003)	0.999 (0.998-1.001)
Total effect	1.38 (1.32-1.44)	1.35 (1.25-1.45)	1.60 (1.43-1.78)	1.15 (1.00-1.33)	1.43 (1.36-1.51)
% of mediated (SE)	NE	NE	NE	NE	NE
Diabetes					
Crude effect	1.38 (1.32-1.43)	1.34 (1.26-1.44)	1.54 (1.39-1.70)	1.22 (1.06-1.39)	1.41 (1.34-1.49)
Natural direct effect	1.36 (1.31-1.41)	1.32 (1.24-1.41)	1.52 (1.38-1.67)	1.17 (1.03-1.32)	1.39 (1.33-1.47)
Natural indirect effect	1.01 (1.00-1.01)	1.004 (1.003-1.007)	1.006 (1.004-1.008)	1.003 (1.001-1.005)	1.006 (1.004-1.008)
Total effect	1.36 (1.31-1.42)	1.33 (1.25-1.42)	1.53 (1.39-1.68)	1.17 (1.03-1.33)	1.40 (1.33-1.47)
% of mediated (SE)	2.2	2.0	1.7	2.4	2.0
Dyslipidemia					
Crude effect	1.30 (1.23-1.37)	1.31 (1.20-1.43)	1.51 (1.32-1.72)	1.16 (0.98-1.38)	1.29 (1.20-1.39)
Natural direct effect	1.32 (1.26-1.38)	1.30 (1.20-1.40)	1.48 (1.33-1.66)	1.13 (0.98-1.31)	1.35 (1.27-1.43)
Natural indirect effect	1.009 (1.008-1.012)	1.003 (1.000-1.007)	1.008 (1.003-1.013)	0.994 (0.988-1001)	1.016 (1.012-1.019)
Total effect	1.33 (1.27-1.40)	1.30 (1.21-1.41)	1.50 (1.34-1.68)	1.13 (0.97-1.30)	1.37 (1.29-1.46)
% of mediated (SE)	3.9	1.5	2.5	NE	5.7



Supplementary Figure 4-1. Trajectory group of BMI in Korean young adult.



Supplementary Figure 4-2. Trajectory group of BMI in Korean young adult men.



Supplementary Figure 4-3. Trajectory group of BMI in Korean young adult women.

Supplementary Table 4-1. General characteristic of study participants, according to trajectory group (N=270,408)

BMI, body mass index; SBP, systolic blood pressure; FBG, fasting blood glucose; TC, serum total cholesterol; cig, cigarettes.

	Trajectory group				
	Group 1	Group 2	Group 3	Group 4	Group 5
N (%)	40,300	76,934	81,021	55,706	16,447
% of female	60	39	20	9	7
Age, mean, y (1992-94)	32.0	33.0	33.8	34.3	34.2
BMI, kg/m2 (1992-94)	19.0	20.9	22.8	24.9	27.6
BMI, kg/m2 (2002-04)	19.6	22.1	24.1	26.3	29.1
SBP, mmHg (1992-94)	112.2	115.0	118.2	121.2	124.6
SBP, mmHg (2002-04)	114.1	118.4	123.0	127.0	131.3
FBG, mg/dL (1992-94)	84.5	85.6	87.2	88.7	89.6
FBG, mg/dL (2002-04)	87.1	89.3	92.6	96.1	101.2
TC, mg/dL (1992-94)	171.7	174.9	182.0	189.1	195.7
TC, mg/dL (2002-04)	183.5	190.4	197.6	202.4	205.8
Alcohol drinking, %	33.9	50.1	65.9	75.2	77.9
Exercise, %	11.8	15.7	18.5	19.8	20.2
Smoking status (1992, %)					
Non-smoker	68.9	52.4	37.1	28.7	26.1
Ex-smoker	6.6	10.9	14.5	15.2	13.4
Current-smoker	24.5	36.7	48.4	56.1	60.5

Supplementary Table 4-2. Basic model with effect of trajectory groups and mediators on ASCVD events, using Cox proportional hazard model

	Ischemic heart disease	Total stroke	Ischemic stroke	Hemorrhagic stroke
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Trajectory group (1992-2004)				
Group 1	1.0	1.0	1.0	1.0
Group 2	1.27 (1.16-1.39)	1.10 (1.00-1.21)	1.18 (1.00-1.39)	0.92 (0.76-1.12)
Group 3	1.47 (1.35-1.61)	1.13 (1.02-1.24)	1.25 (1.07-1.47)	0.76 (0.62-0.93)
Group 4)	1.66 (1.51-1.82)	1.20 (1.09-1.33)	1.35 (1.14-1.59)	0.86 (0.70-1.06)
Group 5	1.71 (1.54-1.90)	1.28 (1.14-1.44)	1.53 (1.26-1.84)	0.90 (0.70-1.16)
Baseline variables (1992-1994)				
Age, year	1.074 (1.068-1.079)	1.066 (1.059-1.073)	1.077 (1.066-1.088)	1.05 (1.03-1.06)
Sex	0.491 (0.449-0.536)	1.140 (1.033-1.257)	0.777 (0.660-0.915)	1.06 (0.86-1.32)
Alcohol drinking	0.795 (0.756-0.835)	1.008 (0.942-1.078)	0.958 (0.867-1.058)	1.09 (0.94-1.27)
Exercise	0.839 (0.796-0.884)	0.945 (0.886-1.007)	1.033 (0.942-1.133)	0.98 (0.86-1.13)
Systolic BP, per 10 mmHg	1.087 (1.066-1.110)	1.104 (1.077-1.131)	1.108 (1.069-1.149)	1.12 (1.06-1.18)
Serum glucose, per 10 mg/dL	1.018 (1.003-1.033)	1.021 (1.003-1.040)	1.051 (1.027-1.075)	1.02 (0.98-1.07)
Total cholesterol, per 10 mg/dL	1.045 (1.037-1.053)	1.020 (1.010-1.030)	1.027 (1.012-1.042)	1.01 (0.99-1.03)

Mediators (2002-2004)				
Systolic BP, per 10 mmHg	1.007 (1.005-1.008)	1.018 (1.016-1.020)	1.019 (1.016-1.022)	1.031 (1.027-1.035)
Serum glucose, per 10 mg/dL	1.005 (1.004-1.005)	1.005 (1.004-1.006)	1.007 (1.006-1.008)	1.004 (1.001-1.006)
Total cholesterol, per 10 mg/dL	1.003 (1.002-1.004)	1.000 (0.999-1.001)	1.001 (1.000-1.002)	0.998 (0.996-1.000)
N	269431	269,568	269921	269964
Number ASCVD event	9952	6560	2882	1365
AIC	233593.4 (DF=16)	153686.3 (DF=16)	66410.9 (DF=16)	31986.0 (DF=16)

AIC: Akaike information criterion; HR, hazard ratio; CI, confidence interval

4.4. Discussion

I examined the association between baseline BMI and the risk of ASCVD among Korean young adults who were aged 20 to 39 years in 1992 and 1994 along with the metabolic mediators measured in 2002 and 2004. In both men and women, higher BMI had strong associations with ASCVD.

I also decomposed the effects of BMI on ASCVD into total, direct, and indirect. I conceptualized the total effects as the effects from covariate-adjusted baseline BMI to ASCVD, direct effects as effects from baseline BMI to ASCVD after additionally adjusted for mediators, and indirect effects as the difference between the total and the direct effects. In both men and women, the direct effects on ASCVD were greater than the indirect effects. The percentage mediated by SBP, FSG, and TC was 45.67% and 27.5% for stroke in men and women, respectively, and 18.7% and 17.63% for IHD in men and women, respectively.

In my study, the percentage mediated by SBP, FSG, and TC was lower than previous findings. Lu and colleagues reported that metabolic mediators explain about half of the adverse effects of high BMI on CHD (Lu et al., 2015). The differences between our study and the previous study can be explained in several ways. First, they used baseline measurements of mediator, while my study used mediators measured after 10 years from baseline. Also, racial differences in the mechanisms of obesity and heart disease between the studies might account for the inconsistent results. Further research is needed to enhance understanding of the association between obesity and heart disease in different populations. My study found that

managing obesity in young adults is expected to help prevent heart disease in their middle age. Also, obese young adults still have a chance to reduce their heart disease risk in their middle age, if they manage their metabolic mediators well in their later life.

Since the direct effect in this study is defined as the direct effect of BMI measured in baseline period (1992 and 1994), checking the repeatedly measured BMI until the mediation period would inform more explanation whether the direct effect of baseline BMI is tend to be underestimated or overestimated. I conducted a group based trajectory analysis using BMI data repeatedly measured seven times by 2 year intervals until 2004 intermediate period and the results were depicted at supplementary figure 4-1 to 4-3. As we can guess, the overall trend of BMI steadily increase in all trajectory groups. The group who had highest BMI records were more likely have highest SBP, FBG, TC and showed higher prevalence of current smoking (Supplementary table 4-2). Groups with higher level of BMI was associated with higher risk of ASCVD incidence, except in Hemorrhagic stroke.

Therefore, trajectory analysis using reputedly measured BMI seems to be underestimated since all trajectory groups showed steadily increasing trend. Thus, early management and intervention might be even more important than the statistically estimated direct effect value of BMI.

In the context of gender difference of BMI distribution between men and women, it supports the previous studies that reported differential susceptibility to obesity between male, female. Hong and her colleagues reported the metabolic

differences between males and females using ovariectomized female mice experiment (Hong et al., 2019). Jacobson and Rowe investigated the genetic and environmental influences on variation in adolescent BMI. Their study reported that shared environmental influences were significant for white female adolescents, while not for black females or males (Jacobson and Rowe., 1998). Understanding these gender based metabolic differences may enable to conduct better preventive and treatment strategies for weight control.

Because early management and intervention plays an important role in preventing CVD, increasing number of researchers have focused on childhood as an early period of vulnerability to insults with the assumption that childhood vulnerability may elevate risks of CVD in adulthood (Miller et al., 2011; Steptoe & Kivim€aki., 2013; Taylor., 2010). However, it has not been studied whether this theory applies to young adults. In other words, it remains to be investigated whether young adults can be a critical period for disease risk in adulthood, including the elderly years. The life course approach to health emphasizes temporal, social perspectives on individuals' or cohort's life experiences across generations for clues to current patterns of health outcomes. Not only the period in utero and early infancy but also childhood and adolescence are conceptualized as critical periods of growth and development in the human life cycle when early risk factors do damage to long-term health. Early risk exposures in critical periods interact with later modifiers to have synergetic effects on health outcomes in middle age (Barker., 1998; Ben-Shlomo, Y., & Kuh, D., 2002; WHO., 2000). With our study design, we aimed to apply the life

course approach to ASCVD management assuming that young adults aged 20-29 may be another critical period in the life course. We conceptualized baseline BMI as an early risk factor and metabolic mediators measured after 10 years as later life factors. The results of this study suggest that young adulthood can be also a critical period for cardiovascular health in later adulthood

The American Heart Association (AHA) defined "ideal cardiovascular health" as the simultaneous presence of three physiologic factors: total cholesterol, blood pressure, and fasting glucose without medication, along with four health behaviors: nonsmoking, normal BMI, adequate physical activity, and healthy diet (Lloyd-Jones., 2010). We incorporated the AHA-defined variables and compared the values between the two study time points: one at the study baseline (young adulthood) and the other in the midst of the study follow-up (later adulthood). The level of TC showed the largest increase between the baseline and intermediate periods of follow-up. Moreover, compared to women, higher levels of SBP or TC had greater risks for ASCVD in men (Table 4-11). Although the effects of changing dietary habits towards a more westernized style might explain the dramatic changes in cholesterol levels (Musso et al., 2003; Connor et al., 1992), more specific studies are needed to clarify the explanations. Nevertheless, another finding that baseline FSG and TC in women were not related to ASCVD may be attributed to the fact that most of the women in this study were premenopausal, indicating that they were at relatively lower risk of CVD (Leviton., 1973).

The main strength of this study is the long-term follow-up period of a large cohort with over 200,000 young population, allowing us to capture changes in disease risk factors over time. Moreover, the complete follow-up for ASCVD events allowed us to examine disease risk in detail across a wide range of BMI. Also, measurement error was minimized by using measured BMI and by using the averages from 1992 and 1994. It was also possible to evaluate the effects of the metabolic mediators by reexamining the same measurements in 2002 and 2004, after 10 years from the baseline.

Several limitations of our study should be acknowledged in terms of the follow-up period and representativeness of our participants. First, 23-year follow-up period is still a short term for assessing the effect on health outcomes in the elderly considering that Korean population is aging rapidly. Second, since only special subjects—civil servants and private school staff—were included in the study, we should be cautious about generalizing these findings.

In conclusion, high BMI in young adults was an independent risk factor for CVD in their middle age. High BMI increased the risk of metabolic mediators in middle age, which explain about 20 to 30% of the adverse effects of high BMI on ASCVD. Our results suggest that ASCVD intervention should focus not only on primary prevention of obesity but also on hypertension, diabetes, and cholesterol.

Chapter V.

Overall discussion: Synthesis of results, comments on young adult health using life course approach and methodology review

5.1. Synthesis of the results

The present thesis aims to explore the health of young adults based on the hypothesis that young adulthood may be another critical period in the life course.

The first study was a life course health study that investigated whether blood cholesterol at baseline (2002-2004) act as an effect modifier in the association between baseline smoking in adulthood (aged 20-29) and cardiovascular diseases occurred during 1992 to 2015. Smoking was found to be a leading risk factor among young adults who had a relatively low level of cholesterol. Moreover, the association was not modified by total cholesterol level.

The second study analyzed the trajectory of cigarette smoking and association with the risk of ASCVD, measured 7 times every two years between 1992 and 2004 in young adults. Those who maintained heavy smoking, and those who maintained heavy smoking but sharply decreased their smoking amount for any reason. As expected, reduction in the number of cigarettes smoked reduced the risk of ASCVD

The third study investigated the association between BMI in young adulthood and the risk of CVD. The study focused to elucidate whether direct or indirect effect of BMI on CVD risk through elevated levels of cholesterol, fasting blood glucose, blood pressure was stronger than the other. In this study, a high BMI in young adults was an independent risk factor for CVD in their middle-age.

5.2. Implications on public health

Legitimacy of managing lifestyle in young adult period

The importance of young adult populations tend to be underestimated in terms of health policy as well as of academic interest. However, young adult populations need more attention in terms of policymaking and research from societal and life course perspective.

In terms of societal perspective, young adulthood period is unique in terms of various events including the transition from institutional and parental protection to social independency. While the majority of teenager adolescents are supervised by institutional education, the socio-economic status of young adults varies (eg, laborers, college students, soldiers, and part time workers). Under this weaken protection; they are exposed more easily to risky behaviors like alcohol drinking and cigarette smoking.

The first study showed that, unlike well known risk factors of ASCVD such as cholesterol in middle age, smoking attributed more fracture in young adult men .The results from second study added details by more advanced methodology, that repeatedly measured smoking amount explained better as an exposure, and high steady smoking amount group was associated with elevated risk of ASDVD.

In the life course health study, young adult period was suggested to be another ‘critical period’ in life course. The conventional concept of critical period in life course health perspective did not tend to define young adult period as a critical

period. In this study, however, revealed that young adults were more vulnerable in exposure to risky health behaviors. This might be due to the fact that they are no more protected by institutional or parental care, so they may also need certain levels of health care. Moreover, health status in young adult period is important since we live longer than ever before.

Throughout out my thesis, I examined the risk factors of young adult period for middle aged ASCVD with emphasis on smoking and BMI level (obesity) since those two risk factors were representative unhealthy behaviors in young adult.

Additional analysis was conducted to verify the combined effects of smoking and

BMI (obesity) on ASCVD on in men and women respectively (Supplementary table 5-1, 5-2). In men, smoking attributed more fraction on all types of ASCVD incidents. However, no significant interaction was found between the models with separated main effects and model with combined effect. In women, due to extremely low smoking prevalence, I had certain limitations to estimate combined effect of smoking and BMI, moreover comparison between main effect model and interaction model was inappropriate.

Ben-Shlomo and Kuh defined Life course approach as the study of long term effects on chronic disease risk of physical and social exposures throughout gestation, childhood, adolescence, young adult hood and later adult life. Life course approach aims to visualize the biological, behavioral and psychosocial pathways by various exposures across human life course, generations (Ben-Shlomo and Kuh., 1997).

Methodological issues in life course epidemiology

Conventional cohort studies recruit middle aged subjects and follow up for health outcomes in future life. Although baseline exposure measures can include early life exposures, such as birth weight or parental socioeconomic status on childhood, these exposures would usually recorded in retrospective recall, and regarded as covariates included in a multivariable model without perception to the temporal association between variables.

Figure 5-1 depicts the conceptualized life course illustration reported by Ben-Shlomo and Kuh. Life course model is not only interested in association between early life exposures with later health outcome, but also potential pathways with particular intermediate variables or confounding factors as follows (Ben-Shlomo and Kuh., 1997).

Path a. predominantly biological pathway: impaired fetal development – future respiratory insults from infectious agents and greater susceptibility – impaired lung function in adulthood.

Path b. predominantly social pathway: disadvantaged childhood socioeconomic status – adverse childhood exposures as well as adult socioeconomic position.

Path c. socio-biological pathway: adverse childhood socioeconomic status – post adult lung function with subsequently poor adult lung function.

Path d. bio-social pathway: repeated childhood illness – adverse educational attainment - poor adult SES.

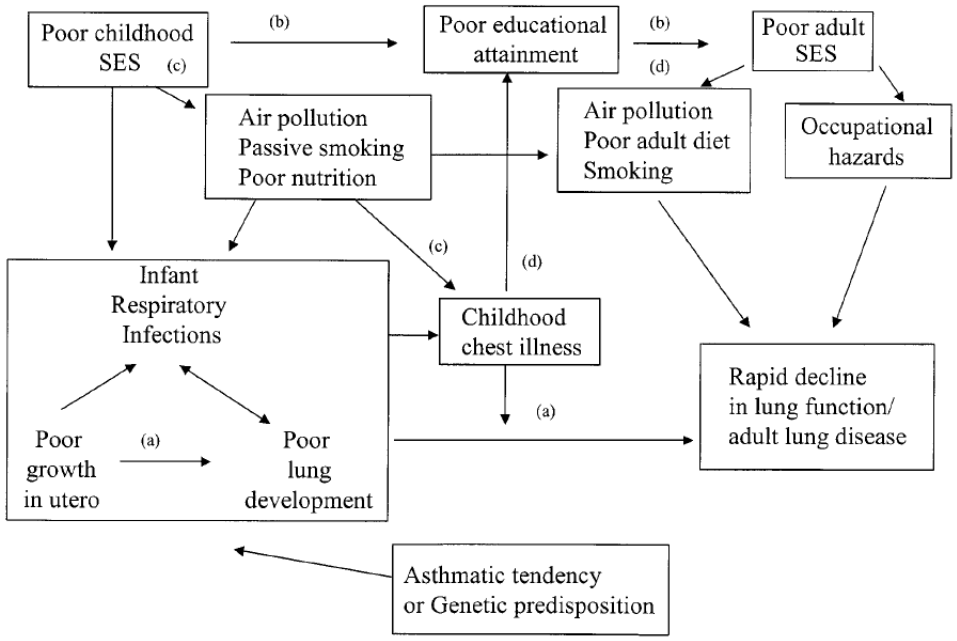


Figure 5-1. Schematic representation of biological and psychosocial exposures acting across the life course that may influence lung function and/or respiratory disease (Ben-Shlomo and Kuh., 1997).

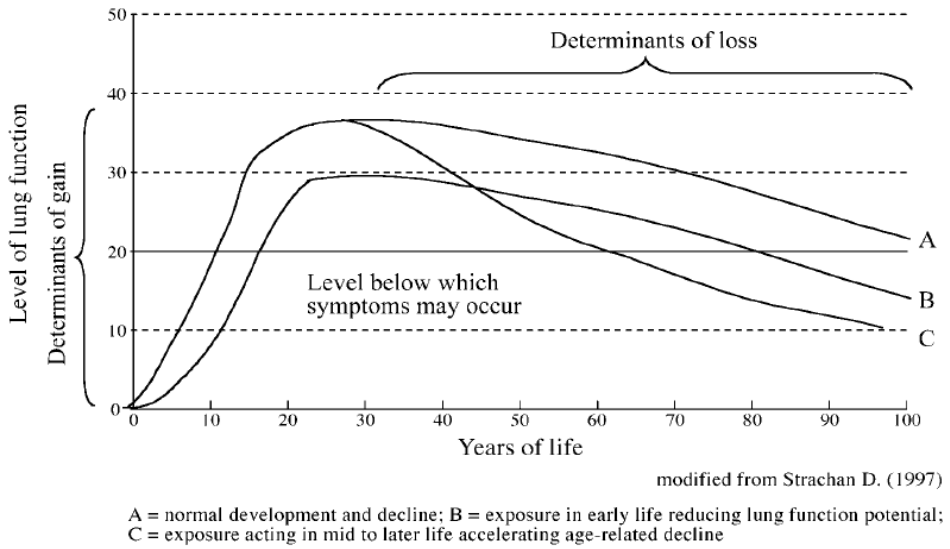


Figure 5-2. Relative importance of exposures acting across different life course time windows in terms of natural history of lung function

Life course approach not only aims to integrate temporal associations between biological and psychosocial pathways, but also requires understanding on the natural history and physiological trajectory of normal biological systems (Figure 2). Different years of life periods across the life course is associated with different biological development. Applying to my findings in regarding smoking trajectory, smoking group of smoking amount clustered into 5 different groups; Low steady, lowering, high steady, rise and fall, very high steady. As expected, reduction in the number of cigarettes smoked reduced the risk of ASCVD. In the context of obesity in young adult period, baseline BMI clustered into 5 trajectory groups based on the BMI repeatedly measured 7 times and were increasing in general, which enabled me to estimate that baseline BMI in young adult is a critical period.

From a preventive view in life course approach, in order to validate the need for preventive intervention in a certain life stage, evidence supporting the criticalness, sensitiveness of the period is required. WHO report defined the critical periodmodel when an exposure acting during a specific period has lasting for lifelong effects which is difficult to modify in any dramatic way by later experience (Kalache & Kickbusch., 1997). Two different form exist in critical period model whether regarding the importance of later life effect modifiers. While the purest form of critical period only critical for those individuals who experience some other exposure, model recognizing the importance of later life effect modifiers states that factors that raise disease risk or promote better health outcome (Mcewen. 1998).

Risk factors exposed in different stages may accumulate over time since adverse or beneficial exposure tends to cluster with another exposure (Ben-Shlomo and Kuh., 1997). Preventive intervention aims to break the chains of risks in a critical period or modify later life risk factors.

Although the concept of life course approach is not new for epidemiologist or policy decision makers, adopting life course approach faced challenges for design since only few researchers have access to a birth cohort study with repeat measures of both psychosocial and biological exposures (Wadsworth et al., 1997; Power. 2001; Golding. 2001). Since Korean Life Course Health Study has major strength in the context of repeatedly measured psychosocial and biological exposures, was able to provide valuable evidence regarding the exposure-health outcome associations that differ across time.

In the context of unique several profiles of the data source, and the socio-economic backgrounds of baseline period, results from my thesis requires careful interpretation to apply as an evidence for intervention.

First, since majority of participants are civil servants and private school teachers they are more likely to manage healthier lifestyle due to their stable socio-economic status then ordinary young adults.

Second, socioeconomic difference between the baseline period which was early 1990s, and current period 2019, typical life course would be differ between two era. While the early 1990s was when Korea was in booming economy, young adults were easily employed without additional job seeking period, young adults in the late 2010s are struggling to get stable job due to internal and external economic factors. Therefore, proportion of job seekers or students who delayed university graduation are higher than early 1990s. Although cohort studies are not prior to emphasize representativeness of participants, we still need to keep in mind the demographic, societal difference of baseline period when we aim to apply this results for young adult health care intervention in current period.

Table 5-1. Risk for atherosclerotic cardiovascular disease by obesity and smoking in men (number of participants: 307,296)

	ASCVD (n=27,403)	Total stroke (n=9,896)	Ischemic stroke (n=4,849)	Hemorrhagic stroke (n=2,390)	IHD (n=15,520)
Model with main effect					
Obesity (ref=No obese)					
Obese	1.25 (1.22-1.29)	1.24 (1.18-1.29)	1.32 (1.24-1.41)	1.19 (1.09-1.30)	1.23 (1.19-1.28)
PAF (%)	5.1	4.9	6.4	3.9	4.6
Smoking status (ref=non smoker)					
Ex-smoker	1.09 (1.04-1.13)	1.01 (0.94-1.08)	0.99 (0.89-1.10)	0.90 (0.78-1.04)	1.13 (1.07-1.19)
Current smoker	1.34 (1.29-1.38)	1.28 (1.21-1.35)	1.46 (1.35-1.58)	1.10 (0.99-1.23)	1.39 (1.07-1.45)
PAF (%)	17.6	15.0	22.5	5.9	19.7
AIC, Degree of freedom (DF)	656643.0, 9	234631.6, 9	113700.3, 9	56,907.3, 9	370,740.1, 9
Model with interaction					
Combined effect					
No obese & non smoker	1.0	1.0	1.0	1.0	1.0
No obese & Ex smoker	1.10 (1.04-1.16)	1.06 (0.97-1.16)	1.01 (0.89-1.15)	0.95 (0.80-1.13)	1.12 (1.04-1.19)
No obese & current smoker	1.37 (1.32-1.43)	1.35 (1.26-1.44)	1.52 (1.38-1.67)	1.21 (1.06-1.38)	1.40 (1.32-1.47)
Obese & non smoker	1.34 (1.26-1.43)	1.42 (1.28-1.57)	1.45 (1.25-1.69)	1.50 (1.23-1.83)	1.24 (1.14-1.35)
Obese & Ex smoker	1.41 (1.32-1.51)	1.28 (1.14-1.43)	1.39 (1.17-1.63)	1.18 (0.94-1.50)	1.45 (1.33-.158)
Obese & current smoker	1.68 (1.61-1.76)	1.62 (1.50-1.74)	1.95 (1.78-2.17)	1.34 (1.15-1.56)	1.70 (1.60-1.80)
AIC, Degree of freedom (DF)	656640.4, 11	234627.4, 11	113701.9, 11	56,904.2, 11	370,741.9, 11
X^2 (AIC difference), DF, P for interaction	2.6, 2, p=0.2725	4.2, 2, p=0.1225	Not applicable	3.1, 2, p=0.57241 .	Not applicable

Adjusted for age, alcohol intake, exercise, systolic blood pressure, fasting glucose, and total cholesterol. ASCVD: atherosclerotic cardiovascular disease, IHD: ischemic heart disease; PAF: Population attributable fraction. AIC: Akaike's information criteria

Table 5-2. Risk for atherosclerotic cardiovascular disease by obesity and smoking in women (number of participants: 123,087)

	ASCVD (n=4,275)	Total stroke (n=2,087)	Ischemic stroke (n=532)	Hemorrhagic stroke (n=498)	IHD (n=1,647)
Model with main effect					
Obesity (ref=No obese)					
Obese	1.41 (1.25-1.58)	1.27 (1.06-1.53)	1.31 (0.92-1.86)	1.31 (0.92-1.87)	1.56 (1.30-1.86)
PAF (%)	1.53	0.23	1.16	1.16	2.08
Smoking status (ref=non smoker)					
Ex-smoker	1.02 (0.66-1.58)	0.75 (0.35-1.59)	0.94 (0.29-3.05)	0.62 (0.09-4.43)	1.18 (0.61-2.29)
Current smoker	0.97 (0.48-1.95)	1.82 (0.68-4.88)	3.98 (0.98-16.1)	4.31 (1.34-13.89)	0.87 (0.28-2.71)
PAF (%)	Not applicable	Not applicable	45.0	49.0	Not applicable
AIC, Degree of freedom (DF)	93477.7, 9	45126.3, 9	11511.1, 9	10869.0, 9	35829.9,9
Model with interaction					
Combined effect					
No obese & non smoker	1.0	1.0	1.0	1.0	1.0
No obese & Ex smoker	1.10 (1.04-1.16)	1.06 (0.97-1.16)	1.01 (0.89-1.15)	0.95 (0.80-1.13)	1.12 (1.04-1.19)
No obese & current smoker	1.37 (1.32-1.43)	1.35 (1.26-1.44)	1.52 (1.38-1.67)	1.21 (1.06-1.38)	1.40 (1.32-1.47)
Obese & non smoker	1.34 (1.26-1.43)	1.42 (1.28-1.57)	1.45 (1.25-1.69)	1.50 (1.23-1.83)	1.24 (1.14-1.35)
Obese & Ex smoker	1.41 (1.32-1.51)	1.28 (1.14-1.43)	1.39 (1.17-1.63)	1.18 (0.94-1.50)	1.45 (1.33-.158)
Obese & current smoker	1.68 (1.61-1.76)	1.62 (1.50-1.74)	1.95 (1.78-2.17)	1.34 (1.15-1.56)	1.70 (1.60-1.80)
AIC, Degree of freedom (DF)	93481.2, 11	45128.1, 11	11514.5, 11	10872.2, 11	35830.7, 11
X^2 (AIC difference), DF, P for interaction	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable

Adjusted for age, alcohol intake, exercise, systolic blood pressure, fasting glucose, and total cholesterol. ASCVD: atherosclerotic cardiovascular disease, IHD: ischemic heart disease; PAF: Population attributable fraction. AIC: Akaike's information criteria

5.3. Discussion for Methodology review: Epidemiological approaches for assessing repeated measurements

Conventional prospective cohort study refers to a longitudinal cohort study that follows up over time a group of participants who differ with respect to certain exposures, to compare how these differences in baseline exposure is associated with a certain outcome (NIH dictionary). In my thesis, I followed up a cohort of young adults who vary in terms of smoking habits, to test the hypothesis that the 20-year incidence of ASCVD will be highest among heavy smokers.

Conventional cohort study is a useful research methodology on the studies on etiology of disorders and disorders. In reality, well designed conventional prospective cohort studies have made monumental contributions to our epidemiologic understanding of the risk factors and etiology. The most distinguishing feature of conventional prospective cohort study is that at the time that the researchers exclude participants who have developed any of the outcomes of interest when the researcher begin to enroll participant and collecting baseline exposure information. After dataset is established with collected baseline information, participants in the cohort are followed longitudinally over a period of time usually for years, to determine whether and when the interested disease outcome occur, and how the differences in baseline exposures change the outcomes. Throughout this process, researchers can eventually use the results to answer many research questions asking the associations between risk factors and disease outcomes.

Although conventional prospective cohort study has several advantages for reporting

the association between exposure risk factor and disease outcome,

First, conventional cohort studies without repeated measurements have important limitation to assess the association between exposure risk factors and disease outcomes. Especially in long term follow up studies that the exposure risk factors change by time varying period. In a time-to-time event or survival analysis using longitudinal prospective data, (Altman, D. G., & Bland, J. M.,.1998) certain bias can occur when exposure risk factors change value after the start of baseline observation, which are so called “time dependent variables”. Biased estimates can occur when analysis are conducted regarding time dependent variables regarded as fixed variables. Although I assessed the association between young adult smoking and ASCVD incidence in thesis Chapter III, cautious interpretation is required since the results to not consider the effect of time-dependent changes of smoking status.

Second, conventional cohort studies have limitations to clarify the complex etiological mechanism that it merely reflects the effect of baseline exposure variable.

However, regarding the fact that chronic disease occurs in complex and multi factor, multi direction, multi routes, methodological approach aiming to clarify how the pathway between exposure and outcome is depicted. In other words, exposures both have direct effect to the outcome but also has indirect effect to the outcome interacting with the third intermediate variables.

Aiming to assess the two different limitations of conventional cohort studies, I made two approaches; group based trajectory (Chapter III) and Mediation analysis (Chapter

IV).

Longitudinal cohort data provide evidence for understanding the critical period of life course perspective. This study examined how smoking and obesity in young adult period affected long-term health. Focusing To compensate the limitation of time varying exposures, I analyzed the same exposure and outcome using group based trajectory analysis and mediation analysis.

First, using group based trajectory analysis of smoking, I found the trajectory patterns of the smoking status measured in the young adult period through the reputedly measured. By this process, I aimed to compensate the first limitation of conventional prospective cohort study which does not reflect the change of exposure. Therefore trajectory analysis has been used as a major methodology for life-course health research (Nagin. 1999). Although this study had limitation that smoking variables were not measured as continuous. Baseline smoking status changed to five trajectories, in particular low steady, high steady group, rise and fall group, very high steady groups. These trajectories influenced the incidence of ASCVD in middle aged, with better prediction power than the conventional prospective cohort study. These results require cautious interpretation that selection bias may occur for only analyzing those who had survived throughout the period when smoking status were repeatedly measured seven times.

Second approach aiming to compensate the conventional cohort study's limitation which is not capable to analyze the complex effect mechanism was mediation analysis. The effects of obesity on ASCVD decomposed to indirect effect through SBP and the

direct effect. We analyzed our data by two mediation analysis method; classic approach and counterfactual approach. Classic approach was capable to estimate the indirect effect by the difference and product method when there is single continuous mediator and exposure. However, classic method has limitation to analyze multiple mediators and concern interaction between exposure and mediator.

Therefore counterfactual analysis was conducted to overcome the limitations from classic method. First, we analyzed the direct and indirect effects of BMI on stroke through SBP using difference and product methods in Classic. In the case where both BMI and SBP are continuous, the indirect effects estimated by the difference and product methods identical. However, when using binary variable, the indirect effects calculated by the difference and product methods are In other words, the computational indirect effect was overestimated by the product method. In this study, the indirect effects of binary variables were estimated through counterfactual methods. In other words, in the case of dichotomous variables, the indirect effect of obesity on stroke through hypertension was greater by the classic method than by the counterfactual method.

In terms of life course perspective, results from mediation analysis can be used to determine whether the preventive intervention's effect on obesity among young adult is larger in indirect intervention or direct intervention. Since our results stated that the direct effects was larger than the indirect effects of obesity on ASCVD, early stage interventions in young adult period before they have metabolic risk factors in middle age.

However, in this study, mediation analysis still needs to be supplemented methodologically. In other words, this study has a limitation in that it does not apply the methodology of analyzing multiple mediators or analyzing interactions at the same time. In addition, we did not attempt to combine the trajectory analysis with the mediation analysis. This needs to be analyzed in the future as the follow-up period becomes longer.

Comparison between conventional model using baseline exposures, model estimated using trajectory data collection from repeated measures of exposures, and model both including trajectory data and adjusted mediation variables. The performance of model (AIC = 51,847.85) with the trajectory group was better than the model using merely baseline smoking status (51,880.44), however was similar with model using trajectory variables + confounding (AIC = 51,846.84) without the trajectory group. Including mediators showed better model performance that trajectory model (AIC = 51,670.78) with mediators in was better than the model (AIC = 51,847.85) without mediators.

In conclusion, smoking and obesity were found to have a significant effect on middle-aged cardiovascular disease through specific trajectories and mediators. In other words, smoking and obesity in youth time provided the basis that should be considered as another early factor from the perspective of life course health.

Healthy habits and health care in youth are important for maintaining middle-aged health and for maintaining the health of the whole life course. Therefore, the future health care policy should include the concept of whole cycle including youth period.

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Yun KE, Chang Y, Yun SC, Davey Smith G, Ryu S, Cho SI, Chung EC, Shin H,

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Appendix 1-1. STROBE Statement—Checklist of items that should be included in reports of cohort studies: Korean Life Course Health Study

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
		- We established a prospective cohort for participants (aged 20-29) who routinely responded to the questionnaire on disease risk factors and chronic diseases, naming this study the Korean Life Course Health Study (KLCHS). - The KLCHS cohort included 307,041 Koreans (142,461 males, 164,580 females) who were screened by KMIC in 1992 and 1994. Of these participants, 205,840(67.0%) were registered in 1992 and 101,201 (33.0%) were registered in 1994. "Prospective cohort study within a national insurance system. Setting: Health screenings provided by national insurance in 1992 and 1994.
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported - This study aimed to analyze the trajectory of smoking in young adults for 12 years, and analyzed the effects of the trajectory group on

		future cardiovascular outcomes in a prospective cohort during another 11 years.
		- The association between smoking and CVD in young adults has not received much attention because at least a long term (over 20 years) follow-up study is needed. This serves as motivation for this study, in which we aimed to examine the effect of smoking on risk of ASCVD in Korean young adults with relatively low serum cholesterol levels. We also investigated whether the effect of smoking can be modified by serum levels of cholesterol.
		- In this study, we examined the association between BMI and ASCVD over a 23-year follow-up in young adults. Specifically, we investigated whether the participants with high BMI in their 20s increased the risk of ASCVD including stroke and ischemic heart disease (IHD) later in their 40s. We also decomposed the effects of BMI on ASCVD into total effect, direct effect, and indirect effect through metabolic mediators in their 30s.
Objectives	3	State specific objectives, including any prespecified hypotheses
		- Analysis of the trajectory using multiple measured smoking rates, rather than the one-time smoking rate in young adults would better reflect the characteristics of youth smoking.
		- If there is an established link between tobacco smoking in young adults and CVD, the campaign will further increase awareness on smoking in

		young adults. - Several mechanisms for the association of BMI with heart disease have been suggested in western countries. However, the mechanisms might be different in Asian populations where the average BMI is lower than that of populations
Methods		
Study design	4	Present key elements of study design early in the paper
		- We established a prospective cohort for participants (aged 20-29) who routinely responded to the questionnaire on disease risk factors and chronic diseases (height, blood pressure, fasting glucose, total cholesterol, or body mass index) - A total of 4,862,438 (10.7%) of the Korean population were covered by KMIC insurance, of which 1,297,833 were employees, and 3,364,605 were dependents - All insured participants are required to participate in a biennial health check-up and Approximately 94% of the insured participants in 1992 and 1994 were examined biennially
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
		- In Korea, the Korean Medical Insurance Corporation (KMIC) provided health insurance for private school staff and civil servants prior to the current insurance system, under which it was

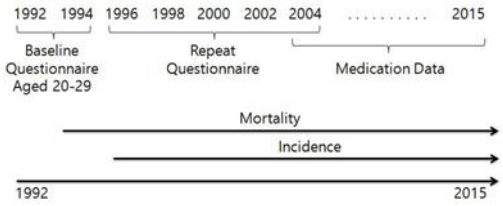
		integrated as National Health Insurance - Our cohort included 307,041 Koreans (142,461 males, 164,580 females) who were screened by KMIC in 1992 and 1994. Of these participants, 205,840 (67.0%) were registered in 1992 and 101,201 (33.0%) were registered in 1994. - The biennial KMIC screening was provided at local hospitals by medical practitioners according to standard protocols. During the two-year interval examination from 1992 to 2008, we examined the variables related to the lifestyle of participants, such as daily smoking amount, duration of smoking, and variables related to drinking
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		- In Korea, the Korean Medical Insurance Corporation (KMIC) provided health insurance for private school staff and civil servants prior to the current insurance system, under which it was integrated as National Health Insurance - All insured participants are required to participate in a biennial health check-up - We established a prospective cohort for participants (aged 20-29) who routinely responded to the questionnaire on disease risk factors and chronic diseases - The study follow-up was nearly 100% complete, as we were able to search ASCVD event data electronically by KMIC registrants regarding the morbidity information of ASCVD
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give

		diagnostic criteria, if applicable
		- From data collected at baseline, participants were defined as ‘current smokers’ if they were smoking currently, ‘never smokers’ if they had no prior history of smoking, and ‘ex-smokers’ if they had previously smoked but at the time of measurement did not smoke. Current smokers were further categorized by amount of cigarettes consumed on average per day (1–9, 10–19, and 20 or greater) as well as duration of smoking (1–9, 10–19, and 20 or more years) following the example of previous studies. - The study outcomes were identified through diagnosis information recorded in hospital admission, and from causes of death using death certificates
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
		- Korean Medical Insurance Corporation (KMIC) provided health insurance for private school staff and civil servants prior to the current insurance system, under which it was integrated as National Health Insurance. - During the two-year interval examination from 1992 to 2008, we examined the variables related to the lifestyle of participants, such as daily smoking amount, duration of smoking, and variables related

		to drinking. From data collected at baseline, participants were defined as ‘current smokers’ if they were smoking currently, ‘never smokers’ if they had no prior history of smoking, and ‘ex-smokers’ if they had previously smoked but at the time of measurement did not smoke. - Current smokers were further categorized by amount of cigarettes consumed on average per day (1–9, 10–19, and 20 or greater) as well as duration of smoking (1–9, 10–19, and 20 or more years) following the example of previous studies.
Bias	9	Describe any efforts to address potential sources of bias
		- We suggested two possible interpretations for insignificant risk of ex-smokers on ASCVD. First, it can be an effect on quitting smoking. Second, even if young people aged 20-29 quit smoking, they did not have a long period of life-time cigarette smoking, which obviously did not have to do with the increased risk of heart disease
Study size	10	Explain how the study size was arrived at
		- The KLCHS cohort included 307,041 Koreans (142,461 males, 164,580 females) who were screened by KMIC in 1992 and 1994. Of these participants, 205,840 (67.0%) were registered in 1992 and 101,201 (33.0%) were registered in 1994. - Of these 307,041 participants, 71,760 (23.4%) who had incomplete data height, blood pressure, fasting glucose, total cholesterol, or body mass index were excluded. We also excluded 6,170 people from our analysis who reported a past history of cancer and ASCVD, as well as 2,091 people who had missing information on smoking,

		exercise, or alcohol drinking, and 65 people who died before start of follow-up. Female participants were excluded, because of the low prevalence of smoking for females in Korea, resulting in a total of 118,531 eligible participants for the analysis.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
		- The definition of hypertension was a systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg. - Body mass index (BMI) was measured as weight (kg) / height (m)2. Serum total cholesterol was grouped as desirable (<200 mg/dl), borderline-high (200-239mg/dl), and high (≥240 mg/dl) - Definition of diabetes was fasting blood glucose ≥126 mg / dl.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		- In considering continuous ASCVD risk factors, we used ordinary least squares regression and coded smoking quantity as an ordinal variable. In this study, the Mantel Haenszel method was applied for dichotomous variables. - To assess the independent effects of smoking on the risk of IHD, stroke, and ASCVD, Cox proportional hazards models were used, controlling for age and the confounding variables such as hypertension, diabetes, high cholesterol, and alcohol drinking. - Proportional assumption was also tested utilizing

		Schoenfeld residuals, and the survival curve according to smoking status was plotted using the life-table method. - I used Levins formula for calculating population attributable risk (PAR).
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed - we excluded all events that had occurred in the first 4 years of follow-up
		(*e*) Describe any sensitivity analyses - we excluded all events that had occurred in the first 4 years of follow-up. These analyses ensured sensitivity in our results. In all analyses, a two-sided significance level of 0.05 was used
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		- Of these 307,041 participants, 71,760 (23.4%) who had incomplete data height, blood pressure, fasting glucose, total cholesterol, or body mass index were excluded. We also excluded 6,170 people from our analysis who reported a past history of cancer and ASCVD, as well as 2,091 people who had missing information on smoking, exercise, or alcohol drinking, and 65 people who died before start of follow-up. Female participants were excluded, because of the low prevalence of smoking for females in Korea,

		resulting in a total of 118,531 eligible participants for the analysis.
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
		
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		- The average age of the study participants was 26.7 ± 2.0 (SD) years. Among the 118,531 men, 78,455 (66.2%) were current smokers, 15,126 (12.8%) were ex-smokers, and 92,403 (15.4%) had hypertension. - For total cholesterol, 94,413 (79.7%) had a total serum cholesterol level < 200 mg/dL, 19,764 (16.6%) had a borderline level of 200-240 mg/dL, and 4,444 (3.8%) had a level of 240 mg/dL or higher. - In terms of amount of smoking, 28.9% smoked more than 20 cigarettes per day while 45.5% and 25.6% of current smokers smoked 1 to 9 and 10 to 19 cigarettes per day, respectively. - Among current smokers, 92.0% smoked for less than 10 years while 7.6% and 0.4% of current smokers smoked for 10 to 19 years and more than 20 years, respectively.
		(b) Indicate number of participants with missing data for each variable of interest

		(c) Summarise follow-up time (eg, average and total amount)
		- During 23 years of follow up (5,191,823 person-years), 2,786 (90 fatal) IHD cases (53/100,000 person year), stroke cases 2,368 (126 fatal) (45.4/100,000 person year), and 6,368 ASCVD cases (306 fatal) (122.7/100,000 person year) occurred
Outcome data	15*	Report numbers of outcome events or summary measures over time
		- After adjusting for age, current smokers had a significantly higher body mass index (P for trend =0.0056), higher consumption of alcohol drinking (P for trend <.0001), and higher prevalence of diabetes (P for trend = 0.0060) than nonsmokers. - The independent effects of smoking on IHD, stroke, and ASCVD were analyzed controlling for confounding factors through Cox proportional hazards models
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		The independent effects of smoking on IHD, stroke, and ASCVD were analyzed controlling for confounding factors such as hypertension, diabetes, high cholesterol, and alcohol drinking through Cox proportional hazards models,
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful

		time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
		To examine whether serum total cholesterol levels could modify the effect of smoking on ASCVD, we divided the cohort participants into quartile of total cholesterol. The risks above were also found throughout the range of serum levels of cholesterol demonstrating that serum total cholesterol levels did not modify the effect of smoking on ASCVD.
Discussion		
Key results	18	Summarise key results with reference to study objectives
		Estimated risk factor prevalence in current studies of smoking and other additional risk factors were used to estimate the PARs for IHD alone, stroke alone and total ASVCD For IHD, current smoking accounts for about 24.9% of events, and hypertension accounts for 8.1% of events. In the case of stroke, smoking was estimated to account for 20.9%, whilst hypertension was estimated to be responsible for 13.3% of stroke cases.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
		this study will not represent the whole population. Moreover, selection bias may be a potential issue,

		since the final sample contains a subset of over 118,531 young male adults (38.6%) out of 307,041 subjects initially selected for our study
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
		We therefore urge conservative interpretations of our study results with regard to the general population.
Generalisability	21	Discuss the generalisability (external validity) of the study results
		There are several studies regarding cardiovascular risk among young people. According to a study conducted by Bernaards et al blood pressure and waist circumference were decreased by lowering weekly tobacco consumption in younger participants Another study conducted by Morotti et al on young women with polycystic ovary syndrome (PCOS) reported an association between smoking habitude in lean PCOS patients, and the increase of soft markers of cardiovascular risk For young adult African Americans, the association between cigarette smoking and carotid intima assuming the genetic variation of smokers was reported and the -930A/G polymorphism modified the association among young healthy adults The study on association between second hand smoking among childhood and cardiovascular event in adulthood was conducted and found that

		the carotid plaque risk in adulthood is increased in children whose parents had smoked
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based
		We appreciate the assistance of the Korean National Health Insurance Service, which provided the data for this study.

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

국문 초록

청년기 건강행태에 따른 중년기 심뇌혈관질환 위험

: Korean Life Course Health Study 를 이용하여

지용호

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그 동안 생애과정 연구는 출생, 소아, 청소년, 그리고 본격적으로 만성질환이 발생하는 중•장년 층의 건강에 대한 것이 많았으나, 청년기를 포함한 연구는 상대적으로 적었다. 연구가 부족했던 이유 중 하나는 청년기가 인간의 생애에서 가장 건강한 시기이고, 각종 만성질환 발생에 대한 위험 인식이 낮은 시기이기 때문이다. 그러나 청년기 건강의 중요성은 다음과 같은 두 가지 맥락에서 의미가 있을 것으로 보인다.

첫째, 생애과정 관점(Life-course perspective)에서 유년기, 청소년기의 early life 의 건강 상태가 중•장년기의 건강에 영향을 준다는 선행 연구들은 이미 많이 보고되었다. 그러나 평균 기대 수명의 증가로 인해, 유년기나 청소년기를 early life 로 바라보던 시각을 보다 확장하여 20 대 청년의 건강이 중•장년기는 물론 노년기 의 건강에 영향을 줄 수 있는지에 대한 근거가 부족하다. 이를 위해 청년들의 대표적인 불건강 행태인 흡연과 비만이 중•장년기의 건강에 미치는 영향을 추적하는 전향적 코호트 연구가 필요하다.

둘째, 보건의료비 지출 측면에서도 청년기의 건강은 중요한 의미를 가진다. 한국사회가 고령화되면서 많은 보건의료 비용을 지출하는 노인 인구가 증가하기

때문에 중•장년기 이전 시기인 청년기의 건강관리는 미래 보건의료 비용 지출을 절감하는데 중요한 의미를 가질 것이다.

이 연구는 생애과정 중 청년기의 흡연과 비만이 중년기의 심뇌혈관질환 발생에 미치는 영향을 다음 세가지면에서 전향적 추적연구를 통해 알아보았다.

첫 번째 연구는 1992 년과 1994 년 공무원 사립학교 교직원 의료보험조합에서 제공한 일반건강검진을 받은 20-29 세 307,041 명을 생애과정 건강연구 (Life course health study) 대상자로 설정하였다. 이들 대상자중 남자 142,461 명에 대하여 baseline 흡연력과 1993 년부터 2015 년까지 발생한 심뇌혈관질환과의 관련성을 분석하였다. 이때 baseline 에서 측정된 혈청 총 콜레스테롤이 흡연력과 심뇌혈관질환과의 관련성에 effect modifier 로 작용하였는지를 알아보았다. 연구 결과 20 대 청년의 baseline 콜레스테롤 수준과 관계없이 흡연은 중년의 허혈성 심질환과 뇌졸중 발생을 유의하게 증가시켰다.

두 번째 연구는 청년들의 대표적인 불건강 습관인 담배 사용의 패턴을 10 년간 반복 측정했을 때 어떠한 형태의 그룹으로 형성되는지를 확인하였다. 그리고 이 그룹에 따라 10 여 년간 추적한 심뇌혈관질환 위험이 어떻게 달라지는지를 보고자 하였다. 즉, 1992 년부터 2004 년까지 7 회에 걸쳐 일반 건강검진에 참여하여 흡연 행태 설문을 수행한 20-29 세 남성 60,709 명을 분석하였으며 1992 년 최초 흡연 상태는 비흡연, 과거흡연, 현재흡연 (1-9 개비, 10-19 개비, 20 개비 이상)으로 분류했다. Group Based Trajectory Model (GBTM)을 이용하여 최초 흡연상태 이후 흡연 행태 변화에 따라 5 개군으로 분류하였다. Baseline 흡연력만 고려한 모델에 비해, 흡연력의 변화를 trajectory group 에 따라 고려하고 중간시점에서 측정한 mediator 까지 고려한 모델이 심뇌혈관질환 위험에 있어 가장 좋은 설명력을 보였으며, trajectory 에 의해 분류된 5 개의 그룹 중 'Very highly steady'군에서 대부분의 심뇌혈관질환의 위험이 유의하게 높았다.

세 번째 연구는 생애과정 건강연구 대상자에 대하여 baseline 체질량 지수 (Body Mass Index, BMI)와 심뇌혈관질환 발생과의 관련성을 분석하였다. 즉, 1992-1994 년에 측정한 체질량 지수가 2002-2004 년에 측정한 혈압, 콜레스테롤,

공복혈당 증가를 통해 2005-2016 년에 심뇌혈관질환 발생 위험에 미치는 직, 간접적 영향을 분석하였다. 분석 결과 청년들의 높은 체질량 지수가 10 년 후의 혈압, 콜레스테롤, 공복혈당을 유의하게 증가시켰고, 이는 곧 중년의 심뇌혈관질환 발생 위험을 높였다. 이때 청년들의 체질량 지수가 중년의 심혈관질환 위험에 미치는 영향은 간접효과보다는 직접효과가 더 큰 것으로 나타났다.

각 연구를 통해 청년시절의 대표적 불건강 행태 중 하나인 흡연력은 추적 기간 동안 다양한 형태로 변화했음을 확인했으며, 향후 연구에서 longitudinal data 를 이용한 흡연의 effect 를 분석 시, 흡연력의 변화에 대한 고려가 필요할 것으로 보였다. 또한 청년시절의 비만은 10 년 후에 측정된 대사증후군 요소를 거쳐 가는 간접 영향이 20 대시절 비만에 의해 직접 가는 영향보다 적었다.

청년의 높은 흡연율과 체질량지수는 중년의 심뇌혈관질환 발생과 직접적으로 관련 있었다. 이 연구는 생애과정적 관점에서 청년기는 중년기 건강의 early life 로서 근거를 제시하였다. 그러므로 중•장년기의 건강을 위해서 청년기의 적극적인 생활습관 관리가 필요하다는 점을 시사한다는 점에서 보건학적으로 의미하는 바가 크다고 할 수 있다.

주요어: 청년, 생애과정, 흡연, 체질량 지수, 비만, 궤적 분석, 중재 분석

학번: 2017-32395