学位論文（要約）

Association of the age at smoking initiation and cessation on all-cause and cause-specific mortality: The Japan Collaborative Cohort Study

(喫煙開始年齢と禁煙年齢の全死亡及び死因別死亡に対する関連: JACC 研究)

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1. Introduction

1.1. Situation of Tobacco use

Tobacco use is a significant public health concern worldwide and is one of the major causes of death and disability in both developed and developing countries. According to the World Health Organization (WHO) 2019 report, tobacco use is currently responsible for more than 8 million and 1.2 million deaths every year, due to active and passive smoking, respectively. With more than 1 billion current smokers globally in 2019, these numbers are likely to increase over the coming decades if countries do not put controlling interventions into practice. The enormous health as well as economic consequences of the global tobacco epidemic make tobacco control a clear and urgent public health priority. Effective implementation and enforcement of tobacco control policies and interventions can both increase healthy life expectancy, decreases tobacco attributed mortality as well as decrease health-care costs.

Despite the clear benefits of quitting tobacco, progress in tobacco control has varied substantially across countries. The first international public health treaty, the WHO framework Convention on Tobacco Control (FCTC), entered in to force and became an international binding law in 2005. Consensus on the importance of tobacco control led 182 countries to ratify the treaty which outlines a suite of recommended demand-reduction tools. These tools include reducing affordability through taxation, passing smoke-free laws, mandating health warnings on packaging, and banning tobacco advertising, promotion, and sponsorship. Since the treaty became effective, an increasing number of countries have implemented evidence based tobacco control measures to the WHO FCTC (MPOWER): Monitoring tobacco use and prevention policies (M); Protecting people from tobacco smoke (P); Offering help to quit tobacco use (O); Warning about the danger of tobacco (W); health warning labels (L) and mass media (MM); Enforcing bans on tobacco advertising, promotion and sponsorship (E) and Raising taxes on tobacco (R). Over this period, countries that successfully implemented some of these measures at the highest recommended level experience substantial reduction of tobacco smoking and tobacco-attributed deaths. Nonetheless, progress has been made in expanding coverage of the best-practice policies, with the number of countries implementing at least one best-practice policy increasing from 43 in 2007 to 136 in 2018.

Japan ratified the WHO FCTC in June 2004. However, implementation has been fragmented and tobacco control remains suboptimal relative to the FCTC standard, with Japan receiving poor (no or minimal policy) ratings in the P, W and E domains in 2018. The 2020 Tokyo

Olympic and Paralympic Games created social pressure and political will, and the tobacco control movement has been somewhat enhanced through the adoption of additional policies such as raising tobacco taxes and implementation of stricter smoke-free regulation. However, despite these new measures connected to the Games and this renewed social and political focus on denormalization of tobacco smoking, progress on tobacco control policy in Japan has been slow compared with other countries.

Although the proportion of regular male smokers has markedly decreased to 27.1% in 2019 from roughly half the proportion in 1989, when it peaked at 55.3%, With regard to age, the highest proportion was observed in men aged 30-69 years (>30%) and among regular smokers, the proportion of those willing to quit smoking was 30.6% in men. Despite, the significant reduction in smoking prevalence over decades, Japan's slow tobacco control progress is reflected in the high smoking prevalence among men, which was higher than other high- income countries, including the United States and several European countries.

1.2. Risk of Tobacco smoking with NCDs

Tobacco is one of the major risk factors for cardiovascular diseases, chronic respiratory diseases, cancers, and diabetes with approximately one in five Non-Communicable Diseases (NCDs) related deaths being attributed to smoking in 2019. Several cohort studies have shown that up to two- thirds of long-term smokers will eventually die from smoking-related diseases. According to the global burden of disease (GBD) study, in 2019, smoking was the second leading risk factors for female (with 1,510.12 thousand deaths worldwide) and the first risk factor for male (with 6,183.25 thousand deaths worldwide). The United Nations Sustainable Development Goals (SDGs) propose to ''reduce premature mortality from non-communicable diseases by one third through prevention and treatment and strengthen implementation of the World Health Organization (WHO) Framework Convention on Tobacco Control in all countries, as appropriate''. Tobacco control has been identified as a critical and necessary part of achieving these goals.

Japan, one of the most developed countries, ranked first in longevity around the world as early as in 1990, and achieved an average life expectancy of 79.9 years for men and 86.3 years for women in 2015. Although NCDs are still leading causes of death in Japan, mainly stroke (120.6 thousand deaths, or 10.1% NCDs deaths), ischemic heart disease (IHD 2.5 thousand deaths, or 8.6% NCDs deaths) and various cancer, the probability of premature deaths from CVD, diabetes, Chronic Obstructive Pulmonary Disease (COPD) and cancers was only 9%. It is reported that

deaths caused by CVD and IHD, the top two causes of death in Japan, increased 15.4% and 24.4% from 2005 to 2015, respectively. Tobacco use and high blood pressure were the two major contributors for adult mortality from NCDs and injuries.

In Japan, 130,000 people die from active smoking and about 15,000 people die from second-hand smoke exposure every year and is also the leading cause of deaths from NCDs. Smoking has been the top risk factor for NCDs mortality in Japanese adults contributing to an estimated 19.1%-24.6% of total deaths in men and 3.6-6% in women. The WHO Global Action Plan for the Prevention and Control of NCDs 2013-2020 established a global target of 30% relative reduction in smoking prevalence by 2025, using 2010 as baseline. Domestically, Japan has a target to achieve 12% smoking prevalence by 2022. However, it is doubtful if Japan can meet either of the targets with its presently suboptimal tobacco control measures.

1.3. Effect of early initiation and Cessation of Tobacco

Benefits of smoking cessation have been well documented through several cohort and meta-analysis studies conducted in the USA, UK, Australia, Europe and among Asian population. It has been consistently reported that former smokers have a substantially reduced total and major cause-specific mortality such as cardiovascular disease (CVD) and lung cancer mortalities, as compared with current smokers. Age has been known a determinant factor for smokers' premature deaths and it has been proven that early smoking initiation increases risks of experiencing smoking-related morbidities and all-cause mortality and cessation earlier in life resulting in greater reductions. In addition, previous studies have shown that early smoking initiation, in addition to immediate effects such as increased cough, fatigue, shortness of breath, and wheezing confers a greater risk for the development of vascular diseases such as CVDs, coronary artery diseases, cerebrovascular diseases peripheral artery diseases, respiratory diseases, and cancers, particularly lung cancer. Moreover, early initiation of smoking is related to increased all-cause and cause-specific mortality. The importance of quitting smoking at an early age has been highlighted in studies. A study conducted among US adults suggests that quitting smoking before the age of 40 reduces the risk of smoking-related cancer mortality by approximately 90%. Similar findings have been reported in a cohort study among Chinese men who quit smoking at a higher age, which was associated with higher all-cause deaths compared to those who quit at a lower age. However, these studies focused on the association of all-cause and cause-specific mortality with either smoking initiation age or cessation age or years since cessation. Studies on all-cause and cause-specific mortality to include age at both initiation and cessation are limited. Information on smoking initiation and cessation age in the same cohort

study provides an ideal setting for examining the risks associated with lifetime smoking and in addition to duration of smoking it provides more evidence on dose-response relationship with regards to age at smoking initiation and cessation.

1.4. Study Aims:

The aim of this study was to evaluate the association between smoking initiation and cessation age with the risk of all-cause, cancer, and CVD mortality among Japanese men in a large cohort study.

2. Materials and Methods

2.1. Study Population

Data was analyzed from the dataset of the Japan Collaboration Cohort Study for Evaluation of Cancer Risk (JACC Study) which was sponsored by the Ministry of Education, Science, Sports, and Culture. Briefly, the cohort study was established from 1988 to 1990 and followed until the end of 2009. A total of 110,585 participants (46,395 men and 64,190 women) aged between 40 and 79 years completed a questionnaire on lifestyle and medical history at baseline. Participants were enrolled from 45 study areas across Japan, mostly during municipal health checkups. The present analysis was restricted to male participants because of the limited number of female ex-smokers (only 963).

Of the 46,395 initial male participants at baseline, we excluded individuals who did not provide data on smoking-related variables, such as smoking status (n = 2,256), smoking-initiation age for current smokers (n = 1,188), and smoking-initiation age or smoking-cessation age for former smokers (n=1,093). Former smokers who reported a smoking-cessation age less than the starting age (n = 147) were excluded. After these exclusions, data from 41,711 men were included in the analysis.

2.2. Ethical considerations

Informed written consent was provided from the participants themselves or the community leaders. The JACC study protocol was approved by the ethics committees of Hokkaido University, Nagoya University and Osaka University.

2.3. Variables Measured at Baseline

Data on cigarette smoking were collected using a cohort-specific self-administered questionnaire in the baseline survey. Participants were then categorized into "current smokers" if the participants smoked currently, "former smokers'' if they had smoked in the past but reported having already quit at the time of the baseline study entry, and "never smokers'' if they had never smoked. Moreover, for current smokers, data on age at smoking initiation and for former smokers, age at both smoking initiation and cessation were obtained. For some participants (n = 126) who did not state their age at smoking cessation but stated the years since quitting, the age at smoking cessation was estimated using the time interval from baseline to the year of smoking cessation. Based on this information, current and former smokers were categorized into four groups according to their age at smoking initiation: <20, 20–24, 25–29, and ≥30 years. Former smokers were further grouped into three categories based on their age at smoking cessation: <40, 40–49, and ≥50 years.

2.4. Statistical Analysis

Cox proportional hazard models were used to derive hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for deaths of current and former smokers, with never smokers as the reference. Missing values for each variable were considered as a single category. Three models were constructed: Model 1 was adjusted for age at baseline and stratified by study area; Model 2 was further adjusted for current and past illnesses (diabetes, CVDs, hypertension, and/or cancer); and Model 3 was further adjusted for marital status, children, education, occupation, exercise, walking, BMI, passive smoking, drinking habit, and number of cigarettes smoked per day.

As participants aged 40–49 years at baseline were excluded from the category of former smokers who quit in their 50s or older by definition, therefore, the same analysis was ran by limiting the participants to those aged ≥50-59 years, ≥60-69 years and ≥70-79 years as a separate analysis to eliminate an age-distribution gap between the subgroups. In addition, another subgroup analysis was perfomed by combining all the subgroups under one category with limiting the participants to those aged ≥50 years. Furthermore, as the effect of smoking cessation on the reduction of mortality risk may be underestimated due to the health problems that participants might have had before the study, a sensitivity analysis was performed after excluding participants who died in the first 3 years of follow-up. An additional sensitivity analysis was conducted by excluding participants who were diagnosed with CVDs or cancer before the baseline. All analysis were conducted using Statistical Package for Social Science (SPSS) version 26, and $p<0.05$ was considered statistically significant.

3. Results

In this study, a dose–response relationship was detected between mortality and the age at smoking initiation among current smokers: specifically, compared with never smokers participants who started smoking at <20 years of age had the highest HR for all-cause (HR, 1.84, 95% CI, 1.72–1.98), cancer (HR, 2.19, 95% CI, 1.95–2.45), and CVD (HR, 1.70, 95% CI, 1.48–1.95) mortality (Fig 2). The HR for cancer mortality was consistently higher than that for CVD mortality. Former smokers who even quit at an older age (≥50 years) demonstrated a lower risk of all-cause and cause-specific mortality than current smokers: all-cause (HR, 1.34, 95% CI, 1.17–1.54), cancer (HR, 1.43, 95% CI, 1.12–1.84), and CVD (HR, 1.32, 95% CI, 1.03–1.70) mortality (Fig 1). However, among former smokers who quit smoking in their 50s or more, the risk of mortality remained high and showed dose dependency with regard to the age at smoking initiation, where the highest HR was detected in those who started smoking at <20 years of age: all-cause (HR, 1.51, 95% CI, 1.29–1.77), cancer (HR, 1.68, 95% CI, 1.27–2.23), and CVD (HR, 1.48, 95% CI, 1.12–1.96) mortality (Fig 2). Among former smokers who quit smoking when younger than 50 years, although the risk for all-cause and CVD mortality was absent or negligible, regardless of the age at smoking initiation, the risk for cancer mortality remained significantly high among those who quit smoking at 40–49 years of age (HR, 1.44, 95% CI, 1.03–2.01) (Fig 2). The result of the subgroup analysis and sensitivity analysis were smiliar and there wasn’t any significant difference among the subgroups.

4. Discussion

In this population-based prospective study in Japan, I found that the age at first smoking is an important determinant of mortality risk, as the risk of all-cause and cause-specific mortality compared to never smokers was 1.5–2.0 times higher among current smokers, especially among those who initiated smoking when younger. Previous report on the JACC study that evaluated smoking cessation and mortality from cardiovascular disease among both Japanese men and women also suggested that, compared with never smokers, current male smokers had a 1.5-fold higher age-adjusted rate of mortality from total stroke, 2.4-fold higher mortality from coronary heart disease, and 1.6-fold higher mortality from total cardiovascular disease. And the excess risks of mortality associated with current smoking were more evident among middle-aged person than elderly person irrespective of dose-response relationship between number of cigarettes smoked daily. Further, the association between age at starting smoking and mortality among current smokers was only found for coronary heart disease for the onset of <20 years (HR, 3.68, 95% CI, 2.33–5.74). Since in this study I used the general term CVDs and not the classifications; and the HR for CVDs for current smokers started smoking in aged <20 years was also found to be the highest among other age groups. These results also confirm the results of previous studies in the general population that found risk of mortality is higher for current smokers who have initiated smoking in younger age. And the reason for the higher mortality risk is due to the fact that early smoking initiation in addition to exposing individuals with longer exposure to smoking (longer smoking years) develops nicotine dependency which will make it harder for the youngsters to quit easily. In addition, early smoking initiation is also associated with the use of other tobacco products simultaneously, such as pipes, cigars or bidis. Adolescents who start smoking earlier in life may also develop psychiatric problems (alcohol dependency, substance abuse disorders) later in their life than their non-smoking counter parts, which might lead to high mortality. In this study, the amount/ number of daily tobaccos used was greater in individuals who started smoking earlier among current smokers. This indicates that not only early initiation of smoking but also higher number of tobaccos used daily might poses a higher mortality risk and have influence on increasing risk of mortality, though after controling for the number of tobaccos used daily the results remained unchanged for both current and former smokers regardless of initiation and cessation time.

These results have important public health implications and indicate the particular importance of non-smoking campaigns among young people.

The main findings of this study regarding the former smokers are as follows. First, smoking cessation is beneficial, regardless of the age at smoking initiation, as former smokers demonstrated a lower risk for all-cause and cause-specific mortality compared to current smokers, with a clear tendency of the reduction being greater when cessation occurred at lower ages. Second, among former smokers who quit smoking in their 50s or more, the mortality risk remained elevated and showed dose dependency with the age at smoking initiation, where the highest HRs were detected in those who started smoking at lower ages.

The first finding suggests that former smokers who initiated smoking when younger but quit smoking earlier in life can gain the largest benefit from cessation. However, even participants who quit smoking during their 50s or when older had, despite higher risks than never smokers, a substantially decreased mortality risk compared to the participants who continued to smoke. This result suggests that smokers will benefit from cessation even later in life, which provides evidence that all smokers should be encouraged to quit smoking, regardless of their age at smoking initiation. This finding is also in line with a prevoius JACC study among Japanese men and women that evaluated smoking cessation and risk of mortality from cardiovascular disease and found that smoking cessation led to a decline in risk of mortality from total cardiovascular disease irrespective of number of tobaccos used, age at starting to smoke and the risk reduction was smiliarly observed among middle aged and older person. Since in the previous JACC study on evaluation of total cardiovascular disease and smoking cessation only age of smoking initiation was considered; and no association was found between risk of mortality and onset of smoking among former smokers. However, in my study both initiation and cessation age were considered, therefore, a positive association was found between age at onsent of smoking and age at quitting. The result of my study for the former smokers is in agreement with studies among western population as well that have examined age at or time since quitting in former Australian smokers in the Sax Institute's "45 and Up" Study, which showed that cessation is beneficial even when attempted in the 50s. Similarly, the Zutphen Study found that, in 1373 men who quit cigarette smoking at age 40, life expectancy increased by 4.6 years and the number of disease-free life years by 3.0 years. Another study among a US population reported that smokers who stopped smoking at 25–34, 35–44, or 45–54 years of age gained approximately 10, 9, and 6 years of life, respectively, as compared to persistent smokers. This study provides strong evidence that tobacco smoking is a major cause of death in Japanese

male population and underscores the importance and urgency of implementing comprehensive tobacco control measures. Strengthening tobacco control in all MPOWER domains to the highest level should be ensured to accelerate the decline in smoking prevalence in Japan. Given that Japan is an aging society; these results challenge the primary health-care systems to implement smoking cessation activities among older adult population. As older adults who smoke often believe that they are too old to receive a benefit from quitting smoking. Therefore, aged-tailored interventions are required to motivate them quit smoking as early as possible.

With regard to the second finding, a possible explanation is that smoking initiation at a lower age induces nicotine addiction and dependency which will further enhances and increases the number of tobaccos taken daily, which leads to lifelong daily smoking and increases the smoking duration and intensity, which results in long-term exposure to smoking in the lifetime. Even when cessation occurred at 50 years or above, the beneficial effects persisted though not considerably high, which suggests that earlier initiation and later cessation do not provide a huge benefit when compared with earlier cessation. In other words, the extent of benefit partly depends on the intensity and duration of prior tobacco smoke exposure. When smoking is initiated at younger age and quit at an older age, the duration in which an individual is exposed to tobacco would also increase which suggest that the longer the duration of smoking the lesser the beneficial effects when quit. Moreover, adolescence is a crucial period for organ development, and early smoking initiation is likely to change immature organs (probably through genetic alteration, to some extent), which may exacerbate the development of cancers and other smoking-related diseases and, in turn, increases the risk of smoking-related premature deaths.

Furthermore, my study suggests that the decline in mortality risk due to smoking cessation is different for cancer and CVD mortality. Although the CVD mortality risk was seemingly eliminated by smoking cessation at <40 years of age, the cancer-related mortality risk remained higher than in never smokers even among former smokers who quit smoking at <50 years of age. This suggests that, to prevent cancer, smoking cessation should occur as early as possible and preferably at lower ages. This is in line with the British doctor study that followed up participants for 50 years and highlighted that, even among former smokers who stopped smoking at age 35–44, excess risk of lung cancer mortality persisted even at 75–84 years of age which indicated a prolonged effect of smoking on cancer that extended beyond several decades. With regard to the association of smoking cessation with CVD mortality, similar findings were observed in several Japanese studies, where the mortality risk of former smokers who abstained

from smoking for 10–15 years was almost equivalent to that of never smokers. These results suggest different biological effects of smoking on CVD and cancer mortality. With regard to the relationship between smoking habits and the increased risk of CVD, smoking enhances both the development of atherosclerosis and the formation of thrombus through various processes and pathways such as the incitement of oxidative stress to vascular injury and the enhancement of platelet aggregation as well as changes in the fibrinolytic system, inflammation, modification of lipids and vasomotor function are involved. Reactive oxygen species (ROS) and free radicals present in cigarettes cause plasma low density lipoprotein (LDL) oxidation, which is a start point of the inflammatory process which stimulates adhesion of monocytes in the intima of the arteries and resulting in increased atherosclerosis. Several clinical and epidemiological studies have indicated that these smoking-related biological changes disappear fully or partly immediately after smoking cessation. In contrast, numerous carcinogenic substances and free radicals in cigarettes act as initiators or promoters of malignancies causing a wide range of cell damage such as inactivation of enzymes, lipid peroxidation, and protein/lipoprotein oxidation. These harmful carcinogens induce mutations that disrupt cell-cycle regulation altering the expression of oncogenes, Deoxyribonucleic acid (DNA) repair mediators, tumor suppressors and apoptosis-related genes through several pathways such as point mutations, deletions, translocations, and gene recombination. In addition, the chemicals present in cigarette influence immune or endocrine systems as well. As carcinogenicity is a long-term multistage process, prolonged exposure to and subsequent accumulation of carcinogenic substances would increase the chance of developing and expanding malignancies. Therefore, it is likely that it takes a long time to diminish the influence of these substances after smoking cessation.

Taken together, the results of this study reinforce the findings from other studies among different populations that, although smoking greatly increases the risks of all-cause and cause-specific mortality, the sooner smokers quit, the lower is their risk of premature death. Moreover, those who quit successfully before the age of 40 (and preferably well before that) could garner great benefits and avoid most of the excess risk of premature death that would otherwise be caused by smoking.

Strengths and limitations

The strength of this study lies in the inclusion of population-based prospective cohorts enrolled from all over Japan. Comprehensive data on lifetime smoking history (initiation age for current smokers and both initiation and cessation ages for former smokers) along with extended follow-up and a large sample size allowed to quantify the time course and magnitude

of the mortality risk of continued smoking as well as the reduction of the risk after smoking cessation. My study has some limitations as well. First, due to only one measurement of smoking status at baseline, we assumed that the same smoking behavior persisted throughout the follow-up period. It is, however, possible that some quitters relapsed into smoking, and some current smokers quit smoking during the follow-up. Furthermore, as the age at smoking initiation and cessation was recorded based on the participants' memory at the time of the baseline study, the possibility of recall bias should not be ignored. Furthermore, as the status of smoking was self-reported and no biological biomarkers were obtained from the participants to confirm the validity of participants smoking status; it it possible that change of smoking status during the follow- up led to underestimation of the association between current smoking and mortality from all-cause and cause-specific. However, it was not possible to update the smoking information because the 5 – year follow- up data was reported only by 38% of the subjects. And those limited follow-up data suggested that the proportions of current smokers who quit smoking were 23% for men and the proportion of former smokers who started smoking was 4% and for never smokers who started smoking was only 1.4%. Therfore, the relative risk of mortality for current smokers might have been sligthly underestimated. In addition, as the causes of smoking cessation are unknown, it was impossible to determine whether smoking cessation occurred as a voluntary choice of participants or due to health-related issues. Among the former smokers who quit smoking <40 years had the highest education and employment rate compared to other age groups so this may suggest that former smokers in this group may be more health conscious and of a higher socio-economic status, while some of them quit smoking because of illness. However, the latter case, if it occurred, is unlikely to have affected our results because the sensitivity analysis after excluding participants who had CVDs or cancer at baseline yielded similar results. Furthermore, the cohorts in this study were aged 40 years and above, I was unable to estimate the impact of tobacco smoking in people younger than 40 years old, though because of the long latency of chronic diseases, most of the smoking-related diseases tend to occur later in life. Finally, the findings are limited to cigarette smoking without considering other types of smoking. However, in Japan, 60–70% of male smokers were cigarette smokers between 1988 and 1990. Therefore, studies should be conducted to investigate the association of other types of tobacco smoking with all-cause and cause-specific mortality.

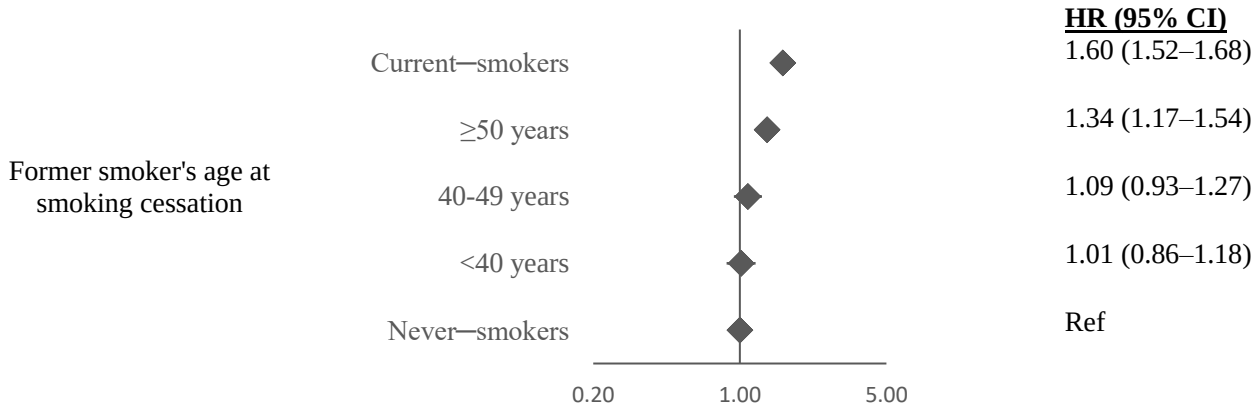
Conclusion

(1) Summary

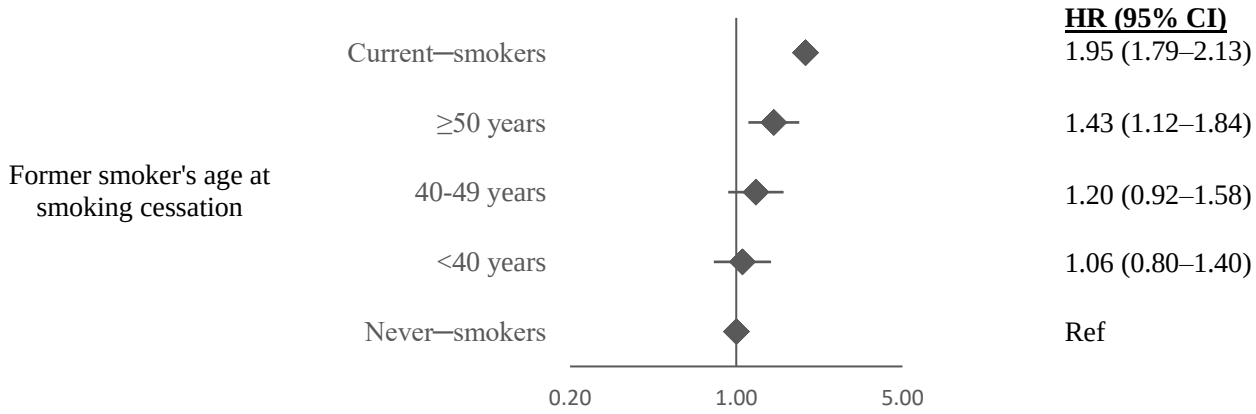
- A-dose response relationship was detected between mortality and the age at smoking initiation; whereas current smokers started smoking at an earlier age had the highest HRs.
- Former smokers demonstrated a lower risk for all-cause and cause-specific mortality than current smokers, with the risk reduction being greater among smokers who quit smoking at a lower age.
- Former smokers who quit smoking in their 50s or above, the mortality risk remained elevated and showed dose dependency with the age at smoking initiation, where the highest HRs were detected in those who started smoking at younger ages.
- Furthermore, smoking cessation at <40 years of age leads to a reduction in CVD mortality; however, the cancer-related mortality risk persisted even when cessation occurred before the age of 50 years.

Fig.1. Dose-Response Relashionship between Age at Smoking Cessation and Mortality Among Male Participants.

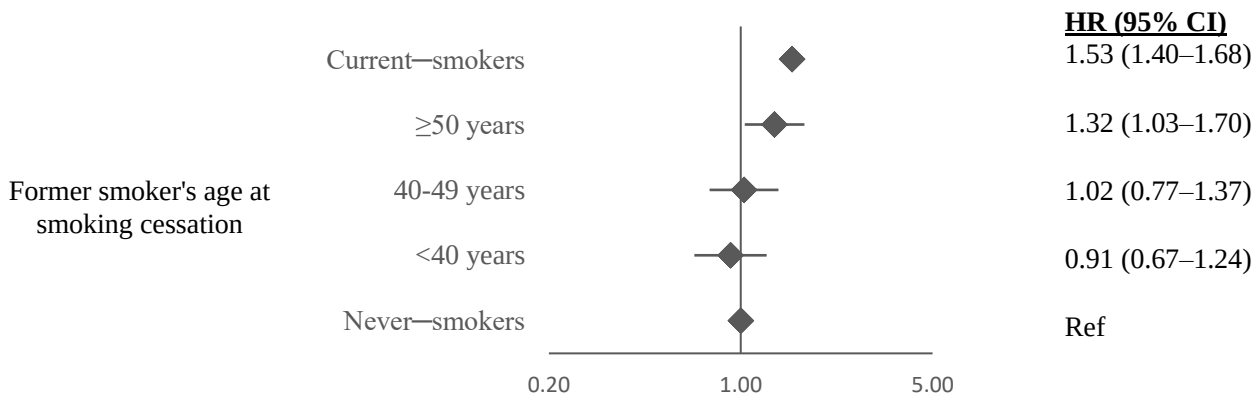
All-cause mortality



Cancer- mortality



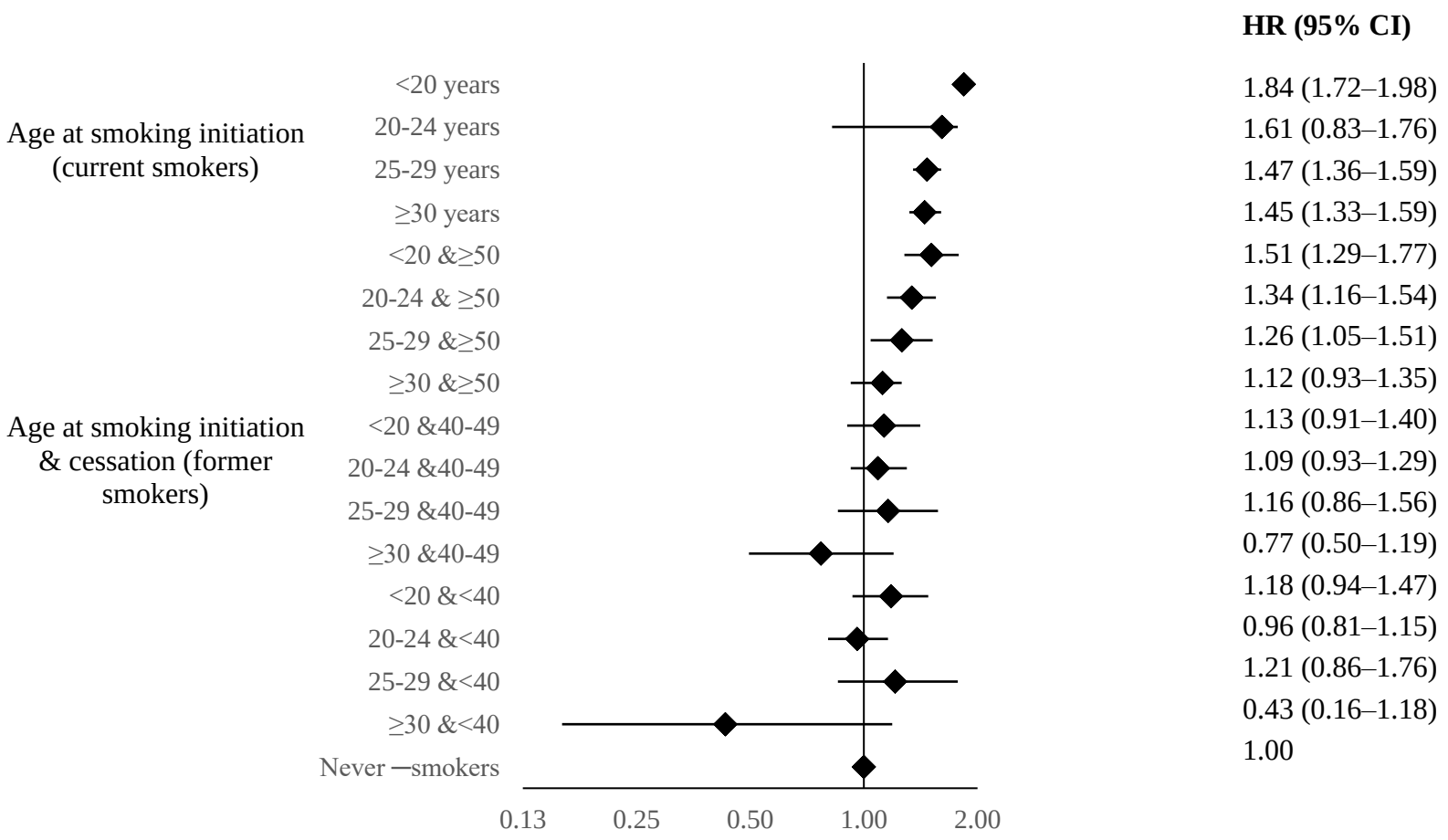
CVD-mortality



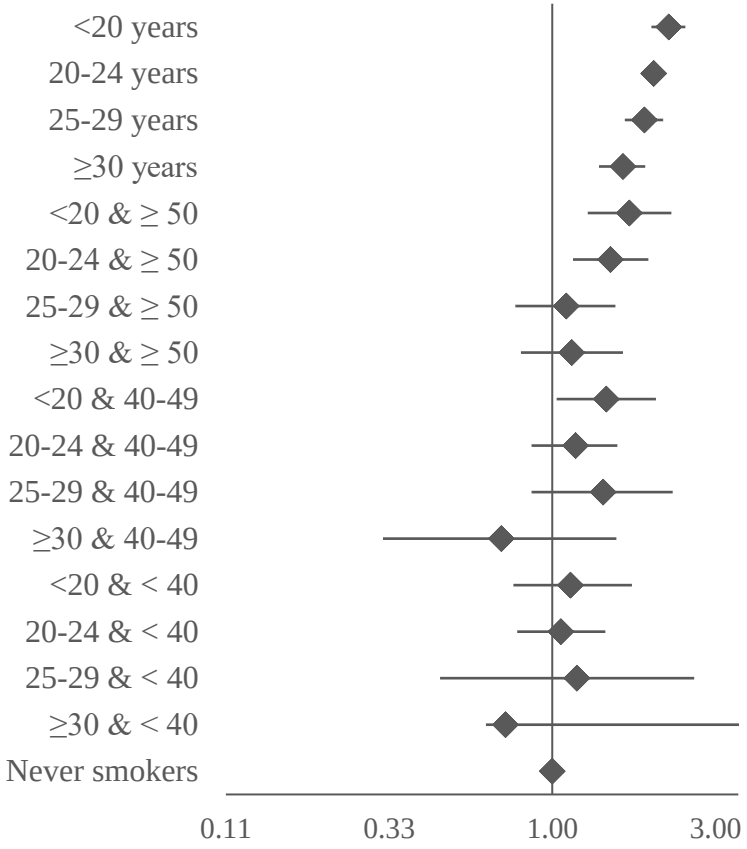
HR: Hazard Ratio; CI: Confidence Interval; CVD: Cardiovascular disease; Ref: Reference
Adjusted with age, study area, cancer, cardiovascular diseases, diabetes, hypertension, marital-status, children, education, occupation, exercise, walking, body mass index, passive-smoking, drinking habit and number of cigarettes smoked/day.

Fig.2. Forest plot presentation of Association of Mortality Risk and the Age at Smoking Initiation and Cessation Among Male Participants

All-cause mortality

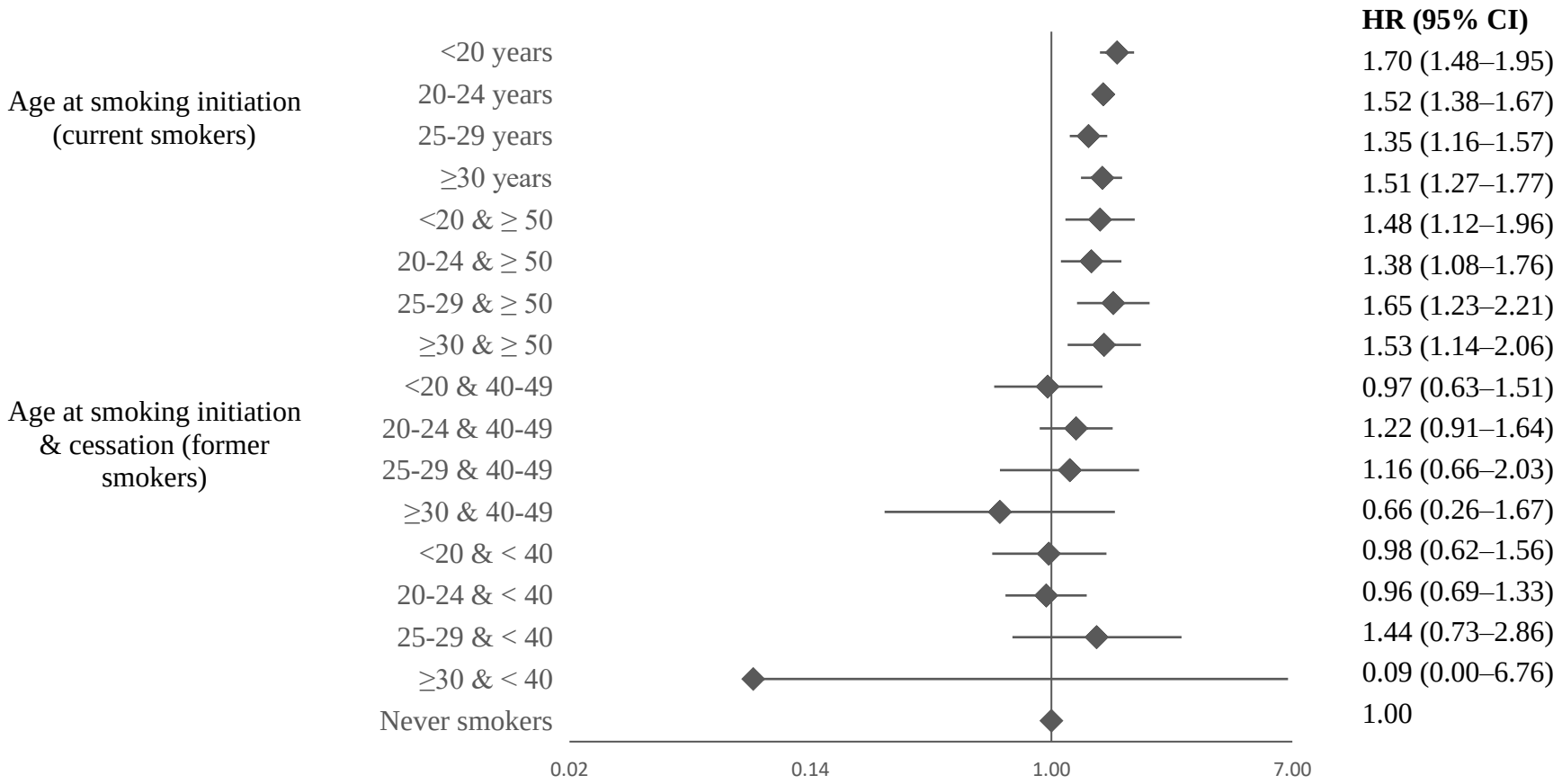


Cancer-mortality



	HR (95% CI)
<20 years	2.19 (1.95–2.45)
20-24 years	1.98 (1.81–2.16)
25-29 years	1.86 (1.63–2.11)
≥30 years	1.61 (1.37–1.87)
<20 & ≥ 50	1.68 (1.27–2.23)
20-24 & ≥ 50	1.48 (1.15–1.91)
25-29 & ≥ 50	1.10 (0.78–1.53)
≥30 & ≥ 50	1.14 (0.81–1.61)
<20 & 40-49	1.44 (1.03–2.01)
20-24 & 40-49	1.17 (0.87–1.55)
25-29 & 40-49	1.41 (0.87–2.25)
≥30 & 40-49	0.71 (0.32–1.54)
<20 & < 40	1.13 (0.78–1.64)
20-24 & < 40	1.06 (0.78–1.43)
25-29 & < 40	1.18 (0.61–2.29)
≥30 & < 40	0.73 (0.18–3.01)
Never smokers	1.00

CVD-mortality



Adjusted with age, study area, Cancer, Cardiovascular diseases, diabetes, hypertension, marital status, children, education, occupation, exercise, walking, BMI, passive smoking, drinking habit, and number of tobaccos smoked/day.