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ORIGINAL RESEARCH ARTICLE

Combined Associations of Changes in Noncombustible Nicotine or Tobacco Product and Combustible Cigarette Use Habits With Subsequent Short-Term Cardiovascular Disease Risk Among South Korean Men

A Nationwide Cohort Study

Seulggie Choi, MD; Kiheon Lee, MD, PhD; Sang Min Park, MD, PhD, MPH

BACKGROUND: The associations of changes in noncombustible nicotine or tobacco product (NNTP) and combustible cigarette (CC) use habits with subsequent cardiovascular disease (CVD) risk are still unclear.

METHODS: The study population consisted of 5 159 538 adult men who underwent health screening examinations during both the first (2014–2015) and second (2018) health screening periods from the Korean National Health Insurance Service database. All participants were divided into continual CC-only smokers, CC and NNTP users, recent (<5 years) CC quitters without NNTP use, recent CC quitters with NNTP use, long-term (≥5 years) CC quitters without NNTP use, long-term CC quitters with NNTP use, and never smokers. Propensity score matching analysis was conducted to further compare CVD risk among CC quitters according to NNTP use. Starting from the second health screening date, participants were followed up until the date of CVD event, death, or December 31, 2019, whichever came earliest. Multivariable Cox proportional hazards regression was used to determine the adjusted hazard ratios (aHRs) and 95% CIs for CVD risk according to changes in NNTP and CC smoking habits.

RESULTS: Compared with continual CC-only smokers, CC and NNTP users (aHR, 0.83 [95% CI, 0.79–0.88]) and initial CC smokers who quit CCs and switched to NNTP use only (recent CC quitters with NNTP use, aHR, 0.81 [95% CI, 0.78–0.84]) had lower risk for CVD. After propensity score matching, recent CC quitters with NNTP use (aHR, 1.31 [95% CI, 1.01–1.70]) had higher risk for CVD than recent CC quitters without NNTP use. Similarly, compared with long-term CC quitters without NNTP use, long-term CC quitters with NNTP use (aHR, 1.70 [95% CI, 1.07–2.72]) had higher CVD risk.

CONCLUSIONS: Switching to NNTP use among initial CC smokers was associated with lower CVD risk than continued CC smoking. On CC cessation, NNTP use was associated with higher CVD risk than CC quitting without NNTPs. Compared with CC smokers who quit without NNTP use, CC quitters who use NNTPs may be at higher future CVD risk.

Key Words: cigarettes ■ electronic nicotine delivery systems ■ heart disease risk factors.

Editorial, see p 1539

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Clinical Perspective

What Is New?

- Among 5 159 538 adult men from a nationwide cohort, the association of transitions in combustible cigarette (CC) and noncombustible nicotine or tobacco product (NNTP) use with subsequent cardiovascular disease (CVD) development was determined.
- Initial CC smokers who subsequently quit CCs and converted to NNTP use was associated with lower incident CVD risk compared with continual CC users.
- Compared with CC quitting without NNTPs, CC cessation with NNTP use was associated with higher CVD risk.

What Are the Clinical Implications?

- Compared with continual CC smoking, those who quit CCs and switch to NNTPs may benefit from lower future CVD risk.
- Nonetheless, NNTP use on CC cessation may lead to higher CVD risk compared with quitting CCs without NNTP use.
- Although NNTP use may be associated with lower CVD risk compared with CC smoking, CC users who quit without NNTPs may benefit the most in reducing the risk of developing future CVD events.

Nonstandard Abbreviations and Acronyms

aHR	adjusted hazard ratio
CC	combustible cigarette
CVD	cardiovascular disease
HTP	heated tobacco product
ICD-10	International Classification of Diseases, Tenth Revision
NHIS	National Health Insurance Service
NNTP	noncombustible nicotine or tobacco product
NVP	nicotine vaping product

Noncombustible nicotine or tobacco products (NNTPs) are novel forms of nicotine consumption composed of nicotine vaping products (NVPs) that vaporize nicotine-containing fluids, and heated tobacco products (HTPs) that heat tobacco products without combustion.[1] NNTPs have recently gained in popularity because of their portrayal as safer modes of smoking compared with traditional combustible cigarettes (CCs).[2] An overwhelming amount of evidence shows that CC smoking is associated with a wide range of diseases including respiratory diseases, cancer, and cardiovascular disease (CVD).[3,4] Moreover, CC smoking has been shown to be one of the major factors in CVD global burden.[5] As such, NNTP-producing companies have marketed their products to imply that NNTPs lead to lower health risks compared with CCs.[2] For example, Philip Morris, the maker of an HTP called IQOS, claimed that their product is safer than CCs, a statement that is not entirely supported in their own clinical data.[6,7] Because of the lack of enough evidence on the safety of NNTPs along with their growing popularity, there is an increasing need for studies that investigate the effects of NNTP on health, especially CVD risk.[8] In particular, whether NNTP use on CC cessation is associated with CVD risk needs to be evaluated to determine the viability of NNTPs as a tool for tobacco-related harm reduction among CC quitters.

Although many previous studies have explored the association of NNTPs with cardiovascular health, most assessed either toxic chemical exposure or intermediate markers related to cardiovascular health rather than actual CVD incidence.[8,9] Taken together, these past studies suggest that NVP or HTP use increases exposure to smoking-related toxic constituents, albeit not as much as when exposed to CCs.[10,11] Furthermore, previous studies have demonstrated that NNTP use is associated with worsening cardiovascular health, such as increased heart rate and blood pressure, arterial stiffness, oxidative stress, and reduced vascular endothelial cell function.[8,12] However, most of these studies are limited in the small study population size or cross-sectional study design. There is a lack of evidence on (1) whether switching to NNTPs among CC smokers leads to lower CVD risk than continued CC use and (2) whether NNTP use on CC cessation is associated with higher CVD risk than CC quitting without NNTPs using actual CVD events as the primary outcome.

In South Korea, NNTPs have increasingly gained popularity in the past 4 to 5 years.[13] The elevated tobacco tax on CCs starting in 2015, coupled with the introduction of HTPs such as IQOS in 2017, has led to increased NNTP use in South Korea, in particular, among previous CC smokers, making South Korea an ideal setting to study CVD risk according to changes in CC and NNTP use.[13,14] In 2018, the South Korean market shares for CC, HTP, and NVP were 86.5%, 13.1%, and 0.4%, respectively.[15] In this nationwide population-based study, the association of transitions in NNTP and CC use habits with CVD risk among South Korean men was determined using the Korean National Health Insurance Service (NHIS) database. The study aimed to assess (1) whether there was a difference in CVD risk between initial CC smokers who transitioned to NNTP use compared with continual CC-only smoking and (2) the CVD risk on CC cessation according to NNTP use.

METHODS

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. The authors do not have the authority to share patient information because the NHIS data are derived from a nationwide administrative health claims database in which the NHIS gives permission to researchers for access after reviewing each research topic. Access to the NHIS data can be requested through the NHIS website.

Study Population

The study population was derived from the NHIS database. In South Korea, the NHIS provides mandatory health insurance for all citizens covering nearly all forms of health services.[16] The NHIS collects all patient clinical data for reimbursement purposes. Furthermore, citizens ≥20 years of age are eligible for a biannual health screening examination, which is composed of a self-reported questionnaire on lifestyle behaviors including smoking, physical activity, and alcohol intake; anthropometric measurements such as height and weight; and blood and urine laboratory examinations.[17] A part of the NHIS data, composed of basic sociodemographic information, all inpatient and outpatient department visits, pharmaceutical prescriptions, and results from the health screening, is provided for research purposes. The NHIS database has previously been used in multiple large epidemiological studies,[18,19] and its validity is explained in detail elsewhere.[16,17,20]

The study population was composed of 6 022 798 adult men ≥20 years of age who underwent health screening examinations during both the first (2014–2015) and second (2018) periods from the NHIS. Attending the first and second health screening examinations were 10 727 577 and 8 141 714 men, respectively. Among them, 263 408 men with CVD before the second health screening date were excluded. An additional 2024 men with missing values for NNTP use were excluded. Then, 233 538 and 363 198 men who were smoking initiators or who had illogical answers for smoking habit change were excluded, respectively. Illogical answers for smoking habit change included being initially (2014–2015) a current CC smoker or past CC smoker, but answering as being a never smoker during the second health screening period (2018). Last, 1092 men with missing values for smoking pack-years (number of packs of CCs smoked per day multiplied by the number of years of CC use) were removed, resulting in a final study population of 5 159 538 men (Figure 1). Beginning from the second health screening date, all participants were followed up until the date of CVD event, death, or December 31, 2019, whichever came earliest.

For CC quitters without NNTP use, propensity score matching was conducted against CC quitters with NNTP use. Recent CC quitters without NNTP use were matched with recent CC quitters with NNTP use. Similarly, long-term CC quitters without NNTP use were matched with long-term CC quitters with NNTP use. Propensity score matching was performed using the total cohort, and after stratification according to age (<40 years and ≥40 years), as well. On propensity score matching, age, household income, employment, area of residence, alcohol intake, exercise, pack-years of smoking, body mass index, systolic blood pressure, fasting serum glucose, and Charlson comorbidity index were considered. Using a caliper of 0.2 times the standard deviation of the logit propensity score, a matching ratio of 1:1 was used to match subjects between different groups by greedy matching.[21] The number of participants excluded after propensity score matching were 391 083, 5769, 1 230 090, and 4605 for recent CC quitters without NNTP use, recent CC quitters with NNTP use, long-term CC quitters without NNTP use, and long-term CC quitters with NNTP use, respectively. The proportions of matched subjects from recent and long-term CC quitters with NNTP use were 85.3% and 64.1%, respectively.

Ethical Considerations

This study was approved by the Seoul National University Hospital Institutional Review Board (number: E-2011-005-1168). The requirement for informed consent was waived because the database was anonymized according to strict confidentiality guidelines before distribution.

Key Variables

Smoking status was assessed from a self-reported questionnaire during each of the first and second health screening periods. During the first health screening period (2014–2015), CC smoking status was determined, which was composed of never smokers, past smokers, and current smokers. To divide CC quitters into long-term (≥5 years) and recent (<5 years) quitters, because it is considered to take 5 years for CC quitters to lower CVD risk to levels comparable to those of nonsmokers, years 2014 to 2015 were selected to assess initial CC user habit.[22] Moreover, initial CC smoking habits before the recent increase in NNTP use during the past 5 to 6 years were determined to evaluate how initial CC smokers who transitioned to NNTP use had their CVD risk altered, in particular, on CC smoking cessation.

During the second (2018) health screening period, both CC and NNTP use habits were assessed. According to the World Health Organization, HTP is defined as a product that heats, but not burns, a tobacco-containing device and produces aerosols containing nicotine and toxic chemicals.[1] The World Health Organization defines NVPs as products that vaporize liquid containing nicotine but does not contain tobacco.[1] The self-reported questionnaire on NNTP use does not explicitly differentiate between HTPs and NVPs, but rather inquires on the frequency of NNTP use in general. The possible answers for the question, "How much have you smoked NNTPs during the past month?" include "none," "0 to 9 days," "10 to 19 days," "20 to 29 days," and "nearly every day." NNTP users were defined as those who smoked NNTP nearly every day for the past month. Based on the answers from the questionnaire, all subjects were divided into continual CC-only smokers, CC and NNTP users, recent (<5 years) CC quitters without NNTP use, recent (<5 years) CC quitters with NNTP use, long-term (≥5 years) CC quitters without NNTP use, long-term (≥5 years) CC quitters with NNTP use, and never smokers. Previous studies using the NHIS database also assessed smoking status based on the self-reported questionnaire in determining CVD outcomes.[23]

The operational definition for CVD was defined as having been hospitalized for ≥2 days because of coronary heart disease or stroke. Diagnosis codes for coronary heart

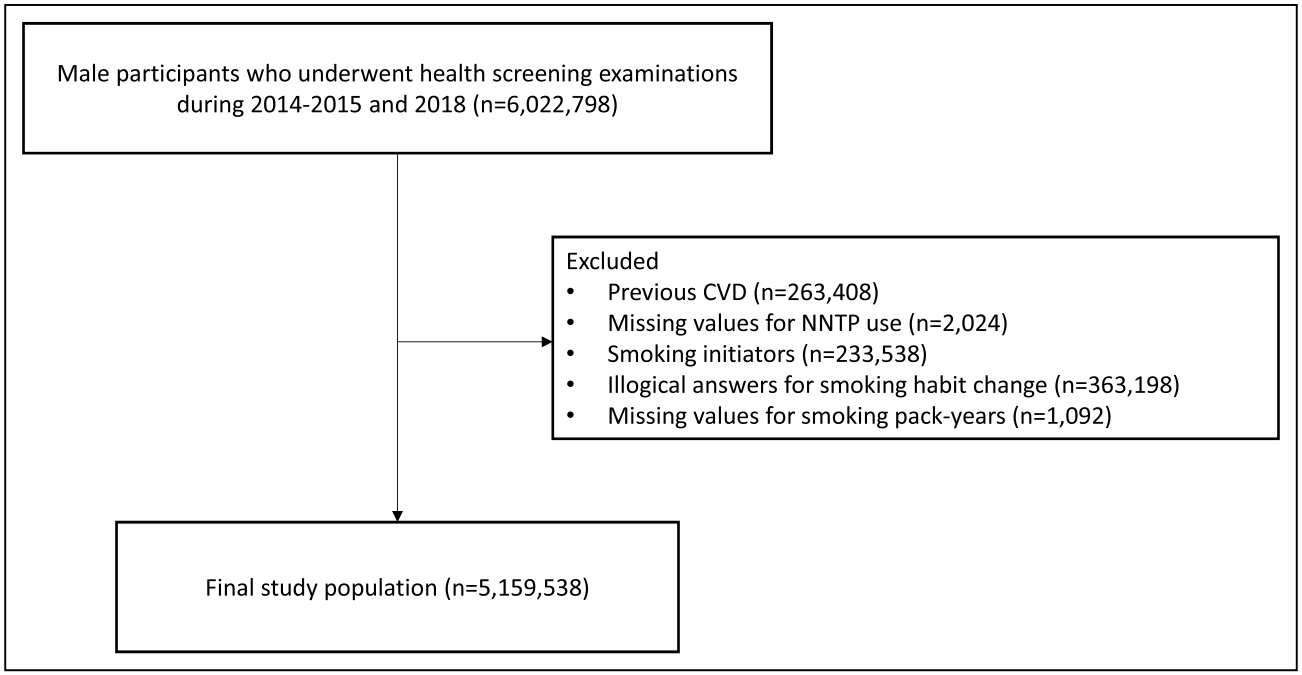


Figure 1. Study flow of the population.
CVD indicates cardiovascular disease; and NNTP, noncombustible nicotine or tobacco product.

disease (I20–I25) and stroke (I60–I69) were based on the *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes by the World Health Organization. The *ICD-10* codes used for CVD, coronary heart disease, and stroke were in accordance with the American Heart Association guidelines.[24] The operational definition used for CVD incidence was derived from a previous study that used the same database.[19] The risk of changes in CC and NNTP use habits for all-cause mortality, lung cancer, and chronic obstructive pulmonary disease (COPD) were also evaluated. Lung cancer was defined as being diagnosed for lung cancer with the critical condition code for cancer (V193, V194). COPD was defined as having an outpatient or inpatient department visit under the diagnosis code for COPD. The *ICD-10* codes used for diagnosis of lung cancer and COPD were C34 and J44, respectively.

On multivariable regression analysis, the considered covariates included age (continuous, years), household income (continuous, 5 percentiles), employment (employed, self-employed, and not employed), area of residence (capitol, metropolitan city, and rural), alcohol intake (categorical, 0, 1–2, 3–4, and ≥5 times per week), physical activity (categorical, 0, 1–2, 3–4, and ≥5 times per week), body mass index (continuous, kg/m^2), systolic blood pressure (continuous, mm Hg), fasting serum glucose (continuous, mg/dL), history of drug abuse (categorical, yes and no), and Charlson comorbidity index (continuous). Smoking pack-years for all current and past smokers were also included as a covariate on determining CVD risk among those with past or current smoking history. Household income was derived from the insurance premium, and body mass index was calculated by dividing the weight in kilograms by height in meters squared. Drug abuse was defined as a diagnosis of mental and behavioral disorders attributable to drugs using *ICD-10* codes. The diagnoses (*ICD-10* codes) used in the definition of drug abuse included mental and behavior disorders attributable to the use of opioids (F11), cannabinoids (F12), sedatives or hypnotics (F13), cocaine (F14), other stimulants including caffeine (F15), hallucinogens (F16), volatile solvents (F18), and other psychoactive substances (F19). The operational definitions for all exposure, outcome variables, and covariates are described in more detail in Table S1 in the Supplemental Material.

Statistical Analysis

Significance in the difference of distribution for covariates among NNTP and CC smoking groups was determined by the χ^2 test for categorical variables and analysis of variance for continuous variables. Standardized differences were used to evaluate the distribution of covariates after propensity score matching. Multivariable Cox proportional hazards regression was used to calculate the adjusted hazard ratios (aHRs) and 95% CIs for CVD, coronary heart disease, and stroke according to changes in CC and NNTP use status. The proportional hazards assumption was graphically tested and verified using the Schoenfeld residual method. Stratified analysis on the association of smoking status with CVD risk according to subgroups of age and pack-years of smoking was conducted. On stratified analysis, subgroups according to age or pack-years of smoking were created. Then, multivariable Cox regression was used to determine CVD risk according to changes in CC and NNTP habits for each of the subgroups, adjusting for all covariates except for the variable used to divide the subgroups. The risk of all-cause mortality according to changes in CC and NNTP use habits were determined. Last, the association of changes in CC and NNTP use habits with subsequent lung cancer and COPD risk were determined.

Statistical significance was declared at a 2-sided $P<0.05$. All data collection and statistical analysis were conducted using SAS Enterprise Guide 7.1 (SAS Institute).

RESULTS

Table 1 depicts the descriptive characteristics of the study population. The numbers (%) of continual CC-only smokers, CC and NNTP users, recent CC quitters without NNTP use, recent CC quitters with NNTP use, long-term CC quitters without NNTP use, long-term CC quitters with NNTP use, and never smokers were 1 541 012 (29.9), 445 885 (8.6), 424 601 (8.2), 39 287 (1.0), 1 238 318 (24.0), 12 833 (0.2), and 1 457 602 (28.3), respectively. The median (interquartile range) number of CCs smoked per day for continual CC-only smokers and CC and NNTP users were 15 (10–20) and 10 (5–20), respectively. Significant differences in the distribution of all covariates were observed (all $P<0.001$).

The risk for CVD according to changes in CC and NNTP use habits is shown in Figure 2 and Table S2 in the Supplemental Material. Compared with continual CC-only smokers, CC and NNTP users (aHR, 0.83 [95% CI, 0.79–0.88]), recent CC quitters with NNTP use (aHR, 0.77 [95% CI, 0.65–0.91]), and long-term CC quitters with NNTP use (aHR, 0.77 [95% CI, 0.58–1.00]) had lower risk for CVD. Figure 3 and Table S3 in the Supplemental Material depict the risk of CVD according to changes in CC and NNTP use habits among those with a smoking history with additional consideration of smoking pack-years. CC and NNTP users (aHR, 0.84 [95% CI, 0.80–0.89]), recent CC quitters with NNTP use (aHR, 0.77 [95% CI, 0.66–0.91]), and long-term CC quitters without NNTP use (aHR, 0.63 [95% CI, 0.62–0.65]) had lower CVD risk than continual CC-only smokers.

Tables S4 and S5 in the Supplemental Material show the descriptive characteristics among recent and long-term CC quitters according to NNTP use after propensity score matching, respectively. For both cohorts, the distribution of covariates was similar in CC quitters with and without NNTP use after propensity score matching (absolute value of standardized differences for all covariates<0.1). The risk of CVD according to changes in CC and NNTP habits compared with NNTP users is shown in Figure 4 and Table S6 in the Supplemental Material. Compared with recent CC quitters without NNTP use, recent CC quitters with NNTP use had higher CVD risk (aHR, 1.31 [95% CI, 1.01–1.70]). Similarly, long-term CC quitters with NNTP use had significantly higher CVD risk compared with long-term CC quitters without NNTP use (aHR, 1.70 [95% CI, 1.07–2.72]). After propensity score matching among those <40 years and ≥40 years of age, the CVD risk increasing association of NNTP use among recent and long-term CC quitters tended to be preserved and was not affected by subgroups of age (Table S7 in the Supplemental Material, all P for interaction>0.05).

Results from the stratified analysis on the association of smoking status with CVD according to subgroups of age and pack-years of smoking are shown in Table 2. There did not appear to be significant differences in the association of changes in CC and NNTP use habits with CVD risk according to subgroups of age and pack-years of smoking (all P for interaction >0.05). Table S8 in the Supplemental Material depicts the association of CC and NNTP use habit change with all-cause mortality risk. Compared with continual CC-only smokers, CC and NNTP users (aHR, 0.78 [95% CI, 0.70–0.87]) and long-term CC quitters without NNTP use (aHR, 0.57 [95% CI, 0.55–0.60]) had lower mortality risk. The risk for lung cancer and COPD according to transitions in CC and NNTP use habits is shown in Table S9 in the Supplemental Material. Compared with continual CC-only smokers, CC and NNTP users had lower risk for both lung cancer (aHR, 0.76 [95% CI, 0.64–0.90]) and COPD (aHR, 0.81 [95% CI, 0.74–0.88]).

DISCUSSION

In summary, switching to NNTP use among initially CC-only smokers was associated with lower CVD risk than continued CC-only use. On CC cessation, NNTP use was associated with higher CVD risk than CC quitting without NNTPs. To the best of the authors' knowledge, this was the first study to demonstrate the CVD risk associated with transitions in NNTP and CC habits.

One major point of consideration on interpreting the results is the lack of information in the NNTP questionnaire that explicitly differentiates between NVP and HTP use. As a result, the CVD risk associated with NNTP cannot be separated between CVD risk for NVP and HTP use. This is of particular importance because HTPs and NVPs constitute 2 different forms of NNTP use that could potentially result in differing effects on cardiovascular health. The liquid component of NVPs includes solvent carriers, nicotine, and flavorings, all of which have multiple pathophysiological pathways of potentially increasing CVD risk.[11] Solvent carriers, when undergoing thermal degradation through vaping, have been shown to produce carbonyls that could, in turn, increase circulating reactive oxygen species and vascular endothelial dysfunction.[25,26] Flavorings, and heavy metals detected in aerosols of NVPs, as well, may have cardiotoxic effects through increasing oxidative stress and elevating blood pressure.[27,28] In contrast, emissions from HTPs have been shown to produce higher levels of nicotine, benzene, and acrolein than those from NVPs.[29] Inhaled acrolein and benzene could in turn induce vascular endothelial dysfunction and elevate low-density lipoprotein levels.[30] Moreover, HTPs produce more tobacco-specific nitrosamines than NVPs.[31] Uptake of tobacco-specific nitrosamines could lead to increased oxidative stress, resulting in higher cardiovascular risk.[8]

Although direct and comprehensive comparisons of CVD development between HTPs and NVPs are lacking, the current body of literature depicts that HTPs may

Table 1. Descriptive Characteristics of the Study Population

Characteristics	Continual CC-only smokers	CC and NNTP users	Recent (<5 y) CC quitters without NNTP use	Recent (<5 y) CC quitters with NNTP use	Long-term (≥5 y) CC quitters without NNTP use	Long-term (≥5 y) CC quitters with NNTP use	Never smokers	*P* value
No. of participants, n (%)	1 541,012 (29.9)	445 885 (8.6)	424 601 (8.2)	39 287 (1.0)	1 238 318 (24.0)	12 833 (0.2)	1 457 602 (28.3)	
Cardiovascular disease cases								
Number of events, n (%)	13 224 (0.9)	1510 (0.3)	3330 (0.8)	139 (0.4)	10 367 (0.8)	52 (0.4)	9373 (0.6)	
Incidence*	62	25	56	26	59	30	46	
Age, y, mean (SD)	48.1 (11.4)	41.0 (8.0)	48.8 (11.9)	41.2 (9.0)	53.9 (11.7)	42.2 (9.6)	48.4 (14.5)	<0.001
Age groups, y, n (%)								
<40	381 679 (24.8)	209 614 (47.0)	107 409 (25.3)	18 715 (47.6)	147 961 (12.0)	5913 (46.1)	506 753 (34.8)	<0.001
40–49	481 469 (31.2)	170 273 (38.2)	125 944 (29.7)	13 595 (34.6)	307 110 (24.8)	4352 (33.9)	316 518 (21.7)	
50–59	418 481 (27.2)	56 415 (12.7)	106 583 (25.1)	5327 (13.6)	382 541 (30.1)	1749 (13.6)	282 879 (19.4)	
≥60	259 383 (16.8)	9583 (2.2)	400 706 (32.4)	1650 (4.2)	400 706 (32.4)	819 (6.4)	351 452 (24.1)	
Household income, quartiles, n (%)								
1st (highest)	493 402 (32.0)	194 195 (43.6)	168 667 (39.7)	15 628 (39.8)	577 795 (46.7)	6088 (47.4)	610 598 (41.9)	<0.001
2nd	531 875 (34.5)	157 281 (35.3)	137 168 (32.3)	14 250 (36.3)	329 318 (26.6)	4085 (31.8)	412 882 (26.4)	
3rd	287 227 (18.6)	55 618 (12.5)	64 161 (15.1)	5295 (13.5)	175 402 (14.2)	1460 (11.4)	231 122 (28.2)	
4th (lowest)	228 508 (14.8)	38 791 (8.7)	54 605 (12.9)	4114 (10.5)	155 803 (12.6)	1200 (9.4)	194 000 (13.3)	
Employment, n (%)								
Employed	1 195 266 (29.8)	408 071 (91.5)	338 093 (79.6)	35 559 (90.5)	908 048 (73.3)	11 438 (89.1)	1 112 380 (76.3)	<0.001
Self-employed	167 083 (10.8)	19 414 (4.4)	38 730 (9.1)	1875 (4.8)	148 710 (12.0)	726 (5.7)	143 691 (9.9)	
Not employed	178 663 (11.6)	18 400 (4.1)	47 778 (11.3)	1853 (4.7)	181 560 (14.7)	669 (5.2)	201 531 (13.8)	
Area of residence, n (%)								
Capitol	206 374 (13.4)	84 204 (18.9)	64 620 (15.2)	7566 (19.3)	220 321 (17.8)	2750 (21.4)	252 903 (17.4)	<0.001
Metropolitan city	426 918 (27.7)	118 900 (26.7)	117 172 (27.6)	10 222 (26.0)	336 972 (27.2)	3189 (24.9)	373 261 (25.6)	
Rural	907 710 (58.9)	242 781 (54.5)	242 809 (57.2)	21 499 (54.7)	681 025 (55.0)	6894 (53.7)	831 438 (57.0)	
Alcohol intake, times/wk, n (%)								
0	221 953 (14.4)	38 270 (8.6)	65 732 (15.5)	4589 (11.7)	220 395 (17.8)	1316 (10.3)	428 198 (29.4)	<0.001
1–2	819 585 (53.2)	26 362 (59.0)	234 659 (55.3)	23 144 (58.9)	671 355 (54.2)	7684 (59.9)	769 557 (52.8)	
3–4	349 969 (22.7)	108 311 (24.3)	88 656 (20.9)	8630 (22.0)	246 462 (24.8)	2890 (22.5)	188 351 (12.9)	
≥5	149 232 (9.7)	36 142 (8.1)	35 554 (8.4)	2924 (7.4)	100 106 (8.1)	943 (7.4)	71 496 (4.9)	
Exercise, times/wk, n (%)								
0	506 224 (32.9)	111 470 (25.0)	104 400 (24.6)	9222 (23.5)	259 759 (21.0)	2531 (19.7)	366 553 (25.2)	<0.001
1–2	347 841 (22.6)	124 359 (27.9)	94 392 (22.2)	9914 (25.2)	264 886 (21.4)	3307 (25.8)	314 194 (21.6)	
3–4	273 279 (17.7)	92 754 (20.8)	88 503 (20.8)	8301 (21.1)	275 682 (22.3)	2926 (22.8)	301 598 (20.7)	
≥5	413 668 (26.8)	117 302 (26.3)	137 306 (32.3)	11 850 (30.2)	437 991 (35.4)	4069 (31.7)	475 257 (32.6)	
Pack-years of smoking, median (interquartile range)	15 (8–23)	11 (7–19)	13 (7–23)	10 (5–17)	10 (5–20)	8 (4-14)	–	<0.001
CCs smoked per day, median (interquartile range)	15 (10–20)	10 (5–20)	15 (10–20)	10 (5–20)	15 (10–20)	10 (5–20)	–	<0.001
Body mass index, kg/m^2, mean (SD)	24.7 (4.1)	25.7 (3.5)	25.3 (3.2)	25.7 (3.4)	25.0 (4.2)	25.5 (3.3)	24.8 (3.2)	<0.001
Systolic blood pressure, mm Hg, mean (SD)	124.6 (13.6)	123.9 (12.9)	125.4 (13.3)	124.0 (12.6)	126.0 (13.4)	123.9 (12.6)	124.5 (13.5)	<0.001

(*Continued*)

Table 1. Continued

Characteristics	Continual CC-only smokers	CC and NNTP users	Recent (<5 y) CC quitters without NNTP use	Recent (<5 y) CC quitters with NNTP use	Long-term (≥5 y) CC quitters without NNTP use	Long-term (≥5 y) CC quitters with NNTP use	Never smokers	*P* value
Fasting serum glucose, mg/dL, mean (SD)	104.5 (28.0)	102.4 (25.1)	104.6 (25.8)	102.1 (24.4)	104.7 (23.6)	101.5 (23.2)	101.1 (22.6)	<0.001
History of drug abuse, n (%)	1083 (0.1)	199 (0.0)	228 (0.0)	21 (0.0)	524 (0.0)	5 (0.0)	591 (0.0)	<0.001
Charlson comorbidity index, n (%)								
0	940 525 (61.0)	299 362 (67.1)	237 202 (55.9)	8162 (63.6)	633 128 (51.1)	237 202 (55.9)	860 608 (59.0)	<0.001
1–2	488 116 (31.7)	130 043 (29.2)	146 427 (34.5)	3962 (30.9)	460 838 (37.2)	146 427 (34.5)	474 651 (32.6)	
≥3	112 371 (7.3)	16 480 (3.7)	40 972 (9.7)	709 (5.5)	144 352 (11.7)	40 972 (9.7)	122 343 (8.4)	

The *p* values were calculated using a χ^2 test for categorical variables and an analysis of variance for continuous variables. Ordering of variables was not considered on the χ^2 test analysis. CC indicates combustible cigarette; and NNTP, noncombustible nicotine or tobacco product.

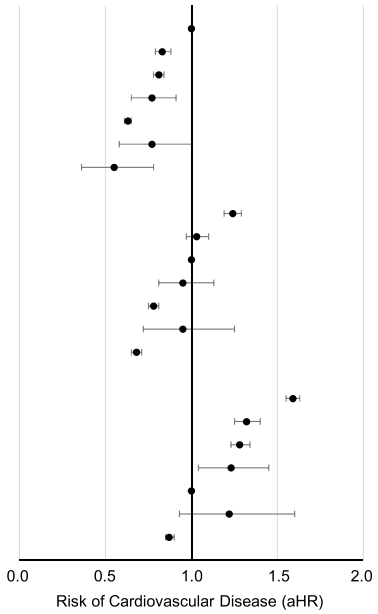
*Incidence was determined as the rate of cardiovascular disease events per 10 000 person-years.

produce higher levels of CVD-associated harmful constituents than NVPs. The greater market share of HTPs during 2018 in South Korea (13.1% for HTPs compared with 0.4% for NVPs)[15] appears to suggest that the CVD risk association from NNTP use in this study is mostly contributed from HTPs. Nonetheless, the difference in inhalants produced from HTPs and NVPs, and the varying pathways of cardiovascular health consequences from the inhalants, as well, warrant further investigation on CVD risk assessment for HTPs and NVPs separately.

Although NNTP use was associated with higher risk than no NNTP use on CC cessation, transitioning to NNTPs among initially CC-only smokers appeared to be associated with lower CVD risk than continual CC use. Results from several previous studies may help explain this relatively lower risk of NNTPs for CVD compared with CC smoking. In 2017, Lüdicke et al[32] investigated the effect of HTP and CC smoking on biomarkers for smoke toxicants among 40 smokers for 5 days and showed that HTP-only smoking was associated with lower levels of harmful constituents than CC smoking. In another study of 30 smokers, it was shown that NVP use after overnight abstinence was associated with smaller increases in exhaled carbon monoxide compared with those from CC smoking (exhaled carbon monoxide of 3 ppm for NVP versus 7 ppm for CC).[33] Last, another randomized trial of 160 smokers from the United States depicted that switching from CC to HTP was associated with lower levels of harmful constituents after 5 days compared with switching from CC to menthol CC.[34] Taken together, the lower incident CVD risk of switching to NNTPs compared with continued CC smoking may be explained by the fact that NNTP switchers may have been exposed to lower levels of harmful toxicants.

One of the reasons behind the increasing popularity of NNTPs is the potentially lower health risks of NNTPs compared with CCs, and thus the possibility of NNTPs as a harm-reduction tool on CC smoking cessation. Smokeless tobacco products such as Swedish snus have previously been shown to be related to lower health risks compared with CCs, and thus could be used as a method of tobacco harm reduction for CC smokers.[35–37] Similar to snus, NNTPs have been proposed to be a method for harm reduction of CCs by providing CC smokers with an alternative method of nicotine consumption in the form of NVPs or HTPs.[6] Determining whether NNTP use on CC smoking cessation is associated with CVD risk is imperative. This study demonstrates that NNTP use is associated with higher CVD risk among both recent and long-term CC quitters, suggesting that NNTP use may lead to higher CVD risk on CC smoking cessation. Therefore, although NNTP use has lower CVD risk compared with continued CC-only smoking, NNTP use on CC quitting may lead to higher CVD risk than CC quitting without NNTP use.

It has been shown that HTP and NVP use is associated with younger age,[7,14] which is also reflected in this study. Moreover, the cumulative exposure to tobacco may also differ among CC and NNTP users. Therefore, stratified analyses on the association of changes in NNTP and CC smoking habits with CVD risk according to subgroups of age and pack-years of smoking were conducted. Furthermore, recent and long-term CC quitters were matched according to NNTP use through propensity score matching. In particular, because age may act as a strong confounder in the association of CC and NNTP use with CVD risk, further propensity score matching after stratification according to age was conducted. NNTP use was associated with higher CVD risk among recent and long-term CC quitters after, but not before, propensity score matching. Based on the difference in age among NNTP users and nonusers within CC quitters, and the higher CVD risk observed after propensity score matching with age stratification, as well, the nonsignificant association of NNTP use with CVD risk among CC quitters before propensity score matching may be explained by the strong confounding effect of age. The propensity score matching analysis

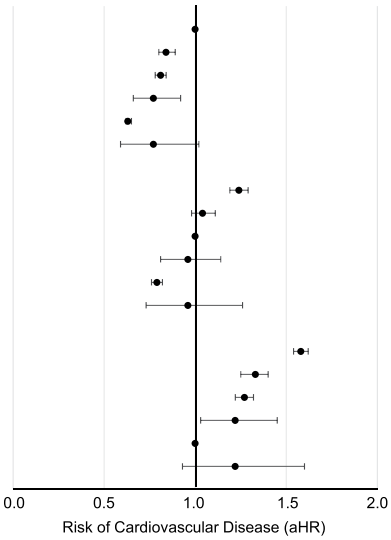


	Events	PYs	Incidence*	aHR (95% CI)
Continual CC only smokers as ref.				
Continual CC only smokers	13,224	2,127,601	62	1.00 (reference)
CC and NNTP users	1,510	596,081	25	0.83 (0.79-0.88)
Recent (<5 years) CC quitters without NNTP use	3,330	593,811	56	0.81 (0.78-0.84)
Recent (<5 years) CC quitters with NNTP use	139	53,609	26	0.77 (0.65-0.91)
Long-term (≥5 years) CC quitters without NNTP use	10,367	1,743,262	59	0.63 (0.61-0.65)
Long-term (≥5 years) CC quitters with NNTP use	52	17,466	30	0.77 (0.58-1.00)
Never smokers	9,373	2,048,485	46	0.55 (0.54-0.57)
Recent (<5 years) CC quitters without NNTP use as ref.				
Continual CC only smokers	13,224	2,127,601	62	1.24 (1.19-1.29)
CC and NNTP users	1,510	596,081	25	1.03 (0.97-1.10)
Recent (<5 years) CC quitters without NNTP use	3,330	593,811	56	1.00 (reference)
Recent (<5 years) CC quitters with NNTP use	139	53,609	26	0.95 (0.81-1.13)
Long-term (≥5 years) CC quitters without NNTP use	10,367	1,743,262	59	0.78 (0.75-0.81)
Long-term (≥5 years) CC quitters with NNTP use	52	17,466	30	0.95 (0.72-1.25)
Never smokers	9,373	2,048,485	46	0.68 (0.65-0.71)
Long-term (≥5 years) CC quitters without NNTP use as ref.				
Continual CC only smokers	13,224	2,127,601	62	1.59 (1.55-1.63)
CC and NNTP users	1,510	596,081	25	1.32 (1.25-1.40)
Recent (<5 years) CC quitters without NNTP use	3,330	593,811	56	1.28 (1.23-1.34)
Recent (<5 years) CC quitters with NNTP use	139	53,609	26	1.23 (1.04-1.45)
Long-term (≥5 years) CC quitters without NNTP use	10,367	1,743,262	59	1.00 (reference)
Long-term (≥5 years) CC quitters with NNTP use	52	17,466	30	1.22 (0.93-1.60)
Never smokers	9,373	2,048,485	46	0.87 (0.85-0.90)

Figure 2. Association of changes in CC and NNTP use habits with cardiovascular disease risk.
The aHRs were calculated by Cox proportional hazards regression after adjustments for age, household income, employment, area of residence, alcohol intake, physical activity, body mass index, systolic blood pressure, fasting serum glucose, history of drug abuse, and Charlson comorbidity index. *Incidence determined as the rate of cardiovascular disease events per 10 000 person-years. aHR indicates adjusted hazard ratio; CC, combustible cigarette; NNTP, noncombustible nicotine or tobacco product; and PYs, person-years.

appears to have reduced this confounding effect to reveal the increased CVD risk on NNTP use compared with no NNTP use among recent and long-term CC quitters.

Several limitations must be considered on interpretation of the results. First, women were not included in this analysis because 97% of all women were nonsmokers. In South Korea, it has previously been shown that there is a discrepancy between smoking status using a self-reported questionnaire compared with actual smoking status determined by urine cotinine levels among women.[38,39] This phenomenon, called the hidden female smoker effect, along with the fact that the majority of all women were



	Events	PYs	Incidence*	aHR (95% CI)
Continual CC only smokers as ref.				
Continual CC only smokers	13,224	2,127,601	62	1.00 (reference)
CC and NNTP users	1,510	596,081	25	0.84 (0.80-0.89)
Recent (<5 years) CC quitters without NNTP use	3,330	593,811	56	0.81 (0.78-0.84)
Recent (<5 years) CC quitters with NNTP use	139	53,609	26	0.77 (0.66-0.92)
Long-term (≥5 years) CC quitters without NNTP use	10,367	1,743,262	59	0.63 (0.62-0.65)
Long-term (≥5 years) CC quitters with NNTP use	52	17,466	30	0.77 (0.59-1.02)
Recent (<5 years) CC quitters without NNTP use as ref.				
Continual CC only smokers	13,224	2,127,601	62	1.24 (1.19-1.29)
CC and NNTP users	1,510	596,081	25	1.04 (0.98-1.11)
Recent (<5 years) CC quitters without NNTP use	3,330	593,811	56	1.00 (reference)
Recent (<5 years) CC quitters with NNTP use	139	53,609	26	0.96 (0.81-1.14)
Long-term (≥5 years) CC quitters without NNTP use	10,367	1,743,262	59	0.79 (0.76-0.82)
Long-term (≥5 years) CC quitters with NNTP use	52	17,466	30	0.96 (0.93-1.60)
Long-term (≥5 years) CC quitters without NNTP use as ref.				
Continual CC only smokers	13,224	2,127,601	62	1.58 (1.54-1.62)
CC and NNTP users	1,510	596,081	25	1.33 (1.25-1.40)
Recent (<5 years) CC quitters without NNTP use	3,330	593,811	56	1.27 (1.22-1.32)
Recent (<5 years) CC quitters with NNTP use	139	53,609	26	1.22 (1.03-1.45)
Long-term (≥5 years) CC quitters without NNTP use	10,367	1,743,262	59	1.00 (reference)
Long-term (≥5 years) CC quitters with NNTP use	52	17,466	30	1.22 (0.93-1.60)

Figure 3. Association of changes in CC and NNTP use habits with cardiovascular disease risk among those with past or current smoking experience and additional consideration of smoking pack-years.
Adjusted hazard ratios calculated by Cox proportional hazards regression after adjustments for age, household income, employment, area of residence, alcohol intake, physical activity, pack-years of CC smoking, body mass index, systolic blood pressure, fasting serum glucose, history of drug abuse, and Charlson comorbidity index. *Incidence determined as the rate of cardiovascular disease events per 10 000 person-years. aHR indicates adjusted hazard ratio; CC, combustible cigarette; NNTP, noncombustible nicotine or tobacco product; and PYs, person-years.

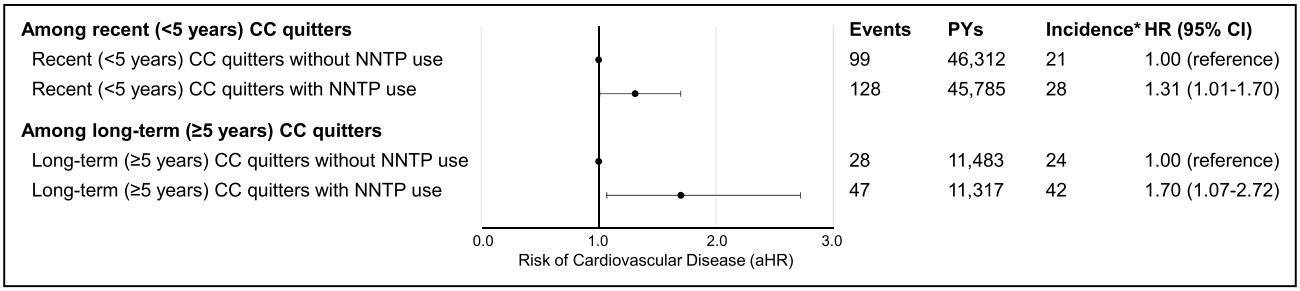


Figure 4. Association of changes in CC and NNTP use habits with cardiovascular disease risk after propensity score matching among CC quitters.

Propensity score matching was performed according to NNTP use within recent and long-term CC quitters. Age, household income, employment, area of residence, alcohol intake, physical activity, pack-years of CC smoking, body mass index, systolic blood pressure, fasting serum glucose, and Charlson comorbidity index were taken into consideration on matching. With the use of a caliper of 0.2 times the standard deviation of the logit propensity score, the greedy matching method was used with a matching ratio of 1:1. HR was calculated by Cox proportional hazards regression. *Incidence was determined as the rate of cardiovascular disease events per 10 000 person-years. aHR indicates adjusted hazard ratio; CC, combustible cigarette; HR, hazard ratio; NNTP, noncombustible nicotine or tobacco product; and PYs, person-years.

nonsmokers led to the exclusion of women in this analysis, which can also be seen in previous studies that used the NHIS database.[23,40] Future studies that determine the association of NNTP and CC smoking with CVD risk among women are needed. Second, smoking status was determined using a self-reported questionnaire, and is thus at risk of misclassification, in particular, between CC and NNTP users. Because NNTP use was determined by NNTP habits during the past 1-month period, there may have been short-term NNTP users with only a few months of NNTP use history grouped into the NNTP user group. Moreover, the greater market share of HTPs compared with NVPs in South Korea may limit the generalizability of the results to other regions. Specifically, because the majority of NNTP users in Western populations tend to be NVP users, the results from this study may have limited implications in regions where NVP use is predominant.

Third, the relatively short follow-up duration along with the possibility of undetected preclinical signs and symptoms that may have affected a subject's CC and NNTP use habit before actual CVD incidence indicate that conclusive inference on causality when describing the association of CC and NNTP habit change with CVD risk is difficult. This short follow-up duration was also part of the reason why this study focused on initial CC smokers and past smokers and did not include smoking initiators in this study. Because CC and NNTP smoking initiators are expected to be composed of young adults, determining CVD risk according to smoking initiation would require longer follow-up durations. Fourth, CVD events could not be validated because of the lack of access to medical chart records. However, multiple previous studies have used the operational definition for CVD from the NHIS database.[19,41] Nonetheless, future studies that use medical chart records to validate CVD events are needed. Fifth, because of the observational nature of the data, the reasons for NNTP use were unclear. This is particularly important in the assessment of CC and NNTP dual users, because they appear to have lower risk than CC-only smokers. Because it may be possible that CC and NNTP users are composed of CC-only smokers transitioning toward smoking cessation, the lower CVD risk may be attributable to CC and NNTP users being more self-aware of their health and undergoing lifestyle modifications. This is reflected in part in the data demonstrating fewer CCs smoked per day and higher physical activity levels among CC and NNTP users compared with continual CC-only users. Therefore, further investigations with detailed assessment of reasons for CC and NNTP habit changes, and markers for health-seeking behavior and health awareness, are needed in the comparison of continued CC users with CC and NNTP dual users. Last, future studies should investigate the association of NNTP use with other health-related outcomes, such as respiratory diseases, cancer, and mortality. Although NNTP use appeared to elevate the risk of all-cause mortality, lung cancer, and COPD, the short follow-up duration warrants future investigations with longer follow-up.

Despite these limitations, a number of strengths exist. First, the large study population and longitudinal study design enhance the generalizability of the results. Second, a wide range of potential confounders were adjusted for. Propensity score matching for NNTP users was conducted in an attempt to minimize the confounding effects of covariates. Furthermore, the nature of the administrative health claims data provides results in a real-world setting. Last, although most past studies focused on the risk of NNTP with CVD by using intermediate markers for CVD such as arterial stiffness, this study determined the risk of changes in NNTP and CC use habits with the development of actual CVD events.

In conclusion, transitioning to NNTPs among CC smokers may result in lower CVD risk compared with continued CC-only use. NNTP use on CC cessation was associated with higher CVD risk compared with CC cessation without NNTPs. Although NNTPs may have lower CVD risk than CCs, quitters of CCs who use NNTPs may be exposed to higher CVD risk than those who quit CCs without NNTP use.

Table 2. Stratified Analysis on the Association of Changes in CC and NNTP Use Habits With Cardiovascular Disease Risk According to Subgroups of Age or Pack-Years of Smoking Among Those With Current or Past History of Smoking

Subgroups	Continual CC only smokers	CC and NNTP users	Recent (<5 y) CC quitters without NNTP use	Recent (<5 y) CC quitters with NNTP use	Long-term (≥5 y) CC quitters without NNTP use	Long-term (≥5 y) CC quitters with NNTP use
Continual CC-only smokers as reference						
Total cohort	1.00 (reference)	0.84 (0.80–0.89)	0.81 (0.78–0.84)	0.77 (0.66–0.92)	0.63 (0.62–0.65)	0.77 (0.59–1.02)
Age, y						
<40	1.00 (reference)	0.79 (0.67–0.93)	0.78 (0.64–0.96)	0.66 (0.40–1.11)	0.73 (0.60–0.88)	0.97 (0.46–2.06)
40–49	1.00 (reference)	0.91 (0.83–1.00)	0.76 (0.68–0.84)	0.75 (0.54–1.03)	0.64 (0.59–0.69)	0.87 (0.51–1.57)
50–59	1.00 (reference)	1.03 (0.94–1.12)	0.81 (0.76–0.87)	0.98 (0.74–1.29)	0.61 (0.58–0.65)	0.92 (0.56–1.50)
≥60	1.00 (reference)	1.02 (0.88–1.17)	0.83 (0.78–0.87)	0.92 (0.66–1.28)	0.66 (0.64–0.68)	0.70 (0.42–1.17)
Pack-years of smoking						
<10	1.00 (reference)	0.80 (0.71–0.91)	0.89 (0.81–0.97)	0.75 (0.52–1.09)	0.68 (0.64–0.72)	0.93 (0.59–1.46)
≥10	1.00 (reference)	0.85 (0.80–0.90)	0.80 (0.77–0.83)	0.79 (0.66–0.96)	0.65 (0.63–0.67)	0.76 (0.54–1.06)
Recent CC quitters without NNTP use as reference						
Total cohort	1.24 (1.19–1.29)	1.04 (0.98–1.11)	1.00 (reference)	0.96 (0.81–1.14)	0.79 (0.76–0.82)	0.96 (0.73–1.26)
Age, years						
<40	1.28 (1.04–1.57)	1.00 (0.80–1.26)	1.00 (reference)	0.85 (0.49–1.45)	0.93 (0.73–1.19)	1.25 (0.58–2.67)
40–49	1.32 (1.19–1.47)	1.21 (1.06–1.37)	1.00 (reference)	0.99 (0.71–1.38)	0.84 (0.75–0.95)	1.15 (0.67–1.96)
50–59	1.23 (1.15–1.32)	1.26 (1.13–1.40)	1.00 (reference)	1.20 (0.90–1.59)	0.75 (0.70–0.81)	1.13 (0.69–1.84)
≥60	1.21 (1.15–1.28)	1.23 (1.06–1.43)	1.00 (reference)	1.11 (0.79–1.55)	0.80 (0.76–0.84)	0.85 (0.51–1.41)
Pack-years of smoking						
<10	1.13 (1.03–1.23)	0.90 (0.78–1.04)	1.00 (reference)	0.85 (0.58–1.23)	0.76 (0.70–0.83)	1.05 (0.66–1.65)
≥10	1.25 (1.20–1.30)	1.06 (0.99–1.14)	1.00 (reference)	0.99 (0.82–1.20)	0.81 (0.77–0.84)	0.94 (0.67–1.33)
Long-term CC quitters without NNTP use as reference						
Total cohort	1.58 (1.54–1.62)	1.33 (1.25–1.40)	1.27 (1.22–1.32)	1.22 (1.03–1.45)	1.00 (reference)	1.22 (0.93–1.60)
Age, years						
<40	1.38 (1.14–1.66)	1.08 (0.87–1.34)	1.08 (0.84–1.38)	0.91 (0.54–1.55)	1.00 (reference)	1.34 (0.63–2.87)
40–49	1.57 (1.45–1.71)	1.43 (1.29–1.59)	1.19 (1.06–1.34)	1.18 (0.85–1.63)	1.00 (reference)	1.37 (0.81–2.32)
50–59	1.63 (1.55–1.71)	1.67 (1.52–1.84)	1.33 (1.23–1.43)	1.59 (1.21–2.10)	1.00 (reference)	1.49 (0.91–2.44)
≥60	1.52 (1.47–1.58)	1.55 (1.34–1.78)	1.26 (1.19–1.32)	1.39 (1.00–1.94)	1.00 (reference)	1.07 (0.64–1.77)
Pack-years of smoking						
<10	1.48 (1.39–1.57)	1.19 (1.04–1.35)	1.31 (1.20–1.44)	1.11 (0.77–1.60)	1.00 (reference)	1.37 (0.88–2.16)
≥10	1.55 (1.50–1.60)	1.32 (1.23–1.40)	1.24 (1.19–1.29)	1.23 (1.02–1.49)	1.00 (reference)	1.17 (0.83–1.64)

Values shown are adjusted hazard ratios (95% CIs). The adjusted hazard ratios were calculated using Cox proportional hazards regression after adjustments for age, household income, employment, area of residence, alcohol intake, physical activity, pack-years of CC smoking, body mass index, systolic blood pressure, fasting serum glucose, history of drug abuse, and Charlson comorbidity index. CC indicates combustible cigarette; and NNTP, noncombustible nicotine or tobacco product.

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Disclosures

None.

Supplemental Materials

Tables S1–S9

REFERENCES

1. World Health Organization. Heated tobacco products information sheet. WHO/NMH/PND/17.5. May 21, 2018. Accessed November 19, 2019. https://www.who.int/publications/i/item/WHO-NMH-PND-17.6.

2. Elias J, Dutra LM, St Helen G, Ling PM. Revolution or redux? Assessing IQOS through a precursor product. *Tob Control.* 2018;27(suppl 1):s102–s110. doi: 10.1136/tobaccocontrol-2018-054327
3. Vineis P, Alavanja M, Buffler P, Fontham E, Franceschi S, Gao YT, Gupta PC, Hackshaw A, Matos E, Samet J, et al. Tobacco and cancer: recent epidemiological evidence. *J Natl Cancer Inst.* 2004;96:99–106. doi: 10.1093/jnci/djh014
4. Bullen C. Impact of tobacco smoking and smoking cessation on cardiovascular risk and disease. *Expert Rev Cardiovasc Ther.* 2008;6:883–895. doi: 10.1586/14779072.6.6.883
5. Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases: part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. *Circulation.* 2001;104:2746–2753. doi: 10.1161/hc4601.099487
6. Schaller JP, Keller D, Poget L, Pratte P, Kaelin E, McHugh D, Cudazzo G, Smart D, Tricker AR, Gautier L, et al. Evaluation of the Tobacco Heating System 2.2. part 2: chemical composition, genotoxicity, cytotoxicity, and physical properties of the aerosol. *Regul Toxicol Pharmacol.* 2016;81(suppl 2):S27–S47. doi: 10.1016/j.yrtph.2016.10.001
7. Nyman AL, Weaver SR, Popova L, Pechacek TF, Huang J, Ashley DL, Eriksen MP. Awareness and use of heated tobacco products among US adults, 2016–2017. *Tob Control.* 2018;27(suppl 1):s55–s61. doi: 10.1136/tobaccocontrol-2018-054323
8. Fried ND, Gardner JD. Heat-not-burn tobacco products: an emerging threat to cardiovascular health. *Am J Physiol Heart Circ Physiol.* 2020;319:H1234–H1239. doi: 10.1152/ajpheart.00708.2020
9. Mallock N, Pieper E, Hutzler C, Henkler-Stephani F, Luch A. Heated tobacco products: a review of current knowledge and initial assessments. *Front Public Health.* 2019;7:287. doi: 10.3389/fpubh.2019.00287
10. Jankowski M, Brożek GM, Lawson J, Skoczyński S, Majek P, Zejda JE. New ideas, old problems? Heated tobacco products - a systematic review. *Int J Occup Med Environ Health.* 2019;32:595–634. doi: 10.13075/ijomeh.1896.01433
11. Kennedy CD, van Schalkwyk MCI, McKee M, Pisinger C. The cardiovascular effects of electronic cigarettes: a systematic review of experimental studies. *Prev Med.* 2019;127:105770. doi: 10.1016/j.ypmed.2019.105770
12. Peruzzi M, Biondi-Zoccai G, Carnevale R, Cavarretta E, Frati G, Versaci F. Vaping cardiovascular health risks: an updated umbrella review. *Curr Emerg Hosp Med Rep.* 2020:1–7. doi: 10.1007/s40138-020-00219-0
13. Lee CM. The impact of heated tobacco products on smoking cessation, tobacco use, and tobacco sales in South Korea. *Korean J Fam Med.* 2020;41:273–281. doi: 10.4082/kjfm.20.0140
14. Kim SH, Cho HJ. Prevalence and correlates of current use of heated tobacco products among a nationally representative sample of Korean adults: results from a cross-sectional study. *Tob Induc Dis.* 2020;18:66. doi: 10.18332/tid/125232
15. Tobacco market trends 2020. Ministry of Economy and Finance of South Korea; 2021. Accessed March 5, 2021. https://eiec.kdi.re.kr/policy/materialView.do?num=210130&topic=
16. Cheol Seong S, Kim YY, Khang YH, Heon Park J, Kang HJ, Lee H, Do CH, Song JS, Hyon Bang J, Ha S, et al. Data resource profile: the National Health Information Database of the National Health Insurance Service in South Korea. *Int J Epidemiol.* 2017;46:799–800. doi: 10.1093/ije/dyw253
17. Seong SC, Kim YY, Park SK, Khang YH, Kim HC, Park JH, Kang HJ, Do CH, Song JS, Lee EJ, et al. Cohort profile: the National Health Insurance Service-National Health Screening Cohort (NHIS-HEALS) in Korea. *BMJ Open.* 2017;7:e016640. doi: 10.1136/bmjopen-2017-016640
18. Choi S, Kim K, Kim SM, Lee G, Jeong SM, Park SY, Kim YY, Son JS, Yun JM, Park SM. Association of obesity or weight change with coronary heart disease among young adults in South Korea. *JAMA Intern Med.* 2018;178:1060–1068. doi: 10.1001/jamainternmed.2018.2310
19. Son JS, Choi S, Kim K, Kim SM, Choi D, Lee G, Jeong SM, Park SY, Kim YY, Yun JM, et al. Association of blood pressure classification in Korean young adults according to the 2017 American College of Cardiology/American Heart Association Guidelines With Subsequent Cardiovascular Disease Events. *JAMA.* 2018;320:1783–1792. doi: 10.1001/jama.2018.16501
20. Lee J, Lee JS, Park SH, Shin SA, Kim K. Cohort profile: the National Health Insurance Service-National Sample Cohort (NHIS-NSC), South Korea. *Int J Epidemiol.* 2017;46:e15. doi: 10.1093/ije/dyv319
21. Wang Y, Cai H, Li C, Jiang Z, Wang L, Song J, Xia J. Optimal caliper width for propensity score matching of three treatment groups: a Monte Carlo study. *PLoS One.* 2013;8:e81045. doi: 10.1371/journal.pone.0081045
22. Lloyd-Jones DM, Huffman MD, Karmali KN, Sanghavi DM, Wright JS, Pelser C, Gulati M, Masoudi FA, Goff DC Jr. Estimating longitudinal risks and benefits from cardiovascular preventive therapies among Medicare patients: The Million Hearts Longitudinal ASCVD Risk Assessment Tool: a special report from the American Heart Association and American College of Cardiology. *Circulation.* 2017;135:e793–e813. doi: 10.1161/CIR.0000000000000467
23. Kim K, Park SM, Lee K. Weight gain after smoking cessation does not modify its protective effect on myocardial infarction and stroke: evidence from a cohort study of men. *Eur Heart J.* 2018;39:1523–1531. doi: 10.1093/eurheartj/ehx761
24. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Delling FN, et al; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2020 update: a report from the American Heart Association. *Circulation.* 2020;141:e139–e596. doi: 10.1161/CIR.0000000000000757
25. Hecht SS, Carmella SG, Kotandeniya D, Pillsbury ME, Chen M, Ransom BW, Vogel RI, Thompson E, Murphy SE, Hatsukami DK. Evaluation of toxicant and carcinogen metabolites in the urine of e-cigarette users versus cigarette smokers. *Nicotine Tob Res.* 2015;17:704–709. doi: 10.1093/ntr/ntu218
26. Lerner CA, Sundar IK, Watson RM, Elder A, Jones R, Done D, Kurtzman R, Ossip DJ, Robinson R, McIntosh S, et al. Environmental health hazards of e-cigarettes and their components: oxidants and copper in e-cigarette aerosols. *Environ Pollut.* 2015;198:100–107. doi: 10.1016/j.envpol.2014.12.033
27. Farsalinos K, Cibella F, Caponnetto P, Campagna D, Morjaria JB, Battaglia E, Caruso M, Russo C, Polosa R. Effect of continuous smoking reduction and abstinence on blood pressure and heart rate in smokers switching to electronic cigarettes. *Intern Emerg Med.* 2016;11:85–94. doi: 10.1007/s11739-015-1361-y
28. Hess CA, Olmedo P, Navas-Acien A, Goessler W, Cohen JE, Rule AM. E-cigarettes as a source of toxic and potentially carcinogenic metals. *Environ Res.* 2017;152:221–225. doi: 10.1016/j.envres.2016.09.026
29. Cancelada L, Sleiman M, Tang X, Russell ML, Montesinos VN, Litter MI, Gundel LA, Destaillats H. Heated tobacco products: volatile emissions and their predicted impact on indoor air quality. *Environ Sci Technol.* 2019;53:7866–7876. doi: 10.1021/acs.est.9b02544
30. Abplanalp W, DeJarnett N, Riggs DW, Conklin DJ, McCracken JP, Srivastava S, Xie Z, Rai S, Bhatnagar A, O'Toole TE. Benzene exposure is associated with cardiovascular disease risk. *PLoS One.* 2017;12:e0183602. doi: 10.1371/journal.pone.0183602
31. Leigh NJ, Palumbo MN, Marino AM, O'Connor RJ, Goniewicz ML. Tobacco-specific nitrosamines (TSNA) in heated tobacco product IQOS. *Tob Control.* 2018;27(suppl 1):s37–s38. doi: 10.1136/tobaccocontrol-2018-054318
32. Lüdicke F, Baker G, Magnette J, Picavet P, Weitkunat R. Reduced exposure to harmful and potentially harmful smoke constituents with the Tobacco Heating System 2.1. *Nicotine Tob Res.* 2017;19:168–175. doi: 10.1093/ntr/ntw164
33. Adriaens K, Gucht DV, Baeyens F. IQOSTM vs. e-cigarette vs. tobacco cigarette: a direct comparison of short-term effects after overnight-abstinence. *Int J Environ Res Public Health.* 2018;15:E2902. doi: 10.3390/ijerph15122902
34. Haziza C, de La Bourdonnaye G, Donelli A, Poux V, Skiada D, Weitkunat R, Baker G, Picavet P, Lüdicke F. Reduction in exposure to selected harmful and potentially harmful constituents approaching those observed upon smoking abstinence in smokers switching to the Menthol Tobacco Heating System 2.2 for 3 months (part 1). *Nicotine Tob Res.* 2020;22:539–548. doi: 10.1093/ntr/ntz013
35. Gartner CE, Hall WD, Chapman S, Freeman B. Should the health community promote smokeless tobacco (snus) as a harm reduction measure? *PLoS Med.* 2007;4:e185. doi: 10.1371/journal.pmed.0040185
36. Gartner CE, Hall WD, Vos T, Bertram MY, Wallace AL, Lim SS. Assessment of Swedish snus for tobacco harm reduction: an epidemiological modelling study. *Lancet.* 2007;369:2010–2014. doi: 10.1016/S0140-6736(07)60677-1
37. Lee PN. The effect on health of switching from cigarettes to snus - a review. *Regul Toxicol Pharmacol.* 2013;66:1–5. doi: 10.1016/j.yrtph.2013.02.010
38. Park MB, Kim CB, Nam EW, Hong KS. Does South Korea have hidden female smokers: discrepancies in smoking rates between self-reports and urinary cotinine level. *BMC Womens Health.* 2014;14:156. doi: 10.1186/s12905-014-0156-z
39. Jung-Choi KH, Khang YH, Cho HJ. Hidden female smokers in Asia: a comparison of self-reported with cotinine-verified smoking prevalence rates in representative national data from an Asian population. *Tob Control.* 2012;21:536–542. doi: 10.1136/tobaccocontrol-2011-050012
40. Choi S, Chang J, Kim K, Kim SM, Koo HY, Cho MH, Cho IY, Lee H, Son JS, Park SM, et al. Association of smoking cessation after atrial fibrillation diagnosis on the risk of cardiovascular disease: a cohort study of South Korean men. *BMC Public Health.* 2020;20:168. doi: 10.1186/s12889-020-8275-y
41. Kim K, Choi S, Hwang SE, Son JS, Lee JK, Oh J, Park SM. Changes in exercise frequency and cardiovascular outcomes in older adults. *Eur Heart J.* 2020;41:1490–1499. doi: 10.1093/eurheartj/ehz768