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CLINICAL RESEARCH
Epidemiology and prevention

Smoking cessation, but not reduction, reduces cardiovascular disease incidence

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See page 4154 for the editorial comment for this article 'Importance of smoking cessation for cardiovascular risk reduction', by A.L. Møller and C. Andersson, https://doi.org/10.1093/eurheartj/ehab541.

Aims The aim of this study was to assess the association of smoking cessation and reduction with risk of cardiovascular disease (CVD).

Methods and results A total of 897 975 current smokers aged ≥40 years who had undergone two consecutive national health examinations (in 2009 and 2011) were included. Participants were classified as quitters (20.6%), reducers I (≥50% reduction, 7.3%), reducers II (20–50% reduction, 11.6%), sustainers (45.7%), and increasers (≥20% increase, 14.5%). During 5 575 556 person-years (PY) of follow-up, 17 748 stroke (3.2/1000 PY) and 11 271 myocardial infarction (MI) (2.0/1000 PY) events were identified. Quitters had significantly decreased risk of stroke [adjusted hazard ratio (aHR) 0.77 95% confidence interval (CI) 0.74–0.81; absolute risk reduction (ARR) -0.37, 95% CI -0.43 to -0.31] and MI (aHR 0.74, 95% CI 0.70–0.78; ARR -0.27, 95% CI -0.31 to -0.22) compared to sustainers after adjustment for demographic factors, comorbidities, and smoking status. The risk of stroke and MI incidence in reducers I (aHR 1.02, 95% CI 0.97–1.08 and aHR 0.99, 95% CI 0.92–1.06, respectively) and reducers II (aHR 1.00, 95% CI 0.95–1.05 and aHR 0.97, 95% CI 0.92–1.04, respectively) was not significantly different from the risk in sustainers. Further analysis with a subgroup who underwent a third examination (in 2013) showed that those who quit at the second examination but had starting smoking again by the third examination had 42–69% increased risk of CVD compared to sustained quitters.

Conclusions Smoking cessation, but not reduction, was associated with reduced CVD risk. Our study emphasizes the importance of sustained quitting in terms of CVD risk reduction.

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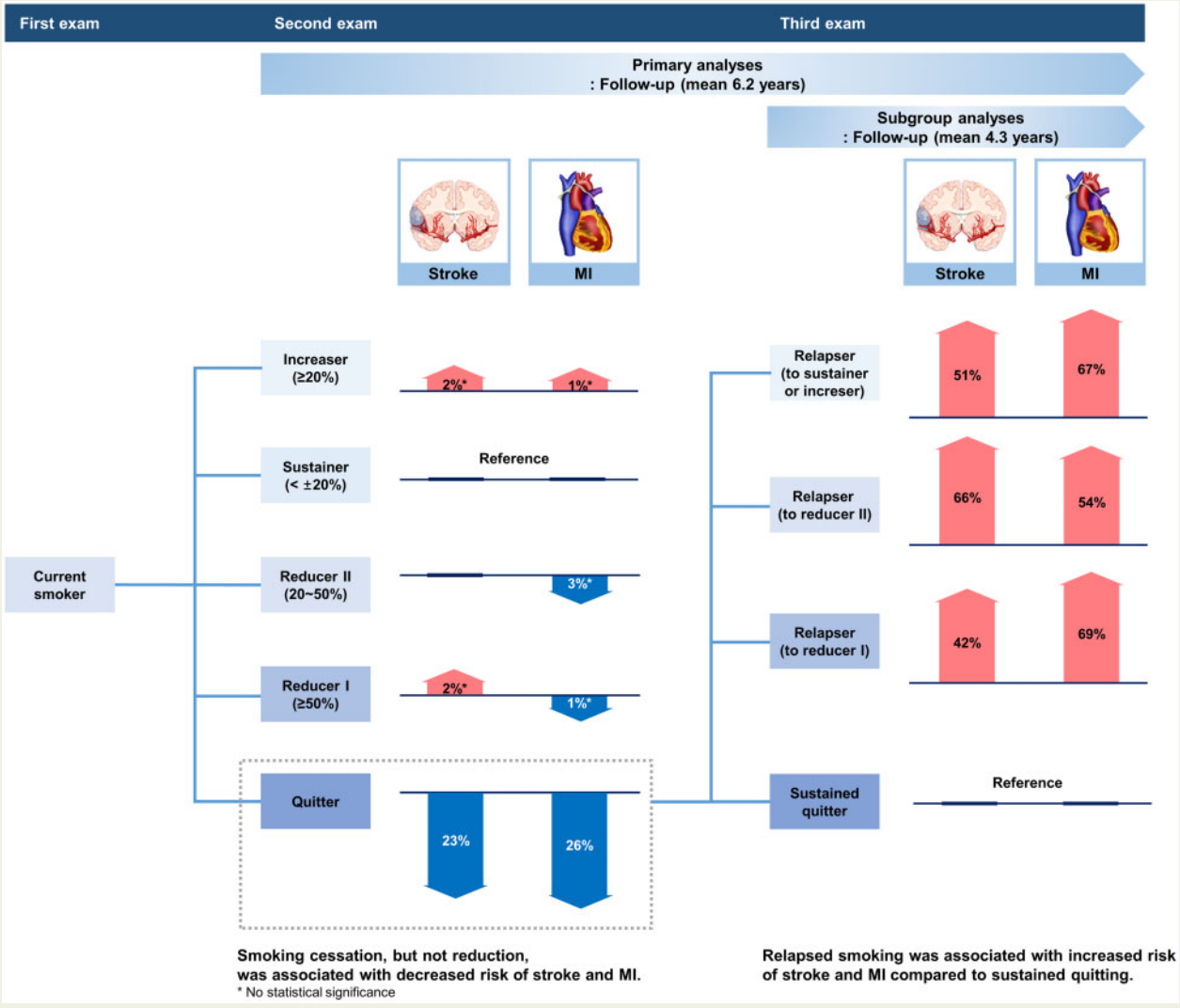
Graphical Abstract



Smoking reduction does not seem to have a definite benefit in reducing cardiovascular disease risk regardless of degree. To reduce cardiovascular disease risk, smoking cessation is necessary. Relapsed smoking is associated with an increased cardiovascular disease risk, which suggests the importance of maintaining smoking cessation. MI, myocardial infarction.

Keywords Smoking cessation • Smoking reduction • Cardiovascular diseases • Stroke • Myocardial infarction

Introduction

Smoking is a major preventable risk factor for cardiovascular disease (CVD) and accounts for 10% of CVD-related deaths worldwide.[1] Although tobacco control policies have led to decreased global tobacco use, the burden of smoking-related CVD risk persists.[2] The effect of smoking cessation on CVD risk reduction has been well-documented.[3] Heavy smokers (≥20 pack-years) who quit smoking had a 39% lower risk of CVD within 5 years compared to heavy smokers.[4] Given the evidence for a dose-response relationship between smoking intensity and risk of CVD,[5] smoking reduction as a CVD risk reduction strategy seemed logical to decrease the harm of smoking.[6] However, the limited health benefits from smoking reduction were noted in a systematic review.[7]

Previous studies assessing the long-term impact of smoking reduction on health outcomes such as risk of CVD development and CVD mortality reported no associations (Supplementary material online, *Table S1*).[8–15] Most studies found that smoking reduction did not lower the risk of incidence[8,9,11] or mortality of CVD.[10,12,13] Only one prospective study of Israeli men ($n = 4633$) reported a significantly

lower risk for CVD mortality in smoking reducers compared to those who maintained their smoking level over a 2-year interval [adjusted hazard ratio (aHR) 0.85, 95% confidence interval (CI) 0.77–0.95].[14] A large cohort study of 475 734 Korean men suggested a possible benefit of smoking reduction on stroke and myocardial infarction (MI) incidence despite the absence of statistical significance (aHR 0.91, 95% CI 0.72–1.15 and aHR 0.80, 95% CI 0.55–1.16, respectively).[8] In a pooled cohort study in Denmark (n = 19 423), smoking reduction did not significantly decrease the risk of MI development.[11]

These inconsistent results might have been caused by different study designs such as definition of smoking reduction, proportion of heavy smokers at baseline, and categorization. The previous studies used two definitions of smoking reduction: (i) decrease in number of cigarettes per day[8,9,12,14] and (ii) reduction of cigarette use by more than 50%.[10,11,13] By capturing trivial reductions, the first definition is more likely to have a higher proportion of smoking reducers. The percentage of heavy smokers at baseline varied from 10% to 40%. The Israeli cohort study included a high proportion of heavy smokers (39.1%) and showed a high reduction proportion among heavy smokers (34.1%).[14] In addition, study populations were limited to diabetic patients[9] or men.[8,14] Importantly, none of these studies evaluated serial change of smoking status through three points of assessment. Although there are high rates of smoking relapse (~50% within 1 year),[16] and various situations after smoking cessation (e.g. relapsed smoking vs. sustained quitting) could be associated differently with CVD risk, few studies have investigated adverse CVD or mortality outcomes related to relapsed smoking in a general population.[17]

Thus, the aim of this study was to evaluate the impact of smoking reduction and smoking cessation on the risk of CVD incidence using health survey, examination, and claims database of the Korean National Health Insurance Service (NHIS). Furthermore, we attempted to document changes in smoking level by collecting data from three periodic examinations.

Methods

Data source and study setting

In South Korea, a universal insurance system provided by a single insurer, the Korean NHIS, covers ~97% of the population. The remaining 3% of the population in the lowest income bracket is covered by the government-financed Medical Aid program that also is administered by the NHIS. The NHIS recommends that all insured individuals (all citizens aged 40 and above and all employees regardless of age) undergo a general health examination at least every 2 years. This national health examination consists of a standard questionnaire (past medical history, current medications, and lifestyle habits that include alcohol consumption, smoking, and exercise), anthropometric measurements (height, weight, body mass index, and blood pressure), and laboratory tests.[18] The serial data of the individuals from the biannual health examinations have been deposited in the NHIS database. In addition, these data can be linked with information on claimed healthcare utilization, which has been widely used for epidemiological studies.[19,20] This study was approved by the Institutional Review Board of Samsung Medical Center (IRB File No. SMC 2020-07-181).

Study population

From the NHIS database of the whole Korean population, we collected participants ≥40 years old who had undergone two consecutive national health examinations, the first in 2009 and the second in 2011, to determine changes in smoking behaviour. We initially selected current smokers (n = 1 006 803) according to the definition of the World Health Organization.[21] Participants who had been diagnosed with CVD (n = 12 940) or any cancer (n = 15 552) prior to the second health examination period were excluded. To reduce the effect of reverse causality, we applied a 1-year lag time by excluding participants who were diagnosed with stroke (n = 2487) or MI (n = 1466) or who died (n = 3494) within 1 year after the second health examination period. Those with missing information in variables used in this study (n = 72 889) were excluded. A total of 897 975 individuals remained for analysis (Supplementary material online, *Figure S1*).

We also established a subgroup of people who participated in three health examinations to assess the effect of further changes in smoking behaviour at a third examination in 2013. Subjects who did not participate in the third examination (n = 196 358), cancer (n = 6712) between second and third examinations, CVD (n = 2166) between 1-year after second and third examinations, CVD (n = 3077) or death (n = 2338) within 1-year after third examination, and missing information (n = 997). Subgroup data from the remaining 686 327 study participants were analysed.

Definition of change in cigarette smoking intensity

Information on smoking status and changes in smoking habits was obtained from a self-administered questionnaire during the biennial NHIS national health examinations. The participants who acknowledged current smoking were questioned on average daily number of cigarettes and duration of smoking in years (Supplementary material online, *Table S2*). According to cigarette smoking frequency at the time of the first examination (2009), study participants were categorized into three groups: (i) light smokers (<10 cigarettes per day), (ii) moderate smokers (10–19 cigarettes per day), and (iii) heavy smokers (≥20 cigarettes per day).[8] Then, study participants were categorized further into five groups based on the changes in the number of cigarettes per day between the first examination (2009) and the second examination (2011): quitter, reducer I, reducer II, sustainer, and increaser. Quitters were those who had completely stopped smoking. Reducers were divided by reduced amount to evaluate any association according to the degree of smoking reduction: reducers I had reduced cigarette use by 50% or more referring to the definitions from previous studies[11] and reducers II were those who had decreased cigarette use by 20% or more but <50%. Sustainers had reduced the number of cigarettes by <20% or increased by <20%, and increasers had increased the number of cigarettes by 20% or more.

In the subgroup of people who participated in the three health examinations, sustained quitters were defined as those who had quit smoking at the second examination and continued to abstain until the third examination, and relapsers were defined as those who had quit at the second examination but had started smoking again by the third examination. Smoking level at the third examination in 2013 was compared to the initial smoking level at the first examination in 2009. We merged sustainers and increasers to reduce the number of categories (from 5 by 5 to 4 by 4) and because the number of increasers was small.

Covariates

Information on covariates was assessed on the day of second examination. Alcohol consumption was classified into four levels according to amount of daily consumption: (i) none, (ii) light (<15 g of alcohol/day), (iii) moderate (15–30 g of alcohol/day), and (iv) heavy (≥30 g/day). Regular exercise was defined as moderate physical activity for >30 min >5 days during the past week. Body mass index was calculated using

weight (kg) divided by height in metres squared (m^2). The presence of hypertension, diabetes mellitus, and dyslipidaemia was defined by claims data before screening [medical claim based on International Classification of Diseases (ICD-10) codes and relevant prescription of at least 1 claim per year] and health examination results: hypertension (I10–I13 or I15 and antihypertensive medication or blood pressure ≥140/90 mmHg), diabetes mellitus (E11–E14 and antidiabetic medication or fasting glucose level ≥126 mg/dL), and dyslipidaemia (E78 and lipid-lowering medications or total cholesterol level ≥240 mg/dL). Chronic kidney disease was defined based on the glomerular filtration rate of <60 mL/min/1.73 m^2 as estimated by the Modification of Diet in Renal Disease equation.[22] Household income was categorized into quartiles based on insurance premium (in Korea, insurance premiums are determined by income level), with those covered by Medical Aid (3% of the poorest) being merged into the lowest income quartile.

Study outcomes and follow-up

The primary endpoints of this study were newly diagnosed stroke and MI, identified on the basis of the ICD-10 codes for stroke and MI. The ICD-10 codes for stroke were I63 or I64 during hospitalization, with claims for brain magnetic resonance imaging or brain computed tomography; the ICD-10 codes for MI were I21 or I22 during hospitalization. These codes were also applied if recorded in at least two outpatient visits.[22] The cohort was followed after 1 year of lag time from the second (in 2011) and third health examination dates (in 2013) to the date of incident stroke or MI, death, or until the end of the study period (31 December 2018), whichever came first (Supplementary material online, *Figure S2*).

Secondary endpoints were overall mortality, fatal stroke, and fatal MI. Mortality data were obtained through routine linkage to the mortality data from the Korean National Statistical Office, but causes of death were not available for this study as they are routinely linked. Fatal stroke and MI were defined when participants died within 1 year from first diagnosis of stroke or MI, respectively.[23]

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD), and categorical variables are presented as number and percentage. Hazard ratio (HR) and 95% CI values for stroke or MI were analysed using the Cox proportional hazards model. The proportional hazards assumption was checked using Schoenfeld residuals. Models were adjusted for age, sex, body mass index, duration of smoking, alcohol consumption, regular exercise, area of residence, income, and presence or absence of comorbidities (hypertension, diabetes mellitus, dyslipidaemia, and chronic kidney disease). In addition to HR, absolute risk reductions (ARRs) for stroke and MI were depicted to show absolute difference across groups by change in smoking intensity.

Stratification analyses by smoking status (smoking intensity and cumulative exposure in pack-years) at the first examination, age (40–49, 50–59, 60–69, and ≥70 years), sex, and comorbidities were performed to determine associations between change in smoking behaviour and incidence of stroke and MI considered as confounding factors.

A number of sensitivity analyses were performed to examine the robustness of our findings. We used the inverse probability of treatment weighting (IPTW) of propensity scores method to balance baseline covariates for each group. Sensitivity analysis with competing risk analyses was performed with the Fine and Gray method to assess the sub-distribution hazard ratio (SHR) for CVD incidence accounting for death from any cause as a competing event. Furthermore, a time-dependent Cox regression analysis was performed to account for time-varying changes in smoking intensity during follow-up.

Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), and a *P*-value of <0.05 was considered statistically significant.

Results

Characteristics of study participants

During a mean follow-up of 6.2 years from 1 year after the second health examination, there were 17 748 stroke events and 11 271 MI events. *Table 1* shows baseline characteristics during the period of the second examination (in 2011) according to change in smoking behaviour (quitters, reducers I, reducers II, sustainers, and increasers). The mean age of the study participants was 53.0 years (SD 9.0), and 94.5% were men. In this study population, 52.8% were heavy smokers, 37.3% were moderate smokers, and the remaining 9.9% were light smokers at the time of the first examination.

Of note, 18.9% reduced their smoking (7.3% and 11.6% in reducer I and reducer II groups, respectively), and 20.6% of total participants quit smoking during the 2-year interval. Compared to the sustainers, reducers I were more likely to be heavy smokers (73.8% vs. 62.6%); quitters were more likely to be light smokers (18.4% vs. 4.1%) with a shorter duration of smoking. Quitters and reducers I tended to be older and have more comorbidities (hypertension, diabetes, dyslipidaemia, and chronic kidney disease) than sustainers.

Association between change in cigarette smoking intensity and risk of cardiovascular disease

Table 2 shows the association between change in cigarette smoking intensity and risk of stroke or MI. The quitters had a significantly decreased risk of stroke (aHR 0.77, 95% CI 0.74–0.81; ARR -0.37, 95% CI -0.43 to -0.31) and MI (aHR 0.74, 95% CI 0.70–0.78; ARR -0.27, 95% CI -0.31 to -0.22) compared to sustainers. The risk of stroke and MI in reducers I (aHR 1.02, 95% CI 0.97–1.08; ARR, 0.03, 95% CI -0.06 to 0.12 for stroke and aHR 0.99, 95% CI 0.92–1.06; ARR -0.01, 95% CI -0.08 to 0.06 for MI) and reducers II (aHR 1.00, 95% CI 0.95–1.05; ARR -0.01, 95% CI -0.09 to 0.07 for stroke and aHR 0.97, 95% CI 0.92–1.04; ARR -0.03, 95% CI -0.09 to 0.03 for MI) was not significantly different from that in sustainers.

Smoking cessation was associated with reduced risk of all-cause mortality (aHR 0.92, 95% CI 0.89–0.94) compared to sustainers, whereas smoking reduction was not associated with reduced risk of mortality (Supplementary material online, *Table S3*). The association of smoking cessation with fatal stroke and MI was consistent with the results for CVD incidence: smoking cessation was associated with a decreased risk of fatal stroke (aHR 0.86, 95% CI 0.73–1.01) and fatal MI (aHR 0.76, 95% CI 0.61–0.95) (Supplementary material online, *Table S4*).

Sensitivity analyses: inverse probability of treatment weighting, competing risk, and time-dependent models

After IPTW, there were no significant differences in any covariates (maximal standardized difference, ≤0.1) (Supplementary material online, *Table S5* and *Figure S3*). Among the quitters, the decreased risk

Table 1 Baseline characteristics of the study population

Variable	Total (n = 897 975)	Change in number of cigarettes daily					P-value	MSD
		Quitter (n = 185 234)	Reducer I (n = 65 434)	Reducer II (n = 104 040)	Sustainer (n = 410 395)	Increaser (n = 132 872)		
Mean age (years), mean ± SD	53.0 ± 9.0	54.4 ± 9.5	54.6 ± 9.8	52.4 ± 8.7	52.4 ± 8.6	52.6 ± 9.0	<0.001	0.166
Age (years), n (%)							<0.001	
40–49	377 960 (42.1)	66 936 (36.1)	23 987 (36.7)	46 097 (44.3)	181 669 (44.3)	59 271 (44.6)		
50–59	320 845 (35.7)	67 334 (36.4)	22 677 (34.7)	37 336 (35.9)	147 342 (35.9)	46 156 (34.7)		
60–69	137 529 (15.3)	33 753 (18.2)	11 970 (18.3)	14 693 (14.1)	58 519 (14.3)	18 594 (14.0)		
≥70	61 641 (6.9)	17 211 (9.3)	6800 (10.4)	5914 (5.7)	22 865 (5.6)	8851 (6.7)		
Male sex, n (%)	848 478 (94.5)	166 504 (89.9)	60 940 (93.1)	99 766 (95.9)	395 959 (96.5)	125 309 (94.3)	<0.001	0.264
Alcohol consumption, n (%)							<0.001	0.340
None	260 976 (29.1)	76 081 (41.1)	19 853 (30.3)	26 703 (25.7)	103 837 (25.3)	34 502 (26.0)		
Mild	305 702 (34.0)	59 461 (32.1)	25 335 (38.7)	38 895 (37.4)	139 028 (33.9)	42 983 (32.3)		
Moderate	192 017 (21.4)	29 415 (15.9)	12 572 (19.2)	23 372 (22.5)	96 757 (23.6)	29 901 (22.5)		
Heavy	139 280 (15.5)	20 277 (10.9)	7674 (11.7)	15 070 (14.5)	70 773 (17.2)	25 486 (19.2)		
Regular physical activity, n (%)	176 887 (19.7)	41 918 (22.6)	14 054 (21.5)	20 661 (19.9)	75 755 (18.5)	24 499 (18.4)	<0.001	0.791
Anthropometrics, mean ± SD								
Body mass index (kg/m^2)	23.9 ± 3.0	24.3 ± 2.9	23.8 ± 3.0	23.9 ± 3.0	23.8 ± 3.0	23.9 ± 3.0	<0.001	0.151
WC (cm)	83.6 ± 7.8	84.2 ± 7.9	83.4 ± 7.7	83.4 ± 7.7	83.4 ± 7.7	83.4 ± 7.9	<0.001	0.093
SBP (mmHg)	124.6 ± 14.4	125.1 ± 14.5	125.0 ± 14.8	124.5 ± 14.3	124.4 ± 14.3	124.3 ± 14.5	<0.001	0.010
DBP (mmHg)	78.1 ± 9.9	78.2 ± 9.9	78.1 ± 9.9	78.1 ± 9.8	78.1 ± 9.8	78.0 ± 9.9	<0.001	0.012
Comorbidity, n (%)								
Hypertension	293 871 (32.7)	67 103 (36.2)	22 870 (35.0)	33 123 (31.8)	128 927 (31.4)	41 848 (31.5)	<0.001	0.101
Diabetes mellitus	125 244 (13.9)	27 107 (14.6)	9971 (15.2)	14 067 (13.5)	55 543 (13.5)	18 556 (14.0)	<0.001	0.049
Dyslipidaemia	198 157 (22.1)	46 924 (25.3)	14 587 (22.3)	22 322 (21.5)	86 376 (21.0)	27 948 (21.0)	<0.001	0.102
CKD	64 533 (7.2)	15 961 (8.6)	5166 (7.9)	7266 (7.0)	27 261 (6.6)	8879 (6.7)	<0.001	0.074
Laboratory findings, mean ± SD								
Glucose (mg/dL)	102.5 ± 27.7	103.1 ± 27.6	103.0 ± 28.7	102.1 ± 27.2	102.2 ± 27.5	102.6 ± 28.7	<0.001	0.003
Cholesterol (mg/dL)	197.6 ± 36.5	199.0 ± 37.3	196.1 ± 37.0	197.3 ± 36.2	197.5 ± 36.1	197.1 ± 36.3	<0.001	0.078
HDL (mg/dL)	51.9 ± 14.5	52.4 ± 14.4	51.9 ± 14.7	51.6 ± 13.9	51.7 ± 14.5	52.1 ± 14.7	<0.001	0.033
LDL (mg/dL)	114.0 ± 34.8	115.6 ± 34.8	112.6 ± 35.1	113.7 ± 34.7	113.8 ± 34.8	113.2 ± 34.9	<0.001	0.088
GFR (mL/min/1.73 m^2)	83.2 ± 34.8	81.8 ± 34.8	83.4 ± 36.9	83.1 ± 31.9	83.6 ± 35.3	83.9 ± 34.6	<0.001	0.042
Urban residency, n (%)	400 835 (44.6)	81 606 (44.1)	28 209 (43.1)	47 424 (45.6)	184 535 (45.0)	59 061 (44.4)	<0.001	0.037
Income (%)							<0.001	0.069
Q1 (lowest)	171 778 (19.1)	35 732 (19.3)	13 962 (21.3)	20 047 (19.3)	76 316 (18.6)	25 721 (19.4)		
Q2	154 113 (17.2)	30 943 (16.7)	12 364 (18.9)	17 696 (17.0)	69 075 (16.8)	24 035 (18.1)		
Q3	240 837 (26.8)	47 180 (25.5)	17 292 (26.4)	27 904 (26.8)	112 419 (27.4)	36 042 (27.1)		
Q4 (highest)	331 247 (36.9)	71 379 (38.5)	21 816 (33.3)	38 393 (36.9)	152 585 (37.2)	47 074 (35.4)		

Continued

Table 1 *Continued*

Variable	Total (n = 897 975)	Change in number of cigarettes daily					*P*-value	MSD
		Quitter (n = 185 234)	Reducer I (n = 65 434)	Reducer II (n = 104 040)	Sustainer (n = 410 395)	Increaser (n = 132 872)		
Smoking status,[a] *n* (%)							<0.001	[b]
Light (<10 cigarettes/day)	89 040 (9.9)	34 063 (18.4)	2984 (4.6)	5786 (5.6)	16 863 (4.1)	29 344 (22.1)		
Moderate (10–19 cigarettes/day)	335 152 (37.3)	73 550 (39.7)	14 184 (21.7)	35 346 (34.0)	136 790 (33.3)	75 282 (56.7)		
Heavy (≥20 cigarettes/day)	473 783 (52.8)	77 621 (41.9)	48 266 (73.8)	62 908 (60.5)	256 742 (62.6)	28 246 (21.3)		
Duration of smoking (years), *n* (%)							<0.001	0.122
<5	75 966 (8.5)	65 429 (35.3)	2549 (3.9)	1462 (1.4)	4193 (1.0)	2333 (1.8)		
5–9	18 681 (2.1)	4493 (2.4)	2474 (3.8)	2086 (2.0)	6439 (1.6)	3189 (2.4)		
10–19	107 537 (12.0)	21 127 (11.4)	11 274 (17.2)	13 773 (13.2)	44 619 (10.9)	16 744 (12.6)		
20–29	349 288 (38.9)	47 399 (25.6)	22 425 (34.3)	45 001 (43.3)	178 685 (43.5)	55 778 (42.0)		
≥30	346 503 (38.6)	46 786 (25.3)	26 712 (40.8)	41 718 (40.1)	176 459 (43.0)	54 828 (41.3)		
Pack-years of smoking, *n* (%)							<0.001	[b]
<10	191 886 (21.4)	88 107 (47.6)	28 645 (43.8)	18 974 (18.2)	40 355 (9.8)	15 805 (11.9)		
10 to <20	234 725 (26.1)	33 084 (17.9)	24 599 (37.6)	43 518 (41.8)	103 324 (25.2)	30 200 (22.7)		
20 to <30	224 458 (25.0)	27 886 (15.1)	8405 (12.8)	22 824 (21.9)	130 942 (31.9)	34 401 (25.9)		
≥30	246 906 (27.5)	36 157 (19.5)	3785 (5.8)	18 724 (18.0)	135 774 (33.1)	52 466 (39.5)		

BP, blood pressure; CKD, chronic kidney disease; DBP, diastolic blood pressure; GFR, glomerular filtration rate; MSD, maximal standardized difference; SBP, systolic blood pressure; SD, standard deviation; WC, waist circumference.
[a]Information related to smoking status is based on data from the first examination (2009).
[b]These variables were not included in inverse probability treatment weighting (see Supplementary material online, *Table S6* and *Figure S3*).

Table 2 Association between changes in cigarette smoking intensity and risk of stroke or myocardial infarction

Smoking status		*n* (%)	Stroke					
2009	**2011**		**Case no.**	**IR per 1000 person-years**	**HR (95% CI)**	**aHR[a] (95% CI)**	**5-Year absolute risk (%) (95% CI)**	**Risk difference (95% CI)**
All current smokers	Quitter	185 234 (20.6)	3481	3.0	0.97 (0.93–1.01)	**0.77 (0.74–0.81)**	1.28 (1.24–1.33)	**−0.37 (−0.43 to −0.31)**
	Reducer I	65 434 (7.3)	1631	4.0	1.30 (1.24–1.37)	1.02 (0.97–1.08)	1.68 (1.60–1.77)	0.03 (-0.06 to 0.12)
	Reducer II	104 040 (11.6)	2004	3.1	1.00 (0.95–1.05)	1.00 (0.95–1.05)	1.65 (1.57–1.72)	-0.01 (-0.09 to 0.07)
	Sustainer	410 395 (45.7)	7923	3.1	1 (Ref.)	1 (Ref.)	1.66 (1.62–1.69)	—
	Increaser	132 872 (14.5)	2709	3.3	1.06 (1.01–1.11)	1.02 (0.98–1.07)	1.69 (1.62–1.75)	0.03 (-0.04 to 0.10)
Light smokers (*n* = 89 040)	Quitter	34 063 (38.3)	688	3.3	0.91 (0.81–1.04)	0.88 (0.77–1.01)	1.63 (1.50–1.77)	-0.21 (-0.45 to 0.03)
	Reducer I	2984 (3.4)	61	3.3	0.94 (0.71–1.23)	0.81 (0.62–1.06)	1.50 (1.13–1.86)	-0.35 (-0.76 to 0.06)
	Reducer II	5786 (6.5)	161	4.5	1.27 (1.06–1.53)	1.07 (0.89–1.29)	1.98 (1.67–2.28)	0.13 (-0.21 to 0.48)
	Sustainer	16 863 (18.9)	371	3.6	1 (Ref.)	1 (Ref.)	1.84 (1.65–2.04)	—
	Increaser	29 344 (33.0)	707	3.9	1.10 (0.97–1.25)	1.13 (1.00–1.29)	2.08 (1.92–2.24)	0.24 (0.00–0.47)
Moderate smokers (*n* = 335 152)	Quitter	73 550 (22.0)	1335	2.9	1.04 (0.97–1.11)	**0.85 (0.79–0.92)**	1.27 (1.20–1.34)	**−0.22 (−0.31 to −0.12)**
	Reducer I	14 184 (4.2)	332	3.8	1.35 (1.21–1.52)	0.97 (0.86–1.09)	1.44 (1.28–1.59)	-0.05 (-0.21 to 0.11)
	Reducer II	35 346 (10.5)	705	3.2	1.14 (1.05–1.25)	1.05 (0.96–1.14)	1.55 (1.44–1.67)	0.07 (-0.06 to 0.19)
	Sustainer	136 790 (40.8)	2390	2.8	1 (Ref.)	1 (Ref.)	1.49 (1.42–1.55)	—
	Increaser	75 282 (22.5)	1405	3.0	1.07 (1.00–1.15)	**1.12 (1.04–1.19)**	1.65 (1.56–1.74)	**0.17 (0.06–0.27)**
Heavy smokers (*n* = 473 783)	Quitter	77 621 (16.4)	1458	3.0	0.93 (0.88–0.99)	**0.73 (0.68–0.78)**	1.23 (1.16–1.30)	**−0.45 (−0.53 to −0.36)**
	Reducer I	48 266 (18.2)	1238	4.2	1.29 (1.21–1.37)	1.02 (0.96–1.08)	1.71 (1.61–1.80)	0.03 (-0.07 to 0.14)
	Reducer II	62 908 (13.3)	1138	2.9	0.90 (0.84–0.96)	0.97 (0.91–1.03)	1.62 (1.53–1.72)	-0.05 (-0.16 to 0.05)
	Sustainer	256 742 (54.2)	5162	3.2	1 (Ref.)	1 (Ref.)	1.68 (1.63–1.72)	—
	Increaser	28 246 (6.0)	597	3.4	1.05 (0.97–1.15)	**1.14 (1.04–1.24)**	1.90 (1.75–2.05)	**0.22 (0.07–0.38)**
Smoking status		***n* (%)**	**Myocardial infarction**					
2009	**2011**		**Case no.**	**IR per 1000 person-years**	**HR (95% CI)**	**aHR[a] (95% CI)**	**5-Year absolute risk (%) (95% CI)**	**Risk difference (95% CI)**
All current smokers	Quitter	185 234 (20.6)	2125	1.8	0.90 (0.86–0.95)	**0.74 (0.70–0.78)**	0.77 (0.74–0.81)	**−0.27 (−0.31 to −0.22)**
	Reducer I	65 434 (7.3)	953	2.4	1.16 (1.08–1.24)	0.99 (0.92–1.06)	1.03 (0.96–1.09)	-0.01 (-0.08 to 0.06)
	Reducer II	104 040 (11.6)	1299	2.0	0.99 (0.93–1.05)	0.97 (0.92–1.04)	1.01 (0.96–1.07)	-0.03 (-0.09 to 0.03)
	Sustainer	410 395 (45.7)	5196	2.0	1 (Ref.)	1 (Ref.)	1.04 (1.01–1.07)	—
	Increaser	132 872 (14.5)	1698	2.1	1.01 (0.96–1.07)	1.01 (0.95–1.06)	1.04 (0.99–1.10)	0.01 (-0.05 to 0.06)
Light smokers (*n* = 89 040)	Quitter	34 063 (38.3)	348	1.6	1.00 (0.84–1.20)	1.02 (0.84–1.25)	0.82 (0.73–0.92)	0.02 (-0.14 to 0.18)
	Reducer I	2984 (3.4)	25	1.4	0.83 (0.55–1.27)	0.76 (0.50–1.15)	0.61 (0.37–0.85)	-0.19 (-0.46 to 0.07)
	Reducer II	5786 (6.5)	70	2.0	1.20 (0.91–1.58)	1.06 (0.80–1.40)	0.85 (0.65–1.05)	0.05 (-0.18 to 0.28)
	Sustainer	16 863 (18.9)	171	1.6	1 (Ref.)	1 (Ref.)	0.81 (0.68–0.93)	—

Continued

Table 2 *Continued*

Smoking status		*n* (%)	Myocardial infarction					
2009	**2011**		**Case no.**	**IR per 1000 person-years**	**HR (95% CI)**	**aHR[a] (95% CI)**	**5-Year absolute risk (%) (95% CI)**	**Risk difference (95% CI)**
	Increaser	29 344 (33.0)	354	1.9	1.19 (1.00–1.43)	**1.21 (1.01–1.45)**	0.97 (0.86–1.08)	**0.16 (0.01–0.32)**
Moderate smokers (*n* = 335 152)	Quitter	73 550 (22.0)	766	1.7	0.96 (0.88–1.05)	**0.76 (0.69–0.84)**	0.69 (0.63–0.74)	**−0.21 (−0.29 to −0.14)**
	Reducer I	14 184 (4.2)	166	1.9	1.09 (0.93–1.28)	0.88 (0.75–1.03)	0.79 (0.67–0.91)	-0.11 (-0.24 to 0.02)
	Reducer II	35 346 (10.5)	401	1.8	1.05 (0.94–1.17)	0.97 (0.87–1.09)	0.88 (0.79–0.96)	-0.02 (-0.12 to 0.07)
	Sustainer	136 790 (40.8)	1484	1.7	1 (Ref.)	1 (Ref.)	0.90 (0.85–0.95)	—
	Increaser	75 282 (22.5)	923	2.0	1.14 (1.05–1.23)	**1.15 (1.06–1.25)**	1.04 (0.96–1.11)	**0.14 (0.05–0.22)**
Heavy smokers (*n* = 473 783)	Quitter	77 621 (16.4)	1011	2.1	0.94 (0.88–1.01)	**0.74 (0.68–0.80)**	0.83 (0.77–0.89)	**−0.30 (−0.37 to −0.23)**
	Reducer I	48 266 (18.2)	762	2.6	1.15 (1.0701.25)	0.99 (0.91–1.07)	1.11 (1.03–1.19)	-0.02 (-0.10 to 0.07)
	Reducer II	62 908 (13.3)	828	2.1	0.95 (0.88–1.03)	0.98 (0.91–1.05)	1.10 (1.02–1.18)	-0.03 (-0.11 to 0.06)
	Sustainer	256 742 (54.2)	3541	2.2	1 (Ref.)	1 (Ref.)	1.13 (1.08–1.17)	—
	Increaser	28 246 (6.0)	421	2.4	1.08 (0.98–1.20)	**1.12 (1.01–1.24)**	1.26 (1.14–1.38)	**0.13 (0.01–0.26)**

aHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio; IR, incidence rate.
[a]Adjusted for age, sex, body mass index, smoking duration, alcohol consumption, regular exercise, area of residence, income, hypertension, diabetes mellitus, dyslipidaemia, and chronic kidney disease.
Statistically significant values are marked in bold.

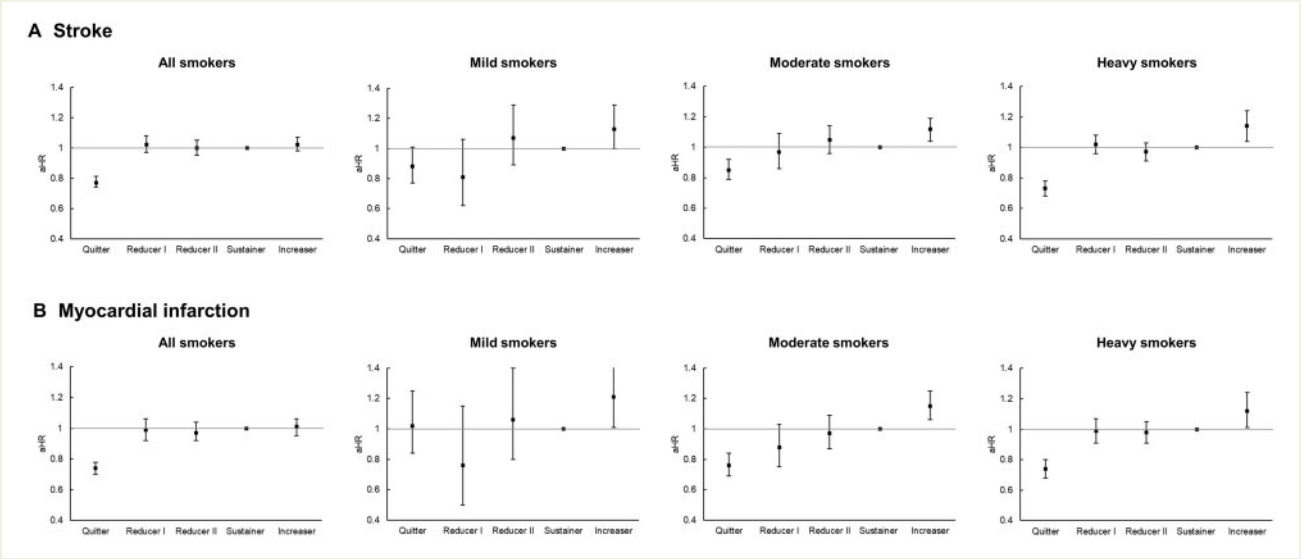


Figure 1 The risk of stroke (*A*) and myocardial infarction (*B*) according to change in smoking intensity. Quitter, those who quit smoking; reducer I, those who reduced the number of cigarettes by 50% or more; reducer II, those who reduced the number of cigarettes by 20–50%; sustainer, those who reduced or increased the number of cigarettes by 20%; increaser, those who increased the number of cigarettes by 20% or more. Adjusted hazard ratio was adjusted for age, sex, body mass index, smoking duration, alcohol consumption, regular exercise, area of residence, income, and presence or absence of comorbidities (hypertension, diabetes mellitus, dyslipidaemia, and chronic kidney disease). aHR, adjusted hazard ratio.

of stroke (aHR 0.87, 95% CI 0.83–0.90) and MI (aHR 0.78, 95% CI 0.74–0.82) remained consistent. Among the reducers, the risk of incident MI or stroke was not significantly reduced from the sustainers, as in the primary analysis (Supplementary material online, *Table S6*). The estimated SHR (95% CI) of stroke and MI was consistent with the results without considering the competing risk (Supplementary material online, *Table S7*). Quitters had a lower risk of stroke (SHR 0.77, 95% CI 0.74–0.81) and MI (SHR 0.74, 95% CI 0.70–0.78) compared to sustainers, whereas reducers showed no significant association. The results with change in smoking intensity as time-varying covariates showed similar trends compared with original analysis (Supplementary material online, *Table S8*).

Stratified analysis by initial smoking status, age, sex, and comorbidities

In stratified analysis by smoking level at the first examination (light, moderate, and heavy smokers), the risks of stroke and MI in quitters of all three groups were decreased compared to those in sustainers (*Table 2*). These associations were more prominent in moderate and heavy smokers. In all groups, reducing cigarette intensity did not significantly decrease the risks of stroke and MI. However, increasers of each group had 12–14% increased risks of stroke and 12–21% increased risks of MI. The pattern of stroke and MI risk is shown in *Figure 1*. The results from stratified analysis by smoking pack-years were similar (Supplementary material online, *Table S9*).

In stratified analyses according to age, sex and comorbidities, the results were consistent with the main findings. The association of smoking cessation with decreased risk of stroke and MI compared to sustainers was stronger in younger age group and men (Supplementary material online, *Tables S10* and *S11* and *Figures S4* and *S5*). However, the magnitude of ARR in quitters was higher in older groups for both stroke (5-year risk estimates, -0.17% in 40–49 years, -0.35% in 50–59 years, -0.58% in 60–69 years, and -1.14% in ≥70 years) and MI (5-year risk estimates, -0.21% in 40–49 years, -0.25% in 50–59 years, -0.39% in 60–69 years, and -0.27% in ≥70 years) than in younger people, as baseline risk was higher in older than younger people.

A decreased risk of CVD incidence among quitters was observed regardless of comorbidities but was not observed among reducers (Supplementary material online, *Table S12* and *Figure S6*).

Association between subsequent change in cigarette smoking intensity in third examination and risk of cardiovascular disease

Mean duration of follow-up was 4.3 years (SD 0.5) for those who underwent a third health examination after a 1-year lag period. The baseline characteristics for the third examination study group are depicted in total and quitter groups (Supplementary material online, *Table S13*). Sustained quitters tended to have higher proportion of comorbidities, long duration of smoking, and high cumulative amount compared to relapsers. At the third examination, relapsed smokers (i.e. those who had quit at the second examination but smoked at the level of reducer I, reducer II, and sustainer/increaser compared to the first examination) had a 42–66% increased risk of stroke (aHR 1.42, 95% CI 1.20–1.69 in reducer I; aHR 1.66, 95% CI 1.39–1.98 in reducer II; and aHR 1.51, 95% CI 1.35–1.68 in sustainer/increaser) and 54–69% increased risk of MI (aHR 1.69, 95% CI 1.36–2.09 in reducer I; aHR 1.54, 95% CI 1.23–1.94 in reducer II; and aHR 1.67, 95% CI 1.46–1.91 in sustainer/increaser) compared to sustained quitters

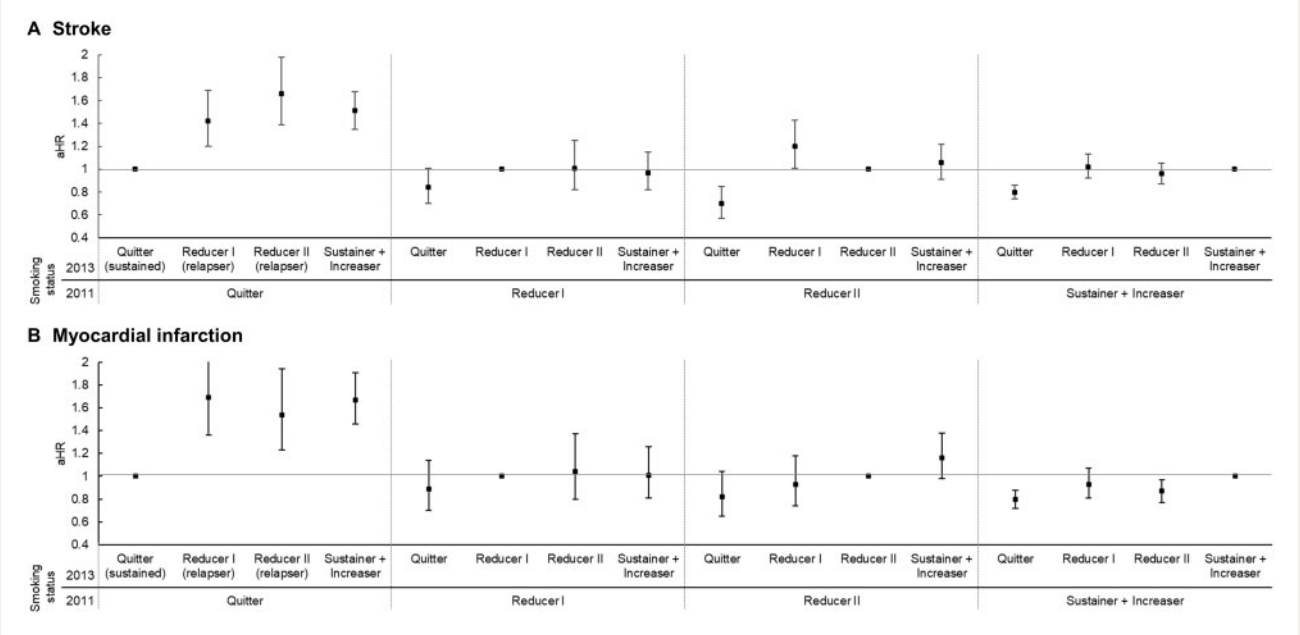


Figure 2 The risk of stroke (*A*) and myocardial infarction (*B*) by change in cigarette smoking intensity at the third examination (2013). Change in smoking behaviour in 2013 was defined based on smoking intensity in the first examination (2009) (Quitter, those who quit smoking; reducer I, those who reduced the number of cigarettes by 50% or more; reducer II, those who reduced the number of cigarettes by 20–50%; sustainer, those who reduced or increased the number of cigarettes by 20%; increaser, those who increased the number of cigarettes by 20% or more.) Sustainer and increaser were combined for analyses due to the low numbers of increasers. Adjusted hazard ratio was adjusted for age, sex, body mass index, smoking duration, alcohol consumption, regular exercise, area of residence, income, and presence or absence of comorbidities (hypertension, diabetes mellitus, dyslipidaemia, and chronic kidney disease). aHR, adjusted hazard ratio.

(*Table 3* and *Figure 2*). Among participants who reduced smoking intensity at the second examination, subsequent quitting at the third examination was associated with a decreased risk of stroke (aHR 0.84, 95% CI 0.70–1.01 in reducer I; aHR 0.70, 95% CI 0.57–0.85 in reducer II; and aHR 0.80, 95% CI 0.74–0.86 in sustainer/increaser) and MI (aHR 0.89, 95% CI 0.70–1.14 in reducer I; aHR 0.82, 95% CI 0.65–1.04 in reducer II; and aHR 0.80, 95% CI 0.72–0.88 in sustainer/increaser). However, additional reduction of smoking intensity compared to that at the second examination was not associated with decreased risk of stroke or MI.

Regarding all-cause mortality, relapsed smoking was associated with an increased risk of all-cause mortality compared to sustained quitting (Supplementary material online, *Table S14*). The consistent association of relapsed smoking with an increased risk of fatal stroke and MI was found (Supplementary material online, *Table S15*).

Discussion

In this study, we demonstrated that smoking cessation was associated with decreased risk of stroke and MI compared to sustained smokers, whereas smoking reduction was not. From subgroup analyses of those who underwent a third follow-up examination, we found that relapsed smoking after smoking cessation was associated with an increased risk of stroke and MI compared to sustained quitting.

Abundant biological evidence supports that cigarette smoking promotes atherosclerosis via induction of endothelial dysfunction and damage, increased oxidation of pro-atherogenic lipids, and inflammation induction. These are processes common to stroke and MI.[24] Our findings related to smoking cessation are consistent with previous results.[8,11] Smoking cessation has been shown to be effective in improving these adverse changes. Smoking cessation improved flow-mediated brachial artery dilation and coronary artery vasomotor function, indices of vascular endothelial function.[25,26]

However, although some biological evidence suggested possible beneficial effects of smoking reduction, epidemiological studies have not confirmed these findings on CVD risk. These data are consistent with the results of our study.[8,11] In previous studies, smoking reduction was associated with modest improvement in cardiovascular biomarkers such as decreased haemoglobin concentration, increased high-density lipoprotein level, and decreased blood pressure and heart rate in the short term.[27,28] There are several possible explanations for the lack of significant association between smoking reduction and CVD risk reduction. First, a nonlinear dose–response relationship that is less steep at higher doses could cause difficulty in finding significant difference. A nonlinear dose–response relationship between number of cigarettes smoked per day and risk of ischaemic heart disease (IHD) was suggested. This might be related to a low threshold effect with a remarkably increased risk of IHD at a low level smoking.[29] This is in line with a recent meta-analysis that reported smoking only one cigarette per day carries a substantial risk for

Table 3 Risk of stroke or myocardial infarction by change in cigarette smoking intensity at the third examination (2013)

Smoking status			No.	Stroke					
2009	2011	2013[a]		Case no.	IR per 1000 person-years	HR (95% CI)	aHR[b] (95% CI)	5-Year absolute risk (%) (95% CI)	Risk difference (95% CI)
All current smokers	Quitter	Quitter (sustained)	91 189	1034	2.6	1 (Ref.)	1 (Ref.)	1.22 (1.14–1.29)	—
		Reducer I (relapser)	8535	145	3.9	1.51 (1.27–1.80)	**1.42 (1.20–1.69)**	1.72 (1.44–2.00)	**0.50 (0.22–0.79)**
		Reducer II (relapser)	8819	138	3.6	1.38 (1.16–1.65)	**1.66 (1.39–1.98)**	2.00 (1.67–2.32)	**0.78 (0.44–1.11)**
		Sustainer + Increaser	34 884	508	3.4	1.29 (1.16–1.44)	**1.51 (1.35–1.68)**	1.82 (1.66–1.98)	**0.61 (0.43–0.78)**
	Reducer I	Quitter	10 220	175	4.0	0.89 (0.74–1.07)	0.84 (0.70–1.01)	1.73 (1.47–1.99)	-0.32 (-0.65 to 0.02)
		Reducer I	17 331	331	4.5	1 (Ref.)	1 (Ref.)	2.05 (1.82–2.27)	—
		Reducer II	7238	119	3.8	0.85 (0.69–1.05)	1.01 (0.82–1.25)	2.07 (1.70–2.44)	0.02 (-0.40 to 0.45)
		Sustainer + Increaser	14 079	232	3.8	0.86 (0.73–1.01)	0.97 (0.82–1.15)	1.99 (1.73–2.24)	-0.06 (-0.39 to 0.27)
	Reducer II	Quitter	12 332	138	2.6	0.90 (0.74–1.09)	**0.70 (0.57–0.85)**	1.10 (0.91–1.29)	**−0.47 (−0.71 to −0.23)**
		Reducer I	10 327	189	4.3	1.48 (1.24–1.76)	**1.20 (1.01–1.43)**	1.88 (1.60–2.15)	**0.30 (0.00–0.61)**
		Reducer II	31 724	394	2.9	1 (Ref.)	1 (Ref.)	1.58 (1.41–1.74)	—
		Sustainer + Increaser	25 063	343	3.2	1.10 (0.95–1.27)	1.06 (0.91–1.22)	1.66 (1.47–1.85)	0.09 (-0.14 to 0.32)
	Sustainer + Increaser	Quitter	61 618	798	3.0	0.97 (0.90–1.05)	**0.80 (0.74–0.86)**	1.26 (1.17–1.34)	**−0.31 (−0.41 to −0.21)**
		Reducer I	22 756	404	4.1	1.35 (1.21–1.49)	1.02 (0.92–1.13)	1.60 (1.44–1.75)	0.03 (-0.13 to 0.19)
		Reducer II	39 403	507	3.0	0.97 (0.88–1.06)	0.96 (0.87–1.05)	1.50 (1.37–1.63)	-0.07 (-0.21 to 0.07)
		Sustainer + Increaser	290 809	3864	3.1	1 (Ref.)	1 (Ref.)	1.56 (1.51–1.62)	—

Smoking status			No.	Myocardial infarction					
2009	2011	2013[a]		Case no.	IR per 1000 person-years	HR (95% CI)	aHR[b] (95% CI)	5-Year absolute risk (%) (95% CI)	Risk difference (95% CI)
All current smokers	Quitter	Quitter (sustained)	91 189	602	1.5	1 (Ref.)	1 (Ref.)	0.74 (0.67–0.80)	—
		Reducer I (relapser)	8535	100	2.7	1.79 (1.45–2.21)	**1.69 (1.36–2.09)**	1.23 (0.99–1.48)	**0.50 (0.25–0.75)**
		Reducer II (relapser)	8819	83	2.2	1.43 (1.13–1.80)	**1.54 (1.23–1.94)**	1.13 (0.89–1.38)	**0.40 (0.15–0.65)**
		Sustainer + Increaser	34 884	355	2.3	1.55 (1.36–1.77)	**1.67 (1.46–1.91)**	1.22 (1.09–1.35)	**0.49 (0.34–0.63)**
	Reducer I	Quitter	10 220	101	2.3	0.91 (0.71–1.15)	0.89 (0.70–1.14)	1.12 (0.88–1.36)	-0.14 (-0.42 to 0.15)
		Reducer I	17 331	188	2.5	1 (Ref.)	1 (Ref.)	1.25 (1.05–1.46)	—
		Reducer II	7238	74	2.4	0.94 (0.72–1.23)	1.04 (0.80–1.37)	1.31 (0.99–1.62)	0.05 (-0.29 to 0.40)
		Sustainer + Increaser	14 079	145	2.4	0.95 (0.76–1.17)	1.01 (0.81–1.26)	1.27 (1.04–1.50)	0.01 (-0.26 to 0.28)
	Reducer II	Quitter	12 332	98	1.8	0.92 (0.73–1.16)	0.82 (0.65–1.04)	0.81 (0.65–0.97)	-0.17 (-0.37 to 0.03)
		Reducer I	10 327	91	2.0	1.03 (0.81–1.31)	0.93 (0.74–1.18)	0.92 (0.73–1.11)	-0.07 (-0.29 to 0.15)
		Reducer II	31 724	272	2.0	1 (Ref.)	1 (Ref.)	0.98 (0.86–1.10)	—
		Sustainer + Increaser	25 063	250	2.3	1.16 (0.98–1.38)	1.16 (0.98–1.38)	1.14 (0.99–1.28)	0.15 (-0.03 to 0.33)
	Sustainer + Increaser	Quitter	61 618	506	1.9	0.90 (0.81–0.99)	**0.80 (0.72–0.88)**	0.89 (0.81–0.98)	**−0.23 (−0.32 to −0.14)**
		Reducer I	22 756	228	2.3	1.10 (0.96–1.26)	0.93 (0.81–1.07)	1.05 (0.90–1.19)	-0.08 (-0.22 to 0.07)
		Reducer II	39 403	315	1.8	0.88 (0.78–0.98)	**0.87 (0.77–0.97)**	0.97 (0.86–1.09)	**−0.15 (−0.26 to −0.03)**
		Sustainer + Increaser	290 809	2659	2.1	1 (Ref.)	1 (Ref.)	1.12 (1.06–1.19)	—

aHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio; IR, incidence rate.
[a]Compared to smoking amount at first examination in 2009.
[b]Adjusted for age, sex, body mass index, smoking duration, alcohol consumption, regular exercise, area of residence, income, hypertension, diabetes mellitus, dyslipidaemia, and chronic kidney disease.
Statistically significant values are marked in bold.

stroke and IHD, ~50% of that for those who smoke 20 cigarettes per day.[30] Our findings also support that there is no safe level of smoking with regard to the risk of CVD. Biologically, some harmful effects of smoking on CVD risk such as platelet aggregation could be maximized even at low doses.[31] Heavy and light smoking had a similar detrimental effect on endothelium-dependent vasodilation and endothelial nitric oxide biosynthesis.[32] In our study, smoking reduction consistently did not have significant association with CVD risk reduction regardless of degree of smoking reduction. Second, smokers who reduced their number of daily cigarettes can negate the benefit through compensatory smoking.[33] The smokers who reduced their smoking tended to take more frequent puffs or deep and long inhalation on each cigarette. Hatsukami *et al.*[34] measured the toxic metabolites in reducers compared with light smokers. Their data suggested that reducers had more than twice the toxic metabolites despite the same frequency of cigarette use as light smokers.

Our study has several important strengths over previous studies. First, subsequent change in smoking level using information from a third examination was considered. No previous studies reflected change of smoking level from more than two time points considering further changes despite a long follow-up period.[8,9,11] In a Danish cohort, the authors were concerned about under- or overestimation of CVD risk in reducers because ~50% continued to smoke at a reduced level, 25% had quit, and another 25% had resumed heavy smoking at a subsequent examination.[11] This Danish study simply tracked additional change in reducers without further analysis on subsequent change, unlike our study. Reflecting change in smoking level at more than two time points provides more stable information, leading to less biased results. Second, some previous studies defined smoking reduction as shift between categories (usually categorized as <10, 10–20, and ≥20 cigarettes per day)[8,9] and are subject to bias (e.g. smoking from 20 to 18 cigarettes can be regarded as smoking reduction). To avoid this, other studies used >50% reduction in the number of cigarettes as smoking reduction.[11] We also used a reduced percentage for the definition of smoking reduction, and we further categorized reduction (20–50% reduction, as reducer II) to investigate a possible dose–response relationship. Third, to address a previous limitation of a Korean study which excluded women, our study included female smokers and compared sex-specific association given a considerable difference in smoking pattern between men and women. Reported smoking rate in Asian women has been very low due to cultural reasons, and many female smokers hide their smoking.[35] While the number of female smokers (n = 49 497, 5.5% of the total study population) is very limited in our study, the large total study population (n = 897 975) enabled comparison of the sex-specific association, in spite of no significant association of change in smoking intensity with the risk of CVD among women.

Analyses of secondary endpoints of fatal events and all-cause mortality showed consistent results with the primary analysis of CVD events and with previous studies showing significantly decreased risk with smoking cessation[10,12,13] but no decreased risk with smoking reduction.[10,12,13] In addition, consistent results of sensitivity analyses with various statistical methods support the robustness of our study findings.

In stratified analyses, younger participants showed a greater CVD benefit when quitting smoking than did older age groups. The effect of smoking on the risk of IHD could differ by age group, with the highest attributable fraction in the younger group (88% in those aged 40–49 years vs. 68% in those aged ≥70 years).[36] This suggests that a large proportion of IHD could be prevented if younger aged smokers were to quit smoking. The different associations by age might be due to a longer exposure before quitting. In a previous report, 99% of smokers in the oldest age group had begun smoking before they were 30 years old.[37] However, ARR is greater in older groups, suggesting the need for smoking cessation even in older age. The stronger association in men than in women might be due to generally lower daily cigarette use in women than in men,[38] consistent with our results that risk reduction was greater in heavy smokers. However, our results might not be generalizable to other countries where the female smoking pattern is different. Stratified analyses by various comorbidities confirmed that CVD benefit of smoking cessation is consistent across comorbidity statuses.

The most important public health implication of this study is that smoking reduction is not beneficial for CVD risk reduction; only smoking cessation reduces the risk of CVD incidence. The European guidelines on cardiovascular prevention supported that there is no evidence of threshold intensity of smoking for the deleterious effects and strongly recommended smoking cessation as a strategy for CVD prevention.[39] In addition, relapsed smoking even after smoking cessation does not guarantee CVD risk reduction. However, smoking reduction may be a prelude to smoking cessation.[40] Smoking reduction increases the chance for future smoking cessation by positively reinforcing self-efficacy in succeeding to decrease smoking.[41,42] However, complete smoking cessation is the only way to reduce the incidence of CVD.

Several limitations should be considered in this study. First, since smoking behaviours were based on self-reported questionnaire without biochemical verification, misclassification bias and underreporting could exist. However, self-reported smoking behaviour seemed to be relatively accurate: sensitivity was 87.5% and specificity was 89.2%.[43] Despite the significant effect of secondhand smoke on CVD events, we could not reflect this information due to the lack of information. Second, follow-up duration was relatively short compared to 15–26 years of median follow-up in other studies.[11,14] However, despite the long follow-up periods in those studies, smoking behaviours were only assessed at two time points with 2–5-year intervals, leading to the wide variation of smoking behaviours during follow-up. Third, a majority of the study population was men due to low smoking rate in Asian women.[44] Fourth, duration of smoking cessation was not adjusted for due to the lack of information. However, with our study design, duration of cessation did not vary significantly (range 0–4 years). Fifth, even though control status of comorbidities and smoking status could have an interactive impact on risk of CVD, optimal treatment status was not taken into account.[45]

In conclusion, smoking reduction was not associated with reduced CVD risk regardless of the degree of smoking reduction. In addition, relapsed smokers had a significantly increased risk of CVD compared to those who remained cigarette-free. To reduce excess CVD risk, smoking cessation and maintenance are necessary.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Author's contributors

SMJ, DWS, and KH contributed to the study design and conception. SMJ, DWS, KH, and DK contributed to data acquisition and analysis. SMJ, KHJ, and DWS drafted the manuscript. SMJ, KHJ, DWS, MHC, CML, KWN, and SPL contributed to interpretation of data. SMJ, KHJ, DWS, MHC, CML, KWN, and SPL critically revised and approved the final manuscript. DWS had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses. DWS and KH are the manuscript's guarantors. The corresponding author attests that all listed authors meet authorship criteria, and that no others meeting the criteria have been omitted.

Ethics approval

This study was approved by the Institutional Review Board of Samsung Medical Center (IRB File No. SMC 2020-07-181). The review board waived the requirement for written informed consent from patients because the data are public and anonymized under confidentiality guidelines.

Data availability

The data from the Korean National Health Insurance Service (NHIS) can be accessed via the Health Insurance Data Service website (http://nhiss.nhis.or.kr). However, researchers should submit a study proposal for approval from each institutional review board, which is reviewed by the NHIS review committee, to access the database. The raw data cannot be retrieved from the NHIS server.

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