Quantifying the association of low-intensity and late initiation of tobacco smoking with total and cause-specific mortality in Asia

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ABSTRACT

Background Little is known about the health harms associated with low-intensity smoking in Asians who, on average, smoke fewer cigarettes and start smoking at a later age than their Western counterparts.

Methods In this pooled analysis of 738 013 Asians from 16 prospective cohorts, we quantified the associations of low-intensity (<5 cigarettes/day) and late initiation (≥35 years) of smoking with mortality outcomes. HRs and 95% CIs were estimated for each cohort by Cox regression. Cohort-specific HRs were pooled using random-effects meta-analysis.

Findings During a mean follow-up of 11.3 years, 92 068 deaths were ascertained. Compared with never smokers, current smokers who consumed <5 cigarettes/day or started smoking after age 35 years had a 16%–41% increased risk of all-cause, cardiovascular disease (CVD), respiratory disease mortality and a >twofold risk of lung cancer mortality. Furthermore, current smokers who started smoking after age 35 and smoked <5 cigarettes/day had significantly elevated risks of all-cause (HRs (95% CIs)=1.14 (1.05 to 1.23)), CVD (1.27 (1.08 to 1.49)) and respiratory disease (1.54 (1.17 to 2.01)) mortality. Even smokers who smoked <5 cigarettes/day but quit smoking before the age of 45 years had a 16% elevated risk of all-cause mortality; however, the risk declined further with increasing duration of abstinence.

Conclusions Our study showed that smokers who smoked a small number of cigarettes or started smoking later in life also experienced significantly elevated all-cause and major cause-specific mortality but benefited from cessation. There is no safe way to smoke—not smoking is always the best choice.

INTRODUCTION

Tobacco causes multiple adverse health outcomes. Global efforts towards tobacco control have reduced the prevalence of smoking worldwide, especially over the past several decades in high-income Western countries.[1] Nevertheless, in an attempt to reduce the risk of smoking, some smokers have reduced their cigarette consumption rather than quitting completely, contributing to an increase in the proportion of light and/or intermittent smokers in the USA and other Western countries.[2 3] For example, the proportion of US smokers who smoked fewer than 10 cigarettes per day and non-daily smokers reached about 25% each in 2014—these are substantial increases compared with the numbers reported in 2005.[2] Despite those changes, emerging evidence indicates that light and non-daily smoking still confer a significantly elevated risk of the development of smoking-related cancers[4 5] and cardiovascular disease (CVD),[6–9] and further pose a high risk of death from CVD, cancer and other causes.[9–13]

To date, epidemiological evidence linking low-intensity smoking to health harms is limited to Western populations. Little is known about whether such associations are observed in other populations, particularly people living in Asian countries who, on average, smoke much less and start smoking later in life[14 15] and, of whom, only a very small fraction quit smoking.[15] Furthermore, among younger generations, the absolute number of smokers, as well as the prevalence of smoking, has increased substantially in many Asian countries[16]; all factors that present a growing public-health challenge in the region. The current pooled analysis aims to assess the impact of low-intensity tobacco smoking on disease mortality in Asian populations, who are the world's largest tobacco consumers but have different smoking patterns from Westerners. Using 16 prospective cohort studies, we investigated the associations of low-dose daily smoking (fewer than five and five to nine cigarettes) and late age of smoking initiation (30–34 and ≥35 years), as well as the effect of quitting, with all-cause and cause-specific mortality in multiple Asian populations.

METHODS

Study population

This pooling project, a part of the Asia Cohort Consortium (ACC), used the de-identified individual-participant data of 16 population-based cohort studies conducted in mainland China,

Japan, South Korea, Singapore, Taiwan, India and Bangladesh. Details of the ACC and each cohort profile have been described elsewhere.[14 15 17] At the baseline survey, each cohort collected data on sociodemographics, smoking behaviour, other lifestyle factors, medical history and anthropometrics. Study participants were followed-up to confirm their health and vital status per each study protocol (ie, via a repeated active follow-up survey, medical record review and data linkage to cancer registries and death certificates). More details on participating cohorts and their follow-up methods are summarised in online supplementary appendix pp 4–5. All data in the current analyses were harmonised by the ACC coordinating centre. Written or oral informed consent was obtained from all the participants who enrolled in each cohort.[17]

After data harmonisation, a total of 831 726 subjects were identified in the participating cohorts. We excluded 28 116 individuals with unavailable or missing data for smoking-related exposures (number of cigarettes smoked per day and age at starting smoking, n=25 376) or outcome variables (vital status and follow-up time, n=2740). Additional exclusions were made to minimise the potential influence of reverse causation—58 351 individuals were excluded from the analysis due to a history of cancer or CVD at baseline (n=36 150) or censoring within the first year after enrolment (n=22 201). Another 7246 individuals aged under 35 years were also excluded due to the consideration that smoking-attributable deaths are rare in early adulthood. Following these exclusions, we defined the analytic sample as a total of 738 013 healthy subjects who survived at least a year after entering the studies (table 1).

Exposure and outcome assessment

Self-reported smoking history was obtained at baseline. Detailed questions about smoking assessment in each cohort are listed in online supplementary appendix pp 6–7. Regular smokers were typically defined as individuals who smoked at least one cigarette per day for at least 6 months or who reported smoking at least 20 packs of cigarettes in their entire life. For bidi smokers (from the South Asian populations), one bidi was equated to a quarter of a cigarette, given the weight of tobacco flakes per bidi (0.25 g) versus cigarette (1.0 g).[14 15] In subsequent questions for smokers, we also collected data on the number of cigarettes smoked per day and their ages of smoking initiation and cessation. The number of cigarettes smoked per day was asked slightly differently among studies but was mostly defined as an average lifetime consumption as a continuous variable. Smoking duration was calculated using ages of starting/quitting smoking for former smokers—for current smokers, the age of quitting smoking was replaced with age at interview. Similarly, cessation duration, that is, years since cessation, was also calculated among former smokers using the age of quitting smoking and age at interview.

Based on the latest follow-up information, we recorded the vital status and cause of death for all study populations. Mortality outcomes were defined using the 9th or 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-9 or ICD-10), coded as the following: deaths from all causes (001-E999 or A00-Y98), lung cancer (162 or C34), CVD (390–459 or I00-I99) and respiratory disease (460–519 or J00-J99). It would be cumbersome to present results from all cause-specific mortality outcomes; thus we presented cause-specific results only for CVD, lung cancer and respiratory disease. The later two diseases were selected as cigarette smoking confers a direct and major adverse effect on them. Study participants were censored at the date of death, end of follow-up or loss-to-follow-up, whichever occurred earliest.

Statistical methods

Using a two-stage meta-analysis approach,[18] we quantified the relative risks of death associated with daily cigarette consumption, age at starting smoking, smoking duration and smoking cessation. Using Cox proportional hazards regression models, we first estimated HRs and 95% CIs in each cohort separately. Subsequently, risk estimates were pooled with the DerSimonian and Laird random-effects meta-analysis.[19] The global goodness-of-fit test with Schoenfeld residuals found no evidence of violation of the proportional hazards assumption. Age at enrolment and age at censoring defined the time scale. Given the heterogeneity across the participants' generation and time of cohort enrolment, Cox models were stratified into 5-year groups by birth year and enrolment year. Using never smokers as the reference, we estimated the relative risk of death from all causes, lung cancer, CVD and respiratory disease associated with daily cigarette consumption (<5, 5–9, 10–19, 20–29 and ≥30 cigarettes per day) and age at starting smoking (<20, 20–29, 30–34 and ≥35 years) among ever smokers. To assess the impact of low-intensity smoking on all-cause and cause-specific mortality, we quantified the associations of age at starting smoking and smoking duration (<15, 15–24, 25–34, 35–44 and ≥45 years) among current smokers who smoked <5 or 5–9 cigarettes per day. We also quantified the associations of age at quitting smoking (<45, 45–54 and ≥55 years) and years since cessation (<5, 5–14 and ≥15 years) among former smokers who reported low-intensity smoking. The associations of smoking duration, age at quitting smoking and years since cessation were also evaluated among smokers who started smoking at a late age: 30–34 or ≥35 years. Covariates included baseline age (years), sex (men and women), educational attainment (no formal education, primary education, secondary education, trade/technical school, university graduate and graduate studies), marital status (single, married and others), residential area (urban and rural) and body mass index (<18.5, 18.5–24.9, 25.0–29.9 and ≥30.0 kg/m^2); all of which were assessed using the cohort-specific baseline questionnaires and harmonised based on the ACC data dictionary. Missing covariates were imputed by assigning the median or mode values of non-missing data. Imputation procedures were conducted separately by cohort. All statistical procedures were performed using SAS V.9.4 (SAS Institute, Cary, North Carolina, USA). Two-sided p values <0.05 were considered to be statistically significant.

RESULTS

Table 1 shows the baseline characteristics of participating cohorts. A total of 738 013 individuals were followed for a mean of 11.3 years. Mean age at baseline was 53.6 years, and 48.7% of the subjects were women. Among the 738 013 individuals, 92 068 deaths were ascertained, including 6585 deaths from lung cancer, 29 258 deaths from CVD and 8640 deaths from respiratory disease. The overall prevalence of current and former smoking was 27.9% and 6.9%, respectively. About one-quarter of the current smokers consumed fewer than 10 cigarettes per day: 12.8% smoked <5 and 11.6% smoked 5–9 cigarettes. Smokers who started smoking after age 30 made up 15.5% (7.8% for 30–34 years and 7.7% for ≥35 years) of the total (table 1).

Low-intensity tobacco smoking was significantly associated with a higher risk of mortality (table 2 and online supplementary

Table 1 Characteristics of participating cohorts in the Asia Cohort Consortium

	No. of participants ‡	Follow-up years	Women (%)	Age at baseline§	Ever smokers (%)		Cigarettes smoked per day (%) *		Age at starting smoking (%)†		No. of deaths			
					Current	Former	<5	5–9	30–34	≥35	All causes	Lung cancer	CVD	Respiratory disease
China														
CHEFS	135153	7.8	51.7	55.5	34.9	2.2	22.7	10.2	9.9	9.0	14776	860	6514	725
SCS	18010	16.4	0.0	55.2	50.6	6.7	5.4	10.5	12.1	14.3	4902	621	1660	523
SMHS	56165	9.6	0.0	54.4	61.0	9.4	4.1	10.2	8.4	7.6	3886	573	1031	275
SWHS	67268	15.0	100.0	51.8	2.3	0.4	27.3	24.4	14.5	54.5	5637	515	1629	242
Japan														
3Pref Aichi	29347	11.9	50.8	56.1	33.7	16.2	2.5	6.4	4.7	7.2	5209	346	1814	606
JPHC1	40859	21.1	52.4	49.5	28.4	11.3	2.7	5.2	4.1	4.5	6771	518	1633	550
JPHC2	52829	17.9	53.3	54.0	27.2	11.6	1.5	3.9	3.6	4.4	11213	850	2760	1288
3Pref Miyagi	26852	11.9	56.2	56.4	31.7	8.9	2.2	6.5	6.1	10.1	4879	245	1880	502
Miyagi	36295	16.5	47.4	51.4	36.7	9.6	1.4	4.3	6.6	6.6	4138	348	1064	309
Ohsaki	42132	11.4	54.6	59.9	27.4	11.1	1.6	5.5	6.9	7.7	7319	482	2123	979
Korea														
KMCC	10321	13.6	67.5	55.7	19.5	7.1	5.8	7.7	7.8	9.9	1806	133	438	149
Seoul Male	12126	15.6	0.0	49.0	51.1	26.1	2.3	6.5	3.9	2.3	719	77	108	21
Singapore														
SCHS	57714	11.7	56.1	56.1	19.6	10.2	14.1	25.8	9.3	NA	8234	874	2725	1216
Taiwan														
CVDFACTS	3540	14.9	56.5	53.6	22.9	NA	7.4	10.0	9.4	13.3	673	44	167	71
India														
Mumbai	143201	5.3	40.9	50.7	15.2	3.5	45.0	30.6	10.4	10.6	11273	68	3438	1092
Bangladesh														
HEALS	6201	12.3	44.7	44.0	39.4	10.4	15.5	18.3	7.5	7.3	633	31	274	92
Total	738013	11.3	48.7	53.6	27.9	6.9	12.8	11.6	7.8	7.7	92068	6585	29258	8640

*The proportion of low-dose smoking intensity among current smokers.
†The proportion of late smoking initiation among ever smokers.
‡Including only participants eligible for the current analysis.
§Mean age at the enrolment of the baseline (smoking) survey.
CHEFS, China National Hypertension Survey Epidemiology Follow-up Study; CVD, cardiovascular disease; CVDFACTS, Cardiovascular Disease Risk Factor two-Township Study; HEALS, Health Effects for Arsenic Longitudinal Study; JPHC, Japan Public Health Centre-based Prospective Study; KMCC, Korean Multicentre Cancer Cohort Study; Miyagi, Miyagi Cohort; Mumbai, Mumbai Cohort Study; NA, not available; Ohsaki, Ohsaki National Health Insurance Cohort Study; 3Pref Aichi, Three Prefecture Aichi Study; 3Pref Miyagi, Three Prefecture Miyagi Study; SCHS, Singapore Chinese Health Study; SCS, Shanghai Cohort Study; Seoul Male, Seoul Male Cancer Cohort; SMHS, Shanghai Men's Health Study; SWHS, Shanghai Women's Health Study.

Table 2 Risk of death associated with smoking intensity and age at starting smoking among Asian current and former smokers

		All causes		Lung cancer		Cardiovascular disease		Respiratory disease	
	No. of participants	No. of deaths	HR (95% CI)*†	No. of deaths	HR (95% CI)*†	No. of deaths	HR (95% CI)*†	No. of deaths	HR (95% CI)*†
Current smokers									
Never smokers	480 948	47 892	1 (reference)	1858	1 (reference)	16 023	1 (reference)	4047	1 (reference)
Cigarettes smoked per day									
<5	26 433	3756	1.27 (1.17 to 1.37)	180	2.20 (1.69 to 2.87)	1357	1.27 (1.12 to 1.43)	319	1.41 (1.18 to 1.68)
5–9	23 858	3668	1.40 (1.30 to 1.51)	258	2.42 (1.82 to 3.20)	1211	1.37 (1.26 to 1.48)	390	1.53 (1.29 to 1.81)
10–19	58 729	10 113	1.51 (1.38 to 1.65)	1131	4.07 (3.37 to 4.92)	3110	1.46 (1.32 to 1.62)	978	1.45 (1.26 to 1.66)
20–29	70 065	11 752	1.61 (1.47 to 1.77)	1643	5.34 (4.35 to 6.56)	3412	1.57 (1.40 to 1.75)	1034	1.62 (1.38 to 1.90)
≥30	26 816	4647	1.83 (1.65 to 2.02)	846	8.69 (7.11 to 10.6)	1116	1.59 (1.38 to 1.85)	363	1.89 (1.58 to 2.27)
Age at starting smoking (years)									
<20	57 562	9895	1.79 (1.61 to 1.99)	1358	6.32 (5.02 to 7.94)	3020	1.74 (1.53 to 1.97)	933	1.85 (1.58 to 2.15)
20–29	114 799	18 851	1.56 (1.43 to 1.69)	2298	4.85 (3.98 to 5.91)	5416	1.47 (1.33 to 1.62)	1723	1.53 (1.34 to 1.73)
30–34	16 691	2474	1.34 (1.21 to 1.48)	234	3.39 (2.54 to 4.53)	803	1.27 (1.14 to 1.41)	210	1.32 (1.08 to 1.62)
≥35	16 849	2716	1.24 (1.13 to 1.35)	168	2.14 (1.71 to 2.69)	967	1.27 (1.12 to 1.43)	218	1.16 (0.92 to 1.46)
Former smokers									
Never smokers	480 948	47 892	1 (reference)	1858	1 (reference)	16 023	1 (reference)	4047	1 (reference)
Cigarettes smoked per day									
<5	4988	937	1.27 (1.16 to 1.38)	33	1.80 (1.26 to 2.56)	362	1.33 (1.12 to 1.57)	108	1.60 (1.31 to 1.94)
5–9	5947	1056	1.19 (1.10 to 1.28)	43	1.94 (1.41 to 2.68)	329	1.12 (0.94 to 1.33)	173	1.88 (1.48 to 2.38)
10–19	14 202	2840	1.25 (1.17 to 1.33)	168	2.08 (1.73 to 2.49)	880	1.23 (1.10 to 1.37)	459	1.83 (1.52 to 2.22)
20–29	15 667	3185	1.29 (1.18 to 1.41)	233	2.73 (2.16 to 3.44)	873	1.14 (1.00 to 1.29)	469	1.94 (1.52 to 2.46)
≥30	10 360	2222	1.36 (1.25 to 1.47)	192	3.41 (2.85 to 4.08)	585	1.19 (1.08 to 1.32)	300	1.88 (1.42 to 2.48)
Age at starting smoking (years)									
<20	14 557	2798	1.41 (1.31 to 1.52)	230	3.27 (2.69 to 3.97)	849	1.35 (1.20 to 1.51)	420	2.02 (1.63 to 2.50)
20–29	30 368	6082	1.25 (1.16 to 1.35)	383	2.30 (1.99 to 2.65)	1723	1.15 (1.01 to 1.32)	912	1.79 (1.51 to 2.13)
30–34	3342	741	1.21 (1.13 to 1.31)	34	1.71 (1.20 to 2.42)	247	1.18 (1.04 to 1.34)	99	1.67 (1.22 to 2.30)
≥35	2897	619	1.13 (1.04 to 1.22)	22	1.55 (1.01 to 2.38)	210	1.08 (0.94 to 1.24)	78	1.40 (1.11 to 1.76)

*Never smokers were used as a reference group for each analysis.
†All models were stratified by 5-year groups of birth year and enrolment year and adjusted for age, sex, education, marital status, rural/urban residence and body mass index.

appendix pp 3). Compared with never smokers, current smokers who consumed fewer than five cigarettes per day had a 27%–41% increased risk of death from any cause, CVD or respiratory disease (HRs (95% CIs)=1.27 (1.17 to 1.37), 1.27 (1.12 to 1.43) and 1.41 (1.18 to 1.68), respectively) and showed a 2.20-fold increased risk of lung cancer mortality (2.20 (1.69 to 2.87)). The corresponding HRs (95% CIs) for 5–9 cigarettes smoked per day among current smokers were 1.40 (1.30 to 1.51), 1.37 (1.26 to 1.48), 1.53 (1.29 to 1.81) and 2.42 (1.82 to 3.20), respectively. The HRs for deaths associated with daily cigarette consumption gradually increased with cigarette quantity. Late initiation of smoking also conferred substantial risks to current smokers: those who started smoking at 30–34 or ≥35 years had a 24%–34% increased risk of death overall, as well as a 3.39-fold and 2.14-fold increased risk of lung cancer mortality, respectively, relative to never smokers. Similar associations were observed among former smokers. In particular, former smokers who had smoked at low intensity had an almost twofold increased risk of lung cancer mortality relative to never smokers. Furthermore, the associations of low-intensity tobacco smoking with mortality remained consistent even when stratified by sex (online supplementary appendix pp 8–9).

All current smokers who smoked fewer than five and five to nine cigarettes per day had a higher risk of all-cause and cause-specific mortality than never smokers, regardless of starting age (table 3). For those with a daily cigarette consumption of less than five, the HRs (95% CIs) for initiation after age 35 were 1.14 (1.05 to 1.23) for all causes, 1.27 (1.08 to 1.49) for CVD and 1.54 (1.17 to 2.01) for respiratory disease. Lung cancer mortality increased 3.10-fold with initiation at 30–34 years, relative to never smokers. For current smokers who smoked five to nine cigarettes per day, the pattern of associations was very similar to that for those who smoked fewer than five cigarettes per day. The risk of low-intensity daily cigarette consumption tended to gradually increase with smoking duration: current smokers who smoked fewer than five or five to nine cigarettes per day for over 45 years had a 3.15-fold and 4.35-fold increased risk of lung cancer mortality, respectively, compared with never smokers (HR (95% CI)=3.15 (1.90 to 5.22) and 4.35 (3.38 to 5.59), respectively).

Despite quitting, former smokers who smoked fewer than five and five to nine cigarettes per day also had a higher mortality risk than never smokers (table 4). Even smokers who smoked fewer than five cigarettes per day and quit smoking before the age of 45 had a 16% higher risk of all-cause mortality. However, the risk declined further with an increasing number of years since smoking cessation: the HRs (95% CIs) for <5 vs ≥15 years were 1.41 (1.25 to 1.59) vs 1.11 (1.00 to 1.24) for all-cause mortality, 3.45 (1.94 to 6.13) vs 1.98 (1.03 to 3.83) for lung cancer mortality, 1.63 (1.35 to 1.98) vs 1.17 (0.97 to 1.40) for CVD mortality and 1.99 (1.35 to 2.94) vs 1.65 (1.19 to 2.30) for respiratory disease, respectively.

Unfortunately, we were unable to examine how associations varied by smoking duration, age at quitting and years since

Table 3 Risk of death associated with age at starting smoking and smoking duration among Asian low-intensity current smokers

	All causes		Lung cancer		Cardiovascular disease		Respiratory disease	
	No. of deaths	HR (95% CI)*†	No. of deaths	HR (95% CI)*†	No. of deaths	HR (95% CI)*†	No. of deaths	HR (95% CI)*†
<5 cigarettes smoked per day								
Age at starting smoking (years)								
<20	1247	1.51 (1.29 to 1.77)	70	3.45 (2.10 to 5.68)	436	1.46 (1.13 to 1.89)	127	2.00 (1.66 to 2.41)
20–29	1517	1.28 (1.16 to 1.41)	73	2.62 (1.95 to 3.53)	540	1.17 (1.07 to 1.28)	104	1.39 (1.04 to 1.86)
30–34	388	1.14 (1.02 to 1.28)	19	3.10 (1.59 to 6.07)	141	1.11 (0.94 to 1.31)	32	1.42 (1.00 to 2.02)
≥35	604	1.14 (1.05 to 1.23)	18	1.53 (0.95 to 2.45)	240	1.27 (1.08 to 1.49)	56	1.54 (1.17 to 2.01)
Smoking duration (years)								
<15	250	1.02 (0.90 to 1.15)	8	‡	85	1.13 (0.91 to 1.40)	20	1.83 (1.17 to 2.86)
15–24	382	1.32 (1.10 to 1.59)	17	3.11 (1.88 to 5.13)	125	1.49 (1.14 to 1.94)	25	2.23 (1.50 to 3.33)
25–34	727	1.35 (1.25 to 1.46)	28	2.07 (1.41 to 3.06)	214	1.25 (1.06 to 1.46)	45	1.60 (1.18 to 2.17)
35–44	990	1.29 (1.21 to 1.38)	59	2.65 (2.00 to 3.52)	353	1.22 (1.08 to 1.39)	75	1.49 (1.17 to 1.89)
≥45	1407	1.22 (1.07 to 1.38)	68	3.15 (1.90 to 5.22)	580	1.16 (1.01 to 1.35)	154	1.55 (1.17 to 2.05)
5–9 cigarettes smoked per day								
Age at starting smoking (years)								
<20	1123	1.57 (1.41 to 1.75)	114	4.63 (3.20 to 6.70)	364	1.47 (1.32 to 1.64)	145	2.15 (1.69 to 2.73)
20–29	1660	1.41 (1.30 to 1.52)	101	2.59 (2.07 to 3.25)	544	1.42 (1.24 to 1.61)	169	1.54 (1.30 to 1.82)
30–34	398	1.32 (1.18 to 1.48)	16	2.01 (1.22 to 3.31)	125	1.27 (1.00 to 1.61)	42	1.84 (1.22 to 2.76)
≥35	487	1.14 (1.04 to 1.25)	27	2.34 (1.58 to 3.45)	178	1.19 (1.02 to 1.38)	34	1.22 (0.86 to 1.71)
Smoking duration (years)								
<15	203	1.18 (1.02 to 1.35)	5	‡	64	1.38 (1.03 to 1.86)	11	1.67 (0.92 to 3.06)
15–24	377	1.36 (1.18 to 1.57)	17	2.57 (1.33 to 4.98)	103	1.39 (1.11 to 1.76)	18	1.80 (1.12 to 2.88)
25–34	748	1.40 (1.26 to 1.56)	41	2.36 (1.71 to 3.26)	239	1.49 (1.31 to 1.70)	47	1.46 (1.09 to 1.96)
35–44	1116	1.49 (1.35 to 1.64)	95	2.93 (2.07 to 4.14)	368	1.39 (1.25 to 1.55)	124	1.74 (1.44 to 2.10)
≥45	1224	1.41 (1.25 to 1.58)	100	4.35 (3.38 to 5.59)	437	1.28 (1.13 to 1.44)	190	1.81 (1.52 to 2.16)

*Never smokers were used as a reference group for each analysis: the numbers of deaths among never smokers were 47 892 for all causes, 1858 for lung cancer, 16 023 for cardiovascular disease and 4047 for respiratory disease.
†All models were stratified by 5-year groups of birth year and enrolment year and adjusted for age, sex, education, marital status, rural/urban residence and body mass index.
‡Not estimated due to small sample size (<10 events).

cessation among smokers who started smoking later in life due to insufficient sample size.

DISCUSSION

In the current pooled analyses of nearly 750 000 Asians, we found that participants smoking a small number of cigarettes (even fewer than five per day) and starting late in life (even after age 35) had a 16%–41% increased risk of death from any cause, CVD and respiratory disease, and a greater than twofold increased risk of lung cancer mortality relative to never smokers. Furthermore, even smokers who both started smoking after age 35 and smoked fewer than five cigarettes per day had higher risks of mortality during follow-up than never smokers. Higher risks were observed even among low-intensity smokers who quit smoking before the age of 45. Our findings provide further evidence that there is no safe way to smoke tobacco: not smoking is always the best choice.

Several studies have addressed the impact of low-intensity smoking on various health outcomes, including mortality[4–13]; all of which have consistently indicated that there is no level of tobacco smoking without adverse consequences. An average of even one cigarette (or less) per day carries significant risks of disease morbidity and mortality. For example, the National Institutes of Health (NIH)–AARP Diet and Health Study has reported that lifelong low-intensity smokers who consumed fewer than one cigarette per day had an increased risk of death from all causes (HR (95% CI)=1.64 (1.07 to 2.51)), lung cancer (9.12 (2.92 to 28.47)) and CVD (2.78 (1.49 to 5.18)) compared with never smokers.[12] That study has also shown that lifelong low-intensity smokers were still at a high risk of developing smoking-related cancers (1.89 (0.90 to 3.96) for less than one cigarette per day and 2.34 (1.86 to 2.93) for 1–10 cigarettes per day).[5] In addition, a recent meta-analysis of 141 cohort studies[6] found a 1.65-fold and 1.52-fold increased risk for coronary heart disease and stroke, respectively, among men and women who smoked one cigarette per day. The corresponding risk estimates for five cigarettes smoked per day were 1.72 and 1.63, respectively.[6]

However, most existing studies to date have been conducted in Western populations; evidence from non-Western populations, especially individuals who smoked much less and started smoking later in life than Westerners, remains sparse. Some Asian studies have indicated a dose-response relationship for cigarette consumption and mortality,[14 20] but they have not focused on very low quantities of cigarettes. In this study, we investigated the impact of low-intensity smoking on the subsequent mortality in Asian populations and found that smoking even fewer than five cigarettes per day and initiation of smoking after age 35 were associated with higher risks of mortality. Intervention strategies for Asian smokers should communicate the potential health harms associated with low-intensity smoking and encourage people not to start smoking and smokers to quit, rather than reducing smoking intensity.

Our findings suggest that the risk among low-intensity smokers increases with longer smoking duration and later age

Table 4 Risk of death associated with smoking cessation among Asian low-intensity former smokers

	All causes		Lung cancer		Cardiovascular disease		Respiratory disease	
	No. of deaths	HR (95% CI)*†	No. of deaths	HR (95% CI)*†	No. of deaths	HR (95% CI)*†	No. of deaths	HR (95% CI)*†
<5 cigarettes smoked per day								
Age at quitting smoking (years)								
<45	258	1.16 (1.03 to 1.32)	6	‡	90	1.29 (1.05 to 1.59)	31	1.76 (1.18 to 2.61)
45–54	194	1.43 (1.24 to 1.65)	5	‡	79	1.71 (1.21 to 2.42)	14	1.56 (0.92 to 2.65)
≥55	459	1.34 (1.22 to 1.47)	22	3.25 (2.11 to 5.01)	182	1.37 (1.13 to 1.66)	61	2.03 (1.57 to 2.63)
Years since cessation								
<5	262	1.41 (1.25 to 1.59)	12	3.45 (1.94 to 6.13)	106	1.63 (1.35 to 1.98)	26	1.99 (1.35 to 2.94)
5–14	306	1.44 (1.28 to 1.62)	11	3.46 (1.87 to 6.41)	122	1.62 (1.22 to 2.15)	33	2.05 (1.45 to 2.90)
≥15	343	1.11 (1.00 to 1.24)	10	1.98 (1.03 to 3.83)	123	1.17 (0.97 to 1.40)	47	1.65 (1.19 to 2.30)
5–9 cigarettes smoked per day								
Age at quitting smoking (years)								
<45	269	1.05 (0.93 to 1.19)	6	‡	82	1.19 (0.93 to 1.52)	38	1.81 (1.16 to 2.80)
45–54	267	1.26 (1.12 to 1.43)	8	‡	79	1.24 (0.95 to 1.62)	34	1.98 (1.23 to 3.17)
≥55	505	1.25 (1.15 to 1.37)	28	3.40 (2.17 to 5.34)	164	1.13 (0.92 to 1.39)	99	2.19 (1.78 to 2.69)
Years since cessation								
<5	291	1.38 (1.16 to 1.65)	16	3.47 (2.04 to 5.92)	85	1.32 (1.02 to 1.71)	55	2.73 (2.08 to 3.59)
5–14	367	1.22 (1.07 to 1.38)	16	3.00 (1.69 to 5.32)	106	1.01 (0.73 to 1.39)	61	2.14 (1.52 to 3.01)
≥15	383	1.08 (0.94 to 1.24)	10	1.54 (0.81 to 2.92)	134	1.22 (0.92 to 1.62)	55	1.36 (1.04 to 1.79)

*Never smokers were used as a reference group for each analysis: the numbers of deaths among never smokers were 47 892 for all causes, 1858 for lung cancer, 16 023 for cardiovascular disease and 4047 for respiratory disease.
†All models were stratified by 5-year groups of birth year and enrolment year and adjusted for age, sex, education, marital status, rural/urban residence and body mass index.
‡Not estimated due to small sample size (<10 events).

at cessation, but decreases with later age at initiation and earlier cessation. Similar findings were also observed in other studies: the International Head and Neck Cancer Epidemiology consortium reported that the ORs for head and neck cancers associated with low cigarette consumption gradually increased with smoking duration.[4] The NIH-AARP study found stronger associations between <10 cigarettes smoked per day and smoking-related cancer among smokers who smoked for >30 years, compared with those who smoked for <10 years.[5] Furthermore, late cessation significantly increased the risk of all-cause/cause-specific mortality and incident smoking-related cancers among low-intensity smokers.[5 12 21] A recent study reported that a decrease in daily cigarette consumption reduced the risk of dying from any cause, cancer, CVD and respiratory disease.[21] However, the risk reduction did not reach the potential benefits of smoking cessation, especially cessation before the age of 40. Along with our findings, all of the epidemiological evidence to date indicates that long-term smoking can cause future health harms regardless of the absolute number of cigarettes smoked per day or the age at starting smoking, while abstinence from tobacco smoking reduces the risk and earlier cessation results in better outcomes. Public-health providers should deliver strong messages that there are no alternatives to smoking cessation: the best way to avoid the adverse effects of cigarette smoking is to quit sooner rather than later or better yet, never start.

Early initiation of tobacco smoking is a well-known risk factor for a broad spectrum of disease outcomes. However, the impact on health of late initiation has not yet been adequately addressed, particularly in combination with low-dose tobacco consumption. Smoking initiation at an earlier age is generally considered to be a predisposing factor for heavy smoking, nicotine dependence and a low likelihood of smoking cessation[22]; however, this does not mean that starting smoking at a later age is safe. Our study showed that late initiation of tobacco smoking also conferred a significantly higher risk of death, especially from lung cancer, among both current and former smokers. Furthermore, even among smokers with low-dose tobacco consumption (fewer than five and five to nine cigarettes per day), smoking initiation after age 30 was associated with a 14%–84% increased risk of all-cause, CVD and respiratory disease mortality, as well as up to a 3.1-fold increased risk of lung-cancer mortality. In Asia, many smokers, especially women, tend to start smoking at a late age and continue smoking until later in life—only a very small fraction quit smoking before middle age.[15] Given that median life expectancy has increased rapidly in Asia, it is possible that we will face a growing health burden of smoking-related disease morbidity and mortality among elderly populations in the region. Our results emphasise that none of any age should start smoking and all smokers should quit. Public policy has to consider approaches that encourage abstinence throughout life.

This large prospective investigation using multiple Asian populations and long-term follow-up data enabled us to quantify the relative risks of all-cause and cause-specific mortality associated with both low-dose cigarette consumption and late age of smoking initiation in Asia. The availability of data from 750 000 participants yielded excellent statistical power. Our consortium includes studies throughout the Asian region; the consistent findings provide evidence of their robustness. All study participants were free of severe underlying diseases and survived at least one year after enrolment, which reduced the potential influence of reverse causality and/or residual bias on our study results. Using detailed information on the participants' smoking history, we comprehensively investigated the impact of a broad array of smoking-related factors on the association between low-intensity smoking and mortality. Nevertheless, some study limitations should be acknowledged. Although the epidemiological literature indicates high reliability and accuracy of self-reported lifetime smoking history, including age at

starting and overall quantity,[23–25] some errors may exist in self-reported smoking habits in our study. The errors should be non-differential, and thus tend to bias the risk estimates towards the null. Because smoking-related data were collected once at baseline, we could not consider changes in smoking status, quantity or relapse following cessation during follow-up. These limitations are also likely to bias the association towards the null. Due to the lack of information on secondhand smoke and co-use of other non-cigarette tobacco products, we could not consider them as potential confounders in the analysis, which might have influenced our risk estimates. However, the associations of secondhand smoke with disease/mortality outcomes reported to date are typically weak. For example, an RR of around 1.5 or lower has been reported for lung cancer in association with secondhand smoke in previous studies,[26–29] which is weaker than the association observed in this study for low-intensity active smoking (RR=2.2). The prevalence of concurrent use of other tobacco products may vary by study populations, likely to be high in India and rural China while low in urban China, Japan and Korea. However, consistent associations were found with low-intensity smoking across all study populations, suggesting that cocurrent use of other tobacco products is unlikely to substantially affect the results from this study. In addition, we should take into consideration possible residual confounders such as family history of cancer or CVD, alcohol consumption and physical activity in the interpretation of our study results. Despite our large sample size, some subgroup analyses lacked numbers and thus sufficient statistical power, particularly analyses of participants starting smoking later in life. Finally, participating cohorts in the present study are limited to mostly East and some South Asian populations—future investigations including other Asian countries will help improve the generalisability of the study findings.

CONCLUSIONS

Our study shows that smoking even a small number of cigarettes and starting smoking later in life each increase mortality risk in Asia. These results provide an important message to smokers who may incorrectly believe that low-intensity smoking, reducing cigarette consumption or delaying initiation would alleviate the negative health consequences of tobacco smoking. Of note, studies have reported that many adolescents have a misconception that light and/or non-daily smoking can minimise health harms.[30 31] Our study provides strong evidence that there is no safe threshold of smoking and no alternative to smoking cessation. Comprehensive public-health interventions should be strongly implemented to provide accurate information on the harms of low-intensity smoking and to encourage smokers to completely quit rather than reduce consumption.

What this paper adds

- Epidemiological evidence to date linking low-intensity smoking to health harms mostly comes from Western populations.
- Little is known about potential adverse consequences associated with low-intensity smoking in Asian populations who smoked much less and started smoking later in life than their counterparts living in Europe and North America.
- The current study found that light smokers and smokers who started late in life still experienced a significantly elevated risk of deaths due to all causes and major diseases evaluated in our study, including cardiovascular disease, respiratory disease and lung cancer.
- Elevated risks of deaths were also observed even among light smokers who quit smoking before the age of 45 years; however, the risks declined further with an increasing number of years since smoking cessation.
- Smoking even a small number of cigarettes and starting smoking late in life are each associated with a significantly elevated risk of death in Asia.
- There is no safe way to smoke tobacco: the best way to avoid the adverse effects of smoking is to quit sooner and better yet, never start.

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REFERENCES

1 GBD 2015 Tobacco Collaborators. Smoking prevalence and attributable disease burden in 195 countries and territories, 1990-2015: a systematic analysis from the global burden of disease study 2015. *Lancet* 2017;389:1885–906.
2 Jamal A, Phillips E, Gentzke AS, *et al*. Current Cigarette Smoking Among Adults - United States, 2016. *MMWR Morb Mortal Wkly Rep* 2018;67:53–9.
3 NHS Digital. Health survey for England. Available: https://data.gov.uk/dataset/health_survey_for_england [Accessed 1 Feb 2018].
4 Berthiller J, Straif K, Agudo A, *et al*. Low frequency of cigarette smoking and the risk of head and neck cancer in the INHANCE Consortium pooled analysis. *Int J Epidemiol* 2016;45:835–45.
5 Inoue-Choi M, Hartge P, Liao LM, *et al*. Association between long-term low-intensity cigarette smoking and incidence of smoking-related cancer in the National Institutes of Health-AARP cohort. *Int J Cancer* 2018;142:271–80.
6 Hackshaw A, Morris JK, Boniface S, *et al*. Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports. *BMJ* 2018;10:j5855.
7 Schane RE, Ling PM, Glantz SA. Health effects of light and intermittent smoking: a review. *Circulation* 2010;121:1518–22.
8 Rosengren A, Wilhelmsen L, Wedel H, *et al*. Coronary heart disease, cancer and mortality in male middle-aged light smokers. *J Intern Med* 1992;231:357–62.
9 Prescott E, Scharling H, Osler M, *et al*. Importance of light smoking and inhalation habits on risk of myocardial infarction and all cause mortality. A 22 year follow up of 12 149 men and women in the Copenhagen City heart study. *J Epidemiol Community Health* 2002;56:702–6.
10 Inoue-Choi M, McNeel TS, Hartge P, *et al*. Non-Daily cigarette smokers: mortality risks in the U.S. *Am J Prev Med* 2019;56:27–37.
11 Bjartveit K, Tverdal A. Health consequences of smoking 1-4 cigarettes per day. *Tob Control* 2005;14:315–20.
12 Inoue-Choi M, Liao LM, Reyes-Guzman C, *et al*. Association of long-term, low-intensity smoking with all-cause and cause-specific mortality in the National Institutes of Health-AARP diet and health study. *JAMA Intern Med* 2017;177:87–95.
13 Luoto R, Uutela A, Puska P. Occasional smoking increases total and cardiovascular mortality among men. *Nicotine Tob Res* 2000;2:133–9.
14 Zheng W, McLerran DF, Rolland BA, *et al*. Burden of total and cause-specific mortality related to tobacco smoking among adults aged ≥45 years in Asia: a pooled analysis of 21 cohorts. *PLoS Med* 2014;11:e1001631.
15 Yang JJ, Yu D, Wen W, *et al*. Tobacco smoking and mortality in Asia: a pooled meta-analysis. *JAMA Netw Open* 2019;2:e191474.
16 Ng M, Freeman MK, Fleming TD, *et al*. Smoking prevalence and cigarette consumption in 187 countries, 1980-2012. *JAMA* 2014;311:183–92.
17 Zheng W, McLerran DF, Rolland B, *et al*. Association between body-mass index and risk of death in more than 1 million Asians. *N Engl J Med* 2011;364:719–29.
18 Burke DL, Ensor J, Riley RD. Meta-Analysis using individual participant data: one-stage and two-stage approaches, and why they may differ. *Stat Med* 2017;36:855–75.
19 DerSimonian R, Laird N. Meta-Analysis in clinical trials. *Control Clin Trials* 1986;7:177–88.
20 Chen Z, Peto R, Zhou M, *et al*. Contrasting male and female trends in tobacco-attributed mortality in China: evidence from successive nationwide prospective cohort studies. *Lancet* 2015;386:1447–56.
21 Inoue-Choi M, Hartge P, Park Y, *et al*. Reductions in cigarettes per day and mortality among older adults in the United States. *Am J Epidemiol*.
22 National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. *Preventing tobacco use among youth and young adults: a report of the surgeon General*. Atlanta (GA: Centers for Disease Control and Prevention (US), 2012. http://www.ncbi.nlm.nih.gov/books/NBK99237/
23 Brigham J, Lessov-Schlaggar CN, Javitz HS, *et al*. Reliability of adult retrospective recall of lifetime tobacco use. *Nicotine Tob Res* 2008;10:287–99.
24 Soulakova JN, Hartman AM, Liu B, *et al*. Reliability of adult self-reported smoking history: data from the tobacco use supplement to the current population survey 2002-2003 cohort. *Nicotine Tob Res* 2012;14:952–60.
25 Patrick DL, Cheadle A, Thompson DC, *et al*. The validity of self-reported smoking: a review and meta-analysis. *Am J Public Health* 1994;84:1086–93.
26 Kim A-S, Ko H-J, Kwon J-H, *et al*. Exposure to Secondhand smoke and risk of cancer in never smokers: a meta-analysis of epidemiologic studies. *Int J Environ Res Public Health* 2018;15:1981.
27 Kim CH, Lee Y-CA, Hung RJ, *et al*. Exposure to secondhand tobacco smoke and lung cancer by histological type: a pooled analysis of the International lung cancer Consortium (ILCCO). *Int J Cancer* 2014;135:1918–30.
28 Brennan P, Buffler PA, Reynolds P, *et al*. Secondhand smoke exposure in adulthood and risk of lung cancer among never smokers: a pooled analysis of two large studies. *Int. J. Cancer* 2004;109:125–31.
29 Vineis P, Airoldi L, Veglia F, *et al*. Environmental tobacco smoke and risk of respiratory cancer and chronic obstructive pulmonary disease in former smokers and never smokers in the EPIC prospective study. *BMJ* 2005;330:277.
30 Amrock SM, Weitzman M. Adolescents' perceptions of light and intermittent smoking in the United States. *Pediatrics* 2015;135:246–54.
31 Amrock SM, Zakhar J, Zhou S, *et al*. Perception of e-cigarette harm and its correlation with use among U.S. adolescents. *Nicotine Tob Res* 2015;17:330–6.