Smoking and All-Cause Mortality in Older People

Systematic Review and Meta-analysis

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Background: Smoking is an established risk factor of premature death. However, most pertinent studies primarily relied on middle-aged adults. We performed a systematic review and meta-analysis of the empirical evidence on the association of smoking with all-cause mortality in people 60 years and older.

Methods: A systematic literature search was conducted in multiple databases including MEDLINE, EMBASE, and ISI Web of Knowledge and complemented by cross-referencing to identify cohort studies published before July 2011. Core items of identified studies were independently extracted by 2 reviewers, and results were summarized by standard methods of meta-analysis.

Results: We identified 17 studies from 7 countries. Current smoking was associated with increased all-cause mortality in all studies. Relative mortality (RM) compared with never smokers ranged from 1.2 to 3.4 across studies and was 1.83 (95% CI, 1.65-2.03) in the meta-analysis. A decrease of RM of current smokers with increasing age was observed, but mortality remained increased up to the highest ages. Furthermore, a dose-response relationship of the amount of smoked cigarettes and premature death was observed. Former smokers likewise had an increased mortality (meta-analysis: RM, 1.34; 95% CI, 1.28-1.40), but excess mortality compared with never smokers clearly decreased with duration of cessation. Benefits of smoking cessation were evident in all age groups, including subjects 80 years and older.

Conclusions: Smoking remains a strong risk factor for premature mortality also at older age. Smoking cessation is beneficial at any age.

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IT IS WELL ESTABLISHED THAT SMOKing is hazardous to health.[1-3] Smoking is one of the major risk factors for multiple chronic diseases, such as cardiovascular diseases[4-6] and cancer,[7-9] as well as for mortality from the leading causes of death and consequently also for all-cause mortality. Smoking is one of the 10 leading risk factors for death, and according to estimates of the World Health Organization, it is responsible for 12% of male deaths and 6% of female deaths in the world.[2] In the 21st century, a billion deaths due to smoking are expected if no changes in smoking behavior are achieved.[7]

See Invited Commentary at end of article

However, as for most other risk factors, epidemiological evidence mostly relies on studies conducted among middle-aged adults, and specific evidence for the impact of smoking at older age is still sparse. Furthermore, evaluation of the impact of smoking and smoking cessation at old age may be particularly challenging owing to a number of methodological issues, such as attenuated relative risks in the presence of strongly increased absolute levels of mortality among both smokers and nonsmokers and the "depletion of susceptibles" effect.[10,11]

In the present article, we provide a thorough review and meta-analysis of studies assessing the impact of smoking on all-cause mortality in people 60 years and older, paying particular attention to the strength of the association by age, the impact of smoking cessation at older age, and factors that might specifically affect results of epidemiological studies on the impact of smoking in an older population.

METHODS

DATA SOURCES

A protocol was developed based on widely recommended methods for systematic reviews of observational studies.[12,13] A systematic literature search was carried out to identify cohort studies published before July 2011 that report on the association of smoking and all-cause mortality in individuals 60 years and older. The electronic databases MEDLINE, EMBASE, and ISI Web of Knowledge were searched for relevant articles by the following search strategy: (Smoking OR Tobacco OR Cigarette) AND (Aged OR Old OR Elderly) AND (Mortality OR Death OR

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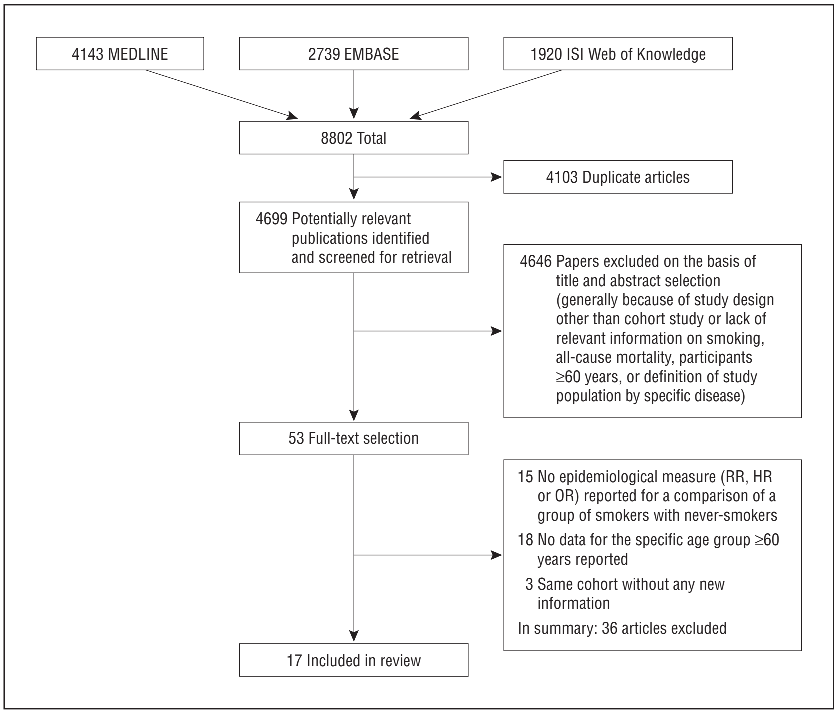

Figure 1. Flow diagram of the systematic literature search. HR indicates hazard ratio; OR, odds ratio; and RR, relative risk.

Dead) AND (Cohort OR Longitudinal). No language restrictions were used.

STUDY SELECTION

To be included, studies had to report smoking status and examine the outcome of interest (all-cause mortality) in people 60 years and older in the general population in a longitudinal cohort study design. We excluded studies that did not publish separate results for older people or did not estimate a relative-effect measure (hazard ratio, odds ratio, or relative risk) for the comparison of current or former smokers with never smokers. Furthermore, studies that did not reflect random general population samples were excluded.

DATA EXTRACTION

Study selection and extraction of study characteristics from included studies were independently performed by 2 reviewers (C.G. and B.S.). Any disagreement was resolved by review and discussion among the authors. Cross-referencing in finally included publications was used to verify the completeness of the literature search. Study quality was evaluated using established protocols.[13,14] Good-quality studies were deemed to have the following features: (1) random recruitment of participants or representative population, (2) detailed ascertainment of smoking variables in face-to-face interview, (3) reporting on completeness of registry-based mortality follow-up, and (4) adjustment (or stratification) for important covariates (age, sex, alcohol, and body mass index). Associations reported in the studies included relative mortality rates and hazard ratios (typically derived from Cox proportional hazards models) and are referred to as "relative mortality" (RM) in this report.

The "Comprehensive Meta-analysis" software (Biostat) was used for the conduction of all meta-analyses. In a conservative approach, the random-effects estimates, which allow for variation of true effects across studies, were taken as "main results."[15] Random-effects estimates were derived using the DerSimonian-Laird method.[16,17] Heterogeneity was assessed by the I^2 and the Q statistics. To explore heterogeneity, we performed subgroup analyses according to study population (age, sex, and region of study conduction), according to characteristics of study design (sample size and follow-up period) and study quality score. The funnel plot, Begg and Mazumdar rank correlation test, and Egger test of the intercept were used to assess indications of publication bias.[18]

RESULTS

The process of the systematic literature search is displayed in a flow diagram in **Figure 1**. In brief, the search in the electronic databases identified 8802 articles. After exclusion of duplicates, title and abstract selection, and full-text selection, 17 studies met the inclusion criteria of this review.[19-35] Cross-referencing did not identify any additional articles.

A description of the baseline characteristics of the included studies is given in **Table 1**. The studies were published between 1987 and 2011 and were conducted in 17 different cohorts. Seven studies were conducted in the United States,[22,23,26,27,29,31,33] 3 in China,[20,25,28] 2 in Australia[19,30] and 2 in Japan.[24,35] The remaining studies were from England,[21] Spain,[34] and France.[32] The follow-up time ranged from 3 to 50 years, and the size of the study populations ranged from 863 to 877 243 participants. Fourteen studies provided data on all-cause mortality according to smoking for both sexes,[19,22-32,34,35] whereas 2 studies[20,21] reported results only for men and 1 study only for women.[33]

Study quality scores (range, 0-4) averaged 2.35, with a proportion of high-quality studies (quality score ≥3) of 35%.

An overview of factors adjusted for in the 17 studies is given in eTable 1 (http://www.archinternmed.com). Age and sex were adjusted for in all studies that were not restricted to a single age group or a single sex. Systolic blood pressure, alcohol consumption, and physical activity were controlled for in 9,[20,23-25,27,28,30,33,35] 9,[20,25-28,30,31,34,35] and 6 studies,[20,23,26,28,33,34] respectively. Other factors were adjusted for to a heterogeneous degree in a minority of studies only.

CURRENT SMOKERS

Estimated RM for current smokers compared with never smokers is given in **Table 2**, stratified by sex and age groups. For currently smoking men, the point estimates of RM compared with never smokers ranged from 1.3 to 3.4, with an outlier of 0.5 in men 90 years or older in the study of Paganini-Hill et al,[29] likely owing to a very small sample size (numbers or confidence intervals not provided). For women, the point estimates of RM ranged from 1.2 to 2.5. Three studies reported

Table 1. Baseline Characteristics of Included Studies

Source	Cohort Name	Country	Age Range (Mean Age), y	Years of Enrollment	End of Follow-up	Length of Follow-up (Mean), y	Sample Size, No. Total	Sample Size, No. Male	Sample Size, No. Female	Deaths	Quality Score
Jamrozik et al,[19] 2011	ALSWH, HIMS	Australia	≥70 (72.1-72.5)	1996	2006	10	23 861	12 154	11 707	6214	2 (R = 1, E = 1, O = 0, C = 0)
Murakami et al,[35] 2011	EPOCH-JAPAN	Japan	40-89[a]	1987-1995	2005	10	183 251	69 502	113 749	17 224	2 (R = 1, E = 0, O = 0, C = 1)
Newman et al,[23] 2009	CHS	USA	≥65 (73)	1989-1990	2006	16 (13)	5888	2495	3393	4248	2 (R = 1, E = 0, O = 1, C = 0)
				1992-1993	2006	13	924	581	343		
Fujisawa et al,[24] 2008	8020 DBS	Japan	80	1998	2002	4	690	275	415	108	2 (R = 1, E = 1, O = 0, C = 0)
Lam et al,[28] 2007	NA	China	≥65 (73)	1998-2000	2003	4 (4.1)	56 167	18 749	37 416	3883	3 (R = 1, E = 0, O = 1, C = 1)
Simons et al,[30] 2005	Dubbo Study	Australia	≥60	1988-1989	2003	15	2805	1233	1572	1293	3 (R = 1, E = 0, O = 1, C = 1)
Doll et al,[21] 2004	BDS	England	>20[a]	1951	2001	50	34 439	34 439	0	25 346	2 (R = 1, E = 0, O = 1, C = 0)
Lam et al,[20] 2002	NA	China	≥60 (63)	1987	1999	12	1268	1268	0	299	3 (R = 1, E = 0, O = 1, C = 1)
Taylor et al,[31] 2002	CPS II	USA	>30 (56)[a]	1982	1996	14	877 243	334 918	542 325	149 351	2 (R = 1, E = 0, O = 1, C = 0)
Tessier et al,[32] 2000	PAQUID	France	≥65	1988	1996	8	2792	1115	1647	935	2 (R = 1, E = 1, O = 0, C = 0)
Enstrom,[22] 1999	NHEFS	USA	65-74	1971	1992	19	863	321	542	641	3 (R = 1, E = 1, O = 1, C = 0)
Ho et al,[25] 1999	OAAS	China	≥70 (80)	1991-1992	1995	3	2032	999	1033	534	4 (R = 1, E = 1, O = 1, C = 1)
Vogt et al,[33] 1996	SOF	USA	≥65	1986-1988	1992	6 (4.9)	9704	0	9704	751	2 (R = 1, E = 0, O = 1, C = 0)
Ruigomez et al,[34] 1995	HISB	Spain	65-97	1986	1991	5 (4.6)	1219	472	747	224	3 (R = 1, E = 1, O = 1, C = 0)
Paganini-Hill and Hsu,[29] 1994	NA	USA	≥60 (73)[b]	1981-1983	1991	5 (4.3)	13 868	4999	8869	4002	2 (R = 1, E = 0, O = 1, C = 0)
LaCroix et al,[27] 1991	NA	USA	≥65	1981-1983	1988	5 (2.3)	7178	2709	4469	2491	1 (R = 1, E = 0, O = 0, C = 0)
Kaplan et al,[26] 1987	HPL	USA	60-94	1965	1982	17	4174	NR	NR	1219	2 (R = 1, E = 0, O = 1, C = 0)

Abbreviations: 8020 DBS, 8020 Data Bank Survey; ALSWH, Australian Longitudinal Study on Women's Health; BDS, British Doctors Study; C, controlled covariates including age, sex, alcohol, and body mass index; CHS, Cardiovascular Health Study; CPS II, Cancer Prevention Study II; E, explanatory variable ascertainment; EPOCH-JAPAN, Evidences for Cardiovascular Prevention From Observational Cohorts in Japan; HIMS, Health in Men Study; HISB, Health Interview Survey of Barcelona; HPL, Human Population Laboratory's Alameda Country Study; NHEFS, NHANES I Epidemiological Follow-up Study; NA, not applicable; NR, not reported; O, outcome variable ascertainment; OAAS, Old Age Allowance Scheme; PAQUID, Personnes Agées QUID; SOF, Study of Osteoporotic Fractures, Quality Score; R, recruitment; USA, United States of America.

[a] Only data for people 60 years and older were used for this review.

[b] Lower age cutoff was not reported, but because study participants are in a retirement community, it was assumed that all participants were older than 60 years.

combined mortality ratios for currently smoking men and women. Those point estimates ranged from 1.4 to 3.0.

Results of meta-analyses are given in **Table 3**, **Figure 2** and eFigures 1, 2, and 3. In a meta-analysis of 15 studies reporting mortality of current smokers compared with never smokers, an RM of 1.83 (95% CI, 1.65-2.03) was found for both sexes and all age groups combined. In this analysis, age- and sex-specific estimates were first combined to a study-specific summary random-effects estimate for those studies that reported RM by age or sex only. In sex-specific meta-analyses, very similar results were obtained for men and women. Meta-analyses of age-specific estimates of RM yielded summary estimates of 1.94 (95% CI, 1.57-2.40), 1.86 (95% CI, 1.55-2.22), and 1.66 (95% CI, 1.30-2.12) for age groups 60 to 69 years, 70 to 79 years, and 80 years or older, respectively. Population-specific meta-analyses indicated lower RM for Asian populations in comparison to European, United States, and Australian populations. There were no indications of publication bias. Despite modest variation of RM estimates across studies, heterogeneity was ascertained in almost all meta-analyses. These high values were mainly driven by the study of Taylor et al,[31] the largest study by far, which showed relatively high estimates of RM. After excluding this study, no indications of heterogeneity persisted.

Table 2. Studies Reporting the Association of Smoking With All-Cause Mortality for Current Smokers and Former Smokers

				RM (95% CI) Compared With Never Smokers					
				Current Smokers			Former Smokers		
Source	Cohort Name	Length of Follow-up (Mean), y	Age Range, y	Male	Female	Both Sexes	Male	Female	Both Sexes
Jamrozik et al,[19] 2011	ALSWH, HIMS	10	≥70	2.28 (2.04-2.55)	2.22 (1.95-2.53)	. . .	1.40 (1.29-1.51)	1.36 (1.24-1.49)	. . .
Murakami et al,[35] 2011	EPOCH-JAPAN	10	60-69	1.96 (1.76-2.19)	1.70 (1.42-2.03)	. . .	1.55 (1.36-1.76)	1.64 (1.14-2.34)	. . .
			70-79	1.53 (1.42-1.65)	1.74 (1.54-1.96)	. . .	1.17 (1.08-1.27)	1.59 (1.28-1.98)	. . .
			80-89	1.30 (1.20-1.42)	1.39 (1.22-1.59)	. . .	1.07 (0.97-1.17)	1.16 (0.92-1.47)	. . .
Fujisawa et al,[24] 2008	8020 DBS	4	80	2.3 (1.0-5.2)	4.2 (1.9-9.5)	. . .	1.1 (0.5-2.4)	2.1 (0.6-7.0)	. . .
Lam et al,[28] 2007	NA	4 (4.1)	≥65	1.75 (1.53-2.00)	1.38 (1.14-1.68)	. . .	1.39 (1.23-1.56)	1.43 (1.25-1.64)	. . .
Simons et al,[30] 2005	Dubbo Study	15	≥60	1.84 (1.44-2.35)	1.63 (1.24-2.15)	. . .	1.34 (1.10-1.63)	1.25 (1.01-1.56)	. . .
Doll et al,[21] 2004	BDS	50	≥60	2.19[a]	. . .	. . .	1.31[a]	. . .	. . .
Lam et al,[20] 2002	NA	12	>60	1.50 (1.11-2.04)	. . .	. . .	1.22 (0.90-1.65)	. . .	. . .
Taylor et al,[31] 2002	CPS II	14	60-69	2.80 (2.76-2.84)	2.51 (2.48-2.54)	. . .	. . .	. . .	1.70 (1.40-2.05)
			70-79	2.52 (2.46-2.58)	2.46 (2.42-2.51)	. . .	. . .	. . .	1.67 (1.42-1.96)
			≥80	1.81 (1.75-1.88)	1.81 (1.76-1.86)	. . .	. . .	. . .	1.41 (1.27-1.56)
Tessier et al,[32] 2000	PAQUID	8	>65	. . .	. . .	1.7 (1.3-2.15)	. . .	. . .	1.3 (1.1-1.6)
Enstrom et al,[22] 1999	NHEFS	19	65-74	2.00 (1.57-2.55)	1.54 (1.17-2.03)	. . .	. . .	. . .	. . .
Ho et al,[25] 1999	OAAS	3	>70	1.4 (0.9-1.9)	1.6 (1.0-2.5)	. . .	1.2 (0.9-1.6)	1.7 (1.2-2.4)	. . .
Vogt et al,[33] 1996	SOF	6 (4.9)	65-69	. . .	2.5 (1.7-3.7)	. . .	. . .	1.5 (1.1-2.1)	. . .
			70-74	. . .	2.3 (1.6-3.3)	. . .	. . .	1.3 (0.9-1.8)	. . .
			≥75	. . .	1.4 (0.9-2.3)	. . .	. . .	1.1 (0.8-1.4)	. . .
Ruigomez et al,[34] 1995	HISB	5 (4.6)	65-97	. . .	. . .	3.0 (1.78-5.04)	. . .	. . .	1.86 (1.10-3.13)
Paganini-Hill and Hsu,[29] 1994	NA	5 (4.3)	>60	1.95 (1.66-2.30)	1.67 (1.46-1.92)	. . .	1.24 (1.13-1.37)	1.20 (1.09-1.33)	. . .
			60-74	2.09	2.08	. . .	. . .	. . .	. . .
			75-79	1.45	1.83	. . .	. . .	. . .	. . .
			80-84	2.09	1.55	. . .	. . .	. . .	. . .
			85-89	1.63	1.26	. . .	. . .	. . .	. . .
			≥90	0.50	1.59	. . .	. . .	. . .	
LaCroix et al,[27] 1991	NA	5 (2.3)	≥65	2.1 (1.7-2.7)	1.8 (1.4-2.4)	. . .	1.5 (1.2-1.9)	1.1 (0.8-1.5)	. . .
			65-69	2.3 (1.5-3.8)	2.4 (1.5-3.8)	. . .	1.5 (0.9-2.5)	0.8 (0.4-1.7)	. . .
			70-74	3.4 (2.1-5.5)	1.8 (1.2-2.7)	. . .	2.2 (1.4-3.4)	1.6 (1.0-2.4)	. . .
			≥75	1.3 (1.0-1.7)	1.2 (0.8-1.7)	. . .	1.1 (0.9-1.4)	0.9 (0.7-1.2)	. . .
Kaplan et al,[26] 1987	HPL	17	60-94	. . .	. . .	1.40 (1.15-1.71)	. . .	. . .	1.22 (0.99-1.50)
			60-69	. . .	. . .	1.46 (1.10-1.94)	. . .	. . .	1.57 (1.16-2.13)
			70-94	. . .	. . .	1.43 (1.08-1.89)	. . .	. . .	1.01 (0.76-1.33)

Abbreviations: NA, not applicable; RM, relative mortality. See Table 1 footnote for cohort name abbreviations.
[a] Results of men born in the 20th century.

FORMER SMOKERS

Estimates of RM for former smokers compared with never smokers are also given inTable 2. The point estimates of RM ranged from 1.1 to 2.2 for male former smokers and from 0.8 to 2.1 for female former smokers. Combined estimates for both sexes are in a comparable range (1.0-1.9).

Results of meta-analyses are given in Table 3, **Figure 3**, and eFigures 4, 5, and 6. A meta-analysis of 14 studies reporting hazard ratios for all-cause mortality for former smokers compared with never smokers showed an RM of 1.34 (95% CI, 1.28-1.40) for both sexes and all age groups combined. In this analysis, age- and sex-specific estimates were first combined to a study-specific summary random-effects estimate for those studies that reported RM by age or sex only. Sex-specific meta-analyses yielded very similar results for men and women. A decrease of RM was observed with age in age-specific meta-analyses, but an increased mortality of former smokers compared with never smokers persisted up to the highest ages. Population-specific meta-analyses showed very similar results for all populations. There were no indications of publication bias. Heterogeneity was found for meta-analyses of age groups 70 to 79 years and 80 years or older and for studies from US populations. After exclusion of the very large study by Taylor et al,[31] no indications of heterogeneity persisted.

Table 3. Results of Meta-analyses by Defined Subgroups and Study Characteristics

Subgroup Analysis	No. of Studies	RM Random Effect (Fixed Effect)	95% CI Random Effect (Fixed Effect)	Heterogeneity *P* Value[a]
Current smokers				
Overall	15	1.83 (1.92)	1.65-2.03 (1.84-2.01)	**<.001**
Male	11	1.90 (1.96)	1.72-2.10 (1.85-2.08)	**.009**
Female	11	1.80 (1.82)	1.59-2.04 (1.71-1.93)	**<.001**
Age, y				
60-69	7	1.94 (2.09)	1.57-2.40 (1.95-2.24)	**<.001**
70-79	7	1.86 (2.41)	1.55-2.22 (2.36-2.47)	**<.001**
≥80	4	1.66 (1.76)	1.30-2.12 (1.72-1.79)	**<.001**
Ethnicity				
Asian populations	5	1.60 (1.59)	1.40-1.82 (1.44-1.75)	.24
Australian populations	2	2.01 (2.15)	1.56-2.58 (1.99-2.32)	**.01**
European populations	2	2.15 (1.88)	1.24-3.72 (1.51-2.35)	.053
US populations	6	1.87 (1.94)	1.60-2.17 (1.80-2.08)	**.002**
Former smokers				
Overall	14	1.34 (1.34)	1.28-1.40 (1.29-1.38)	.16
Male	9	1.34 (1.34)	1.27-1.40 (1.27-1.40)	.56
Female	9	1.32 (1.31)	1.23-1.40 (1.24-1.38)	.26
Age, y				
60-69	6	1.54 (1.54)	1.41-1.68 (1.41-1.69)	.52
70-79	7	1.36 (1.38)	1.25-1.49 (1.32-1.45)	**.04**
≥80	4	1.27 (1.22)	1.04-1.56 (1.14-1.30)	**.001**
Ethnicity				
Asian populations	5	1.37 (1.37)	1.28-1.48 (1.28-1.48)	.85
Australian populations	2	1.37 (1.37)	1.29-1.45 (1.29-1.45)	.46
European populations	2	1.43 (1.37)	1.05-1.95 (1.12-1.66)	.21
US populations	5	1.31 (1.28)	1.17-1.47 (1.21-1.35)	**.03**
Current and former smokers combined				
Follow-up, y				
<10	8	1.85 (1.82)	1.63-2.09 (1.67-1.98)	.10
≥10	7	1.79 (1.97)	1.53-2.10 (1.86-2.07)	**<.001**
Sample size				
0-3000	7	1.78 (1.74)	1.53-2.06 (1.57-1.94)	.12
3001-10 000	3	1.77 (1.74)	1.37-2.28 (1.54-1.97)	**.02**
10 001-99 999	3	1.88 (2.07)	1.52-2.34 (1.93-2.22)	**.002**
≥100 000	2	1.90 (1.93)	1.32-2.74 (1.77-2.11)	**<.001**
Methodological				
QS <3	9	1.90 (1.98)	1.67-2.17 (1.89-2.09)	**<.001**
QS ≥3	6	1.68 (1.68)	1.49-1.91 (1.51-1.87)	.25

Abbreviations: QS, quality score; RM, relative mortality.
[a] Bold numbers indicate significant findings with $P < .05$.

CURRENT AND FORMER SMOKERS COMBINED

No major variation in summary estimates of RM was seen in subgroup meta-analyses by duration of follow-up, sample size, and study quality (Table 3). There were no indications of publication bias. Heterogeneity was found for almost all meta-analyses.

AMOUNT OF SMOKING

eTable 2 provides information on 10 studies reporting on the association of the amount of smoking and all-cause mortality. Seven of the included studies reported on the average number of cigarettes smoked per day in current smokers, and another 2 studies reported on numbers of cigarettes smoked per day among ever smokers (current and former smokers combined). With few exceptions, a clear dose-response relation of increasing mortality with increasing number of cigarettes was observed. In 3 studies, the impact of the amount of smoking on mortality was also investigated using the concept of pack-years, a measure for the amount of smoking over the full life-span.[36] Again, a clear dose-response with RM was observed.

TIME SINCE SMOKING CESSATION

To determine the benefit of smoking cessation at older age, mortality was evaluated in relation to age at smoking cessation and the number of years since smoking cessation of former smokers in 5 studies in which such information was available (eTable 3). With few exceptions, a clear dose-response relationship of decreasing RM with time since cessation was observed consistently.

In eTable 4 absolute mortality rates are presented for studies that either provided them directly or had valid information for calculation of those. A steep rise of absolute mortality rates with increasing age can be seen. Current smokers show highest absolute mortality rates in all studies. In studies with age-specific mortality rates, mortality differences between current smokers and never smokers varied by age groups, but the ranking of

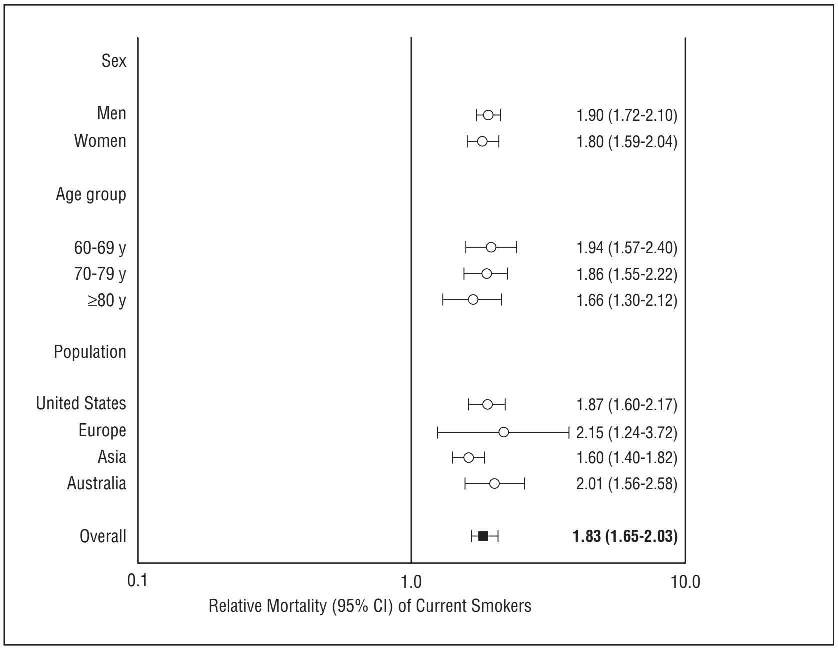

Figure 2. Results of meta-analyses of 15 studies on current smoking and all-cause mortality.

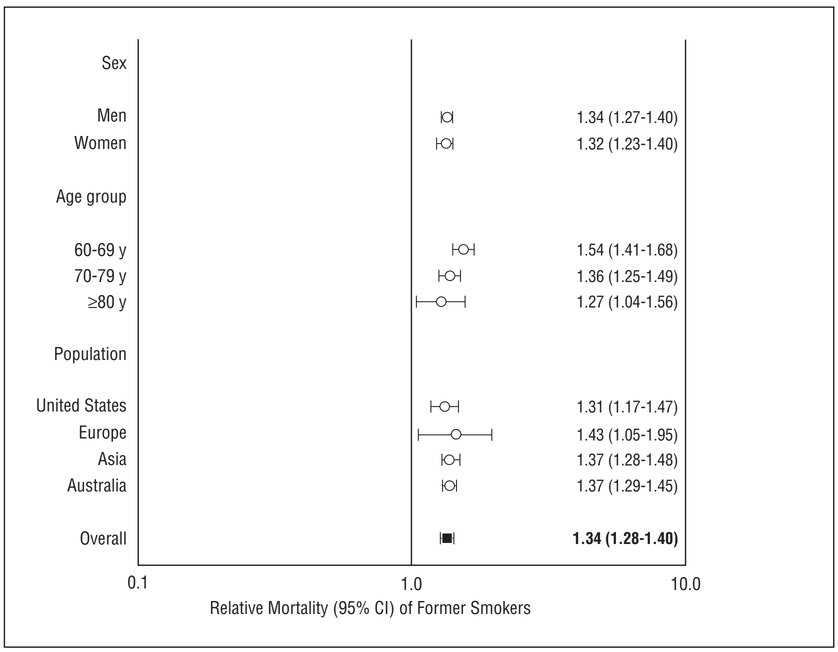

Figure 3. Results of meta-analyses of 14 studies on former smoking and all-cause mortality.

differences by age groups was not consistent across studies.

COMMENT

To our knowledge, this is the first systematic review and meta-analysis on the impact of smoking on all-cause mortality focusing on older people. Summarizing the results from 17 cohort studies, we observed an 83% increased mortality for current smokers and a 34% increased mortality for former smokers compared with never smokers. Relative mortality of former smokers decreased with time since cessation. A dose-response relationship of the amount of currently smoked cigarettes and premature death was consistently observed. Current smoking was significantly associated with increased mortality even in the oldest age groups, for both sexes and people from different geographical regions.

Smoking is an established risk factor for premature mortality.[3,37,38] However, most reviews and studies on smoking and mortality used broad age ranges, focused on middle-aged adults,[37,39,40] included only subjects with certain diseases,[41] or investigated disease-specific incidence or mortality.[3,42-44] For some causes of death, such as cancers of mouth, pharynx, and larynx, an up-to 10-fold increased mortality was reported for current smokers compared with never smokers.[3]

In this review and meta-analysis on the association of smoking and all-cause mortality at older age, current and former smokers showed an approximately 2-fold and 1.3-fold risk for mortality, respectively. Relative mortality for both current and former smokers slightly decreased with increasing age. One plausible explanation can be the "depletion of susceptibles" effect.[10,11] Smokers who are still alive at oldest age might be less likely to die from smoking because they showed a tolerance for harmful smoking effects in the past, while smokers who were more susceptible to harmful smoking effects have died already at younger age and dropped out of the population at risk. A second explanation for the decrease in smoking-related RM risk at older age may be the steep rise of absolute mortality above age 70 years among both smokers and nonsmokers that attenuates the magnitude of relative-effect estimates even in case of an increasing mortality difference on the absolute scale. The finding of a notable excessive mortality up to the oldest ages for both current and former smokers that persists despite these potential reasons for attenuation underlines the strength of smoking as a key risk factor for premature mortality also at older age.

Conversely, smoking cessation is an established preventive factor for premature mortality.[45] However, most studies have been carried out in middle-aged populations.[22,38] This review and meta-analysis demonstrates that the relative risk for death notably decreases with time since smoking cessation even at older age. However, it has to be noted that results are based on former smokers at baseline only, who already have survived some time after cessation. There is a lack of results on baseline current smokers who quit smoking during follow-up compared with those who continued to smoke. Also, analyses are based on former smokers compared with never smokers and not compared with current smokers. Furthermore, some former smokers might have quit smoking owing to ill health, and their mortality risk could be higher than the mortality risk of those who continued smoking. Nevertheless, these results strongly suggest that smoking cessation is effective for mortality reduction also at older age, a suggestion that should be corroborated by intervention studies, ideally with interventions specifically designed and developed for this target group. Although older smokers have been included in successful smoking cessation studies,[45,46] they were typically a minority in the study samples, and there is a lack of specific data on efficacy of smoking cessation programs among older smokers. Perspectives for successful smoking cessation appear to be particularly good after diagnoses of major smoking-related diseases, such as myocardial infarction, stroke, or cancer,[47] when people are personally confronted with the harmful effects of smoking. Preferably, however, smoking cessation should be achieved prior to manifestation of such serious diseases. If smoking cessation cannot be achieved, smoking less may attenuate the mortality risk. Dose-response relationships of the amount of daily smoked cigarettes with total mortality were remarkably constant across all studies.

In the interpretation of the results, several limitations should be kept in mind. Although we searched 3 databases, ie, Ovid MEDLINE, EMBASE, and ISI Web of Knowledge, and performed extensive checks for completeness by cross-referencing, it cannot be guaranteed that all relevant studies were found. In particular, we did not seek additional published or unpublished reports from experts. Other limitations are that the included studies had varying follow-up periods and age ranges. Furthermore, the age ranges did not always completely match with those chosen for the age-specific meta-analyses. Each study was adjusted for a different set of covariates, which might have contributed to heterogeneity in meta-analyses. In addition, important confounders were not always fully controlled for, which might have resulted in some overestimation of effects due to residual confounding. Furthermore, disparities in smoked products (eg, pipes, cigars, cigarillos) and the resulting impact on the outcome of interest could not be differentiated. Another limitation is the lack of information on duration of smoking or age at initiation in most of the included studies. Furthermore, we had to exclude 18 studies with approximately 100 000 participants that did not publish separate results for our target age group. Finally, given the observational nature of cohort studies, causal conclusions should be drawn with due caution. Nevertheless, causality of the associations is strongly supported by a number of important criteria, including the strength of the associations, consistency of results across studies, biological plausibility, and clear dose-response patterns.

Notwithstanding their limitations, the results presented in this systematic review demonstrate the need for effective smoking cessation programs because the hazardous effects of smoking persist even in oldest age. Even older people who smoked for a lifetime without negative health consequences should be encouraged and supported to quit smoking. Because of demographic changes and the need to work longer for sufficient retirement pensions (up to age 67 years in many developed countries), the individual and public health burden of smoking-related morbidity and mortality at older age will further increase substantially unless major progress is made in reducing the prevalence of smoking at all ages, including old age. Future research should include meta-analyses on the impact of smoking on cause-specific mortalities at older age, as well as evaluation of smoking cessation interventions specifically designed for older people and the impact of smoking cessation during follow-up on health-related outcomes.

In conclusion, smoking is a strong risk factor for premature mortality at older age. A dose-response relationship of the number of currently smoked cigarettes with mortality was observed in all age groups, even though the number of studies reporting such data are still rather limited. The longer the time since smoking cessation, the lower the RM of older former smokers; this fact calls for effective smoking cessation programs that are likely to have major preventive effects even for smokers aged 60 years and older.

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