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Evidence of resiliency among long-lived smokers

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Abstract

It is well established that cigarette use contributes to an extraordinary increase in the risk of mortality. Nevertheless, a small proportion of long-term chronic smokers manage to reach extreme old age, potentially suggesting that this sub-population may have distinct biological protection or repair mechanisms that allow it to better cope with the hazards of smoking. Using data from the Third National Health and Nutrition Examination Survey (NHANES III), on 5,423 adults aged 50 and over, we examined how among smokers and never-smokers mortality differs over the age range and whether smoking-related differences in markers of physiological functioning converge with increasing age. Our findings suggest that differences in mortality risk between current smokers and those who have never smoked are significantly less pronounced at older ages, and that smoking did not significantly contribute to subsequent mortality risk for individuals who had survived to at least age 80. Furthermore, among those who were less than 80 years of age, smokers had significantly elevated levels of inflammation in comparison to never-smokers, there were no such differences found between smokers and never-smokers at age eighty and above. Finally, we found a crossover effect for HDL cholesterol—with smokers showing worse levels at younger ages than never-smokers and better levels, although not significant, at older ages. Our study presents evidence that long-lived smokers may represent a distinct and biologically advantaged group, who are less susceptible to the negative side effects of smoking and perhaps other environmental insults.

1 Introduction

The drastic consequences of smoking for death and disease have been well-established by a significant body of research. The Cancer Prevention Study II found that the risk for all-cause mortality may be as much as 2.5 times as high for smokers relative to never-smokers (American Cancer Society Prospective Study 1992) has been pinpointed as one of the major contributions to the United States' surprisingly

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poor relative health status and low life expectancy (Crimmins et al. 2011; Preston and Stokes 2011), as well as a major factor in the mortality gender gap (Warner et al. 1999; Mokdad et al. 2005; Schroeder 2007; Pampel 2001). Smoking also causes significant physiological changes, and as a result, it is hypothesised that cigarette exposure may impact death and disease via its acceleration of the ageing and disease process (Valdes et al. 2005; Csiszar et al. 2009). However, not all people suffer the same negative effects of smoking; a small proportion of smokers manage to survive into extreme old age despite their prolonged exposure to carcinogens and other hazardous toxins—thus presenting an interesting paradox. As a result, these long-lived smokers may provide an informative 'natural experiment' for examining heterogeneity in resiliency to physiological stressors, which underlie ageing, and associated mortality and morbidity.

The rate of physiological deterioration with the ageing process is influenced by the balance between exposure to endogenous and exogenous stressors and counteracting mechanisms of maintenance and repair (Yin et al. 2005). As a result, the goals of optimal ageing and longevity could be reached in one of two ways: (1) through experiencing an ideal social, physical, emotional and/or behavioural environment; or (2) through resiliency to stressors, presumably resulting from genetic or epigenetic factors. Although numerous studies have added to our growing knowledge of optimal environments (Rajpathak et al. 2011; Martin et al. 2011; Seals et al. 2008), little focus has been placed on factors associated with innate resiliency. Using smoking as a proxy for a hazardous environment allows for the potential identification of individuals who, in the presence of an extreme physiological stressor, are able to survive by maintaining the structure and functioning of various physiological systems for significantly longer than expected.

Examining the force of mortality and mortality selection by age may provide a useful way of differentiating such individuals. In a relatively homogeneous population, mortality risks would be equal for all individuals of a particular age (Vaupel et al. 1985). However, in populations with heterogeneity, the hazard of mortality often varies between sub-groups of individuals resulting in variations in the likelihood of dying. If a difference in susceptibility to death exists between two sub-populations, as the frailer sub-population dies off, the hazard of the overall population will begin to more closely resemble the hazard of the robust sub-population. This is one of the explanations for the declining hazard rates observed at the tail-end of most population survival curves as well as the cross-overs between sub-groups (Le Cunff et al. 2013; Wing et al. 1985). For instance, at older ages, cross-over effects in mortality have been reported in the U.S. when comparing Non-Hispanic Blacks and Non-Hispanic Whites. It is hypothesised that black individuals who survive to extreme old ages probably make up a more robust sub-population when compared to blacks who died earlier, whereas the white population who survived may be less selective, given their environmental advantage.

The reasoning behind this is that people who survive hazardous environments are a more robust sub-population than those who did not survive the same environmental challenge. In subpopulations not exposed to hazardous environmental factors,

mortality rates will be lower overall and survivors will be made up of both robust and frail individuals. Sub-populations defined by smoking status provide an example of this process. Young populations of smokers, as well as young and old populations of never-smokers should be made up of both frail and robust individuals. On the other hand, older populations of smokers may be almost entirely made up of robust individuals.

One potential explanation for differences in the susceptibility to death among smokers is that certain individuals may be better equipped to cope with hazardous environmental conditions, such as smoking. As a result, resilient smokers should also display less physiological dysregulation and have biomarker risk levels that reflect this resistance to environmental effects. For example, C-reactive protein (CRP) and white blood cell count (WBC) are often used as markers of inflammatory or immune response, and have been shown to be elevated in smokers (Santos et al. 2004; Gan et al. 2005; Flouris et al. 2012) while HDL cholesterol, which is presumed to be physiologically beneficial, is often lowered as a result of chronic cigarette exposure (Erhardt et al. 2009). However, resilient smokers may have mechanisms that allow them to offset these changes, thus enabling them to survive.

Using data from the third National Health and Nutrition Examination Survey (NHANES III), this study aims to examine: (1) how smoking attributable mortality varies over the age range, and (2) whether smoking-related differences in physiological markers converge with increasing age. We hypothesie that the increased mortality risk associated with smoking will be less pronounced for those already surviving to old age; and that differences in physiological markers, by smoking status, will be apparent at younger ages; however, smokers and never-smokers will show different age trends in these markers indicating a convergence in physiological status at older ages.

2 Materials and methods

2.1 Study population

The study population was made up of subjects from the third National Health and Nutrition Examination Survey (NHANES III), a nationally representative, cross-sectional study conducted by the National Center for Health Statistics (NCHS) between 1988 and 1994. Data for NHANES III were collected during at-home interviews, and physician examinations took place in a Mobile Examination Center (MEC). Respondents eligible for this analysis included persons aged 50 and over who were either current smokers or had never smoked (N = 5,505); among these 98.5% were included in our analytic sample (n = 5,423) for our mortality analyses. Excluded persons were those with missing demographic data (n = 75), or missing mortality follow-up (n = 7). When analysing biomarker data, an additional 1,042 subjects were excluded who had missing data for CRP, WBC, or high-density lipoprotein (HDL).

Subjects with missing biomarker data tended to be slightly older, were less likely to be white and were more likely to die. Further details on recruitment, procedures and study design are available through the Centers for Disease Control and Prevention (U.S. Department of Health and Human 2001).

2.2 Smoking status

Given that the theoretical framework for this paper relies on using smoking as a proxy for a hazardous environment, only the two extremes—never-smokers and current smokers—are considered. Those who reported smoking in the past were excluded, as quitting smoking may over time reverse some of the negative effects of smoking (Pirie et al. 2012). Never-smokers are respondents who had smoked fewer than one hundred cigarettes in their lifetime. In addition to smoking status, for current smokers, years of cigarette use were calculated as the difference between the age at which the subject started smoking and his/her current age. Reports of periods of nonsmoking are also collected and any period of time in which subjects reported cessation was subtracted.

2.3 Mortality

Mortality follow-up was available for all participants, using linked mortality data from the National Death Index through 2006 (U.S. Department of Health and Human 2001). During analysis, violent, accidental and HIV deaths were censored. Person months of follow-up were also provided by NHANES and then converted to years by dividing by twelve. Because participants took part in NHANES III at different points in time between 1988 and 1994, participants who were alive in 2006 were followed for 12 to 18 years. Time of participation in NHANES III was random and should therefore not confound results.

2.4 Physiological and health characteristics

In order to examine links between smoking exposure and physiological resiliency, three indicators of health and physiological status, shown in prior research to be affected by cigarette exposure, are examined CRP, HDL, WBC (Santos et al. 2004; Gan et al. 2005; Flouris et al. 2012; Erhardt et al. 2009). CRP was log-transformed, given that it is not normally distributed. Neither HDL nor WBC warranted transformation.

2.5 Potential confounders

Age, race/ethnicity, education, sex and alcohol consumption were self-reported. Age was top-coded at 90 in the data set by NHANES to protect confidentiality of respondents. In most of the analysis, persons were classified into four age groups (50–59 years, 60–69 years, 70–79 years and 80+). Dummy variables were created to classify subjects into three race/ethnicity categories: non-Hispanic whites, non-Hispanic blacks and Hispanics, most of whom are Mexican Americans. In analyses, Non-Hispanic whites are used as the reference category. Education was based on years of schooling and used as a continuous variable in analysis. Sex was indicated with a dichotomous variable, with females coded as 1 and males as 0. Four categories were created for alcohol consumption—never drinkers, light/moderate (1–34 drinks per week), heavy drinkers (35 or more alcoholic beverages per week) and those with missing values. Finally, BMI (calculated as height in metres divided by weight in kilogrammes squared) was also included in the analysis using five categories—underweight (<18.5), normal (18.5–24.9), overweight (25–29.9), obese (30+) and missing. All of these variables were included as controls because they are related to both smoking status and health outcomes.

2.6 Statistical analysis

Proportional hazard models (Gompertz distribution), using mortality as the outcome, were run for eight smoking-by-age groups, indicated by eight dummy variables. Classification was based on four age groups (50–59 years, 60–69 years, 70–79 years and 80+) and two smoking groups (never-smokers and current smokers), with never-smokers aged 50–59 used as the reference group. The results of this model were then used to calculate predicted ten-year mortality probabilities for each of the eight groups. Next, age-stratified hazard models were used to directly compare the mortality of smokers and never-smokers at each age. Finally, using results from ordinary least squares regression models, we calculated the predicted biomarker levels for the eight smoking-by-age groups. All analyses were run, using sample weights, accounting for complex sample design and controlling for potential confounders including race/ethnicity, education, sex and BMI.

3 Results

3.1 Sample description

As shown in Table 1, 64 per cent of subjects were female. Respondents are approximately equally distributed across their 50s, 60s and 70 and older. Non-Hispanic whites made up about 84 per cent of the sample, while non-Hispanic blacks and Hispanics made up 10 per cent and 6 per cent, respectively. Mean years

Table 1:
Sample characteristics

Characteristic	Value
Age category (%)	
50–59	37.2
60–69	31.2
70–79	20.6
80+	11.0
Race/ethnicity (%)	
Non-Hispanic white	83.6
Non-Hispanic black	10.2
Hispanic	6.2
Years of education, mean (SD)	11.3 (.13)
Female (%)	64.0
BMI (%)	
Underweight	2.6
Normal	31.3
Overweight	31.7
Obese	22.3
Missing	12.3
Alcohol consumption	
Never drinker	19.9
Light/moderate	60.5
Heavy	0.9
Missing	18.8
Current smoker (%)	31.4
Log CRP (mg/l), mean (SD)	1.23 (0.02)
WBC ($\times 10^3$ cells/μl), mean (SD)	7.2 (0.06)
HDL (mg/dl), mean (SD)	52.1 (0.44)
Mortality (% died)	38.8
Person-years, total	65,653

of education was 11.3 years. Subjects with normal or overweight BMI made up approximately 31 per cent of the sample each. Additionally, 22 per cent were obese, 2.6 per cent were underweight and 12 per cent did not have measured BMI. About one-third of subjects were current smokers (31.4%). Mean log CRP, WBC and HDL for the sample were 1.23 mg/l, 7.2×10^3 cells/μl and 52.1 mg/dl, respectively. Finally, the follow-up period covered 65,653 total person-years, with about 40 per cent of subjects dying between baseline and follow-up.

Table 2 lists smoking and socio-demographic characteristics by age group. The proportion of current smokers was highest for those aged 50–59 (43%) and decreased

Table 2:
Demographic characteristics by age and smoking status

	50–59 years		60–69 years		70–79 years		80+ years	
	Never smokers	Current smokers	Never smokers	Current smokers	Never smokers	Current smokers	Never smokers	Current smokers
(%)	57.4	42.6	64.8	35.2	77.7	22.3	92.1	7.9
Female (%)	71.3	44.7	67.8	52.5	77.6	52.8	79.4	58.6
Race/ethnicity (%)								
Non-Hispanic white	81.6	81.0	82.7	82.6	87.0	86.0	88.2	86.7
Non-Hispanic black	9.5	13.5	9.1	11.0	9.5	10.1	9.0	8.2
Hispanic	8.9	5.5	8.2	6.4	3.5	3.9	2.8	5.1
Years of education (μ)	12.3	11.5	11.5	10.8	10.6	10.2	10.0	9.8
BMI (%)								
Underweight	0.5	4.0	0.8	5.8	1.7	4.6	4.3	12.1
Normal	25.6	34.2	27.7	34.3	31.7	43.7	34.6	36.5
Overweight	33.4	29.1	35.9	29.0	32.3	23.1	30.4	26.7
Obese	31.2	21.1	27.3	16.6	21.2	10.5	10.5	2.5
Missing	9.3	11.6	8.5	14.4	13.2	18.2	20.3	22.2
Alcohol consumption								
Never drinker	23.4	5.8	24.2	6.9	31.5	6.1	29.3	4.6
Light/moderate	64.6	75.5	61.4	69.1	49.6	63.7	33.0	57.2
Heavy	0.05	2.3	0.7	2.9	0.2	0.5	0.0	0.7
Missing	12.0	16.4	13.7	21.1	18.7	29.7	37.7	37.5
Died (%)	10.0	29.5	24.6	59.5	59.7	78.9	90.1	86.9

for each subsequent age group (35% for subjects 60–69 years old, 22% for subjects 70–79 years old and 8% for subjects 80 years and older). Overall, smokers at every age were more likely to be male, had lower BMI compared to never-smokers. On the other hand, younger smokers were more likely to be black, while older smokers tended to be white. Based on the smoking-epidemic model, we know that there have been sex, race/ethnic and SES differences in both smoking habits and in mortality risks (Giovino 2002). However, given that historical cohort smoking rates by race/ethnicity and education are not available in NHANES, we cannot determine whether the socio-demographic differences we found in smoking by age are due to cohort variations in smoking patterns or survival effects.

3.2 Effects of smoking on mortality by age

Results from the proportional hazard model for the association between mortality and age by smoking groups are shown in Table 3. As expected, mortality risk was associated with both age and smoking status, with all groups having significantly higher mortality than 50–59 year old never-smokers. From these results, predicted ten-year mortality probabilities were calculated (Table 4). For never-smokers aged 50–59, the predicted probability of mortality over ten years was 7.1 per cent, while

Table 3:
Association between smoking and mortality, by age

	Hazard ratio	95% Confidence interval
Female	0.76	0.67–0.86
Education	0.98	0.96–0.99
Black	1.22	1.07–1.38
Hispanic	0.83	0.69–0.99
White	*(reference)*	
BMI (%)		
Underweight	1.97	1.41–2.77
Normal	*(reference)*	
Overweight	1.00	0.87–1.15
Obese	1.22	1.07–1.41
Missing	0.94	0.74–1.19
Alcohol consumption		
Never drinker	*(reference)*	
Light/moderate	0.94	0.83–1.08
Heavy	2.11	1.28–3.48
Missing	1.42	1.20–1.67
50–59		
Never smoker	*(reference)*	
Current smoker	2.81	2.12–3.72
60–69		
Never smoker	2.60	1.86–3.63
Current smoker	7.37	5.31–10.23
70–79		
Never smoker	8.43	6.24–11.40
Current smoker	14.19	9.73–20.69
80+		
Never smoker	24.87	18.14–34.10
Current smoker	25.38	17.37–37.09

for smokers of the same age it was 18.7 per cent. A similar difference was seen for respondents aged 60–69, with a 17.4 per cent predicted mortality probability for never-smokers, compared to almost three times as high (41.9%) for smokers. The difference in predicted ten-year mortality decreased slightly for those aged 70–79 (46.3% for never-smokers, compared to 64.8% for smokers). Finally, for those 80+, there was very little difference between the predicted ten-year mortality of smokers (84.0%) and never-smokers (84.6%).

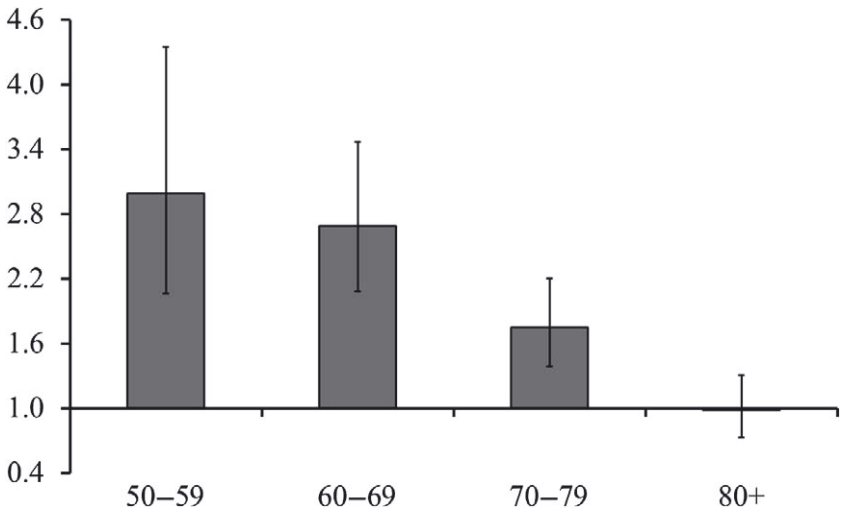
Smokers and never-smokers were also compared more directly using age-stratified hazard models of mortality over the full 12-18 year follow-up which again showed

Table 4:
Predicted 10-year mortality by smoking status and age

	Never-smokers	Current smokers
50–59 years	7.1%	18.7%
60–69 years	17.4%	41.9%
70–79 years	46.3%	64.8%
80+ years	84.0%	84.6%

Note: Adjusted for sex, race/ethnicity, education, BMI and alcohol consumption.

Figure 1:
Association between smoking and mortality, within age, based on 4 age-stratified models



Adjusted for sex, race/ethnicity, education, BMI, and alcohol consumption

that the effect of smoking appeared to decline with age (Figure 1). For subjects in their fifties, current smokers were almost three times more likely to die than never-smokers (HR: 2.99; 95%CI: 2.05–4.35). However, for subjects in their sixties, smokers were two and a half times more likely to die (HR: 2.69; 95%CI: 2.08–3.47), and for those in their seventies, smokers were only 75% more likely to die (HR: 1.75; 95%CI: 1.39–2.20). Finally, for subjects ages eighty and above, current smokers were no longer at a significantly higher risk of death relative to never-smokers (HR: 0.98; 95%CI: 0.73–1.31).

Table 5:
Predicted biomarker values, by smoking status and age

	Predicted value (standard error)								
	Log CRP (mg/l)			WBC ($\times 10^3$ cells/μl)			HDL (mg/dl)		
	Never smokers	Current smokers	p-value	Never smokers	Current smokers	p-value	Never smokers	Current smokers	p-value
50–59 years	1.12 (.03)	1.32 (.05)	.002	6.47 (.09)	8.57 (.14)	<.001	53.7 (.88)	49.7 (1.21)	.006
60–69 years	1.16 (.03)	1.35 (.05)	<.001	6.52 (.09)	8.20 (.14)	< .001	53.0 (.78)	50.5 (.95)	.042
70–79 years	1.20 (.03)	1.38 (.09)	.050	6.88 (.09)	8.12 (.23)	<.001	51.7 (.54)	51.3 (1.24)	.781
80+ years	1.26 (.03)	1.34 (.13)	.559	7.31 (.11)	7.92 (.27)	.038	52.3 (.73)	53.1 (1.96)	.712

Note: Adjusted for sex, race/ethnicity, education, BMI and alcohol consumption.

3.3 Effects of smoking on health by age

Independent regression models with biomarker measures (log CRP, WBC, HDL) serving as the dependent variable were used to examine the health effects of smoking by age. From these models, predicted biomarker values were calculated for each of the eight smoking age groups (Table 5). As the age of the groups increased, the differences between predicted biomarker levels of smokers and never-smokers tended to converge or cross over. For instance, the difference in predicted log CRP between smokers and never-smokers aged 50–59 was 0.20 mg/l, with smokers having a predicted mean of 1.32 mg/l and never-smokers having a predicted mean of 1.12 mg/l. However, the difference decreased slightly (0.19 mg/l) when comparing those aged 60–69, and then again (0.18 mg/l) for those aged 70–79. Finally, when comparing smokers and never-smokers aged 80 and above the difference was only 0.08 mg/l which was not statistically significant ($p = .559$).

Similar patterns were found when looking at differences in WBC. For subjects in their fifties, smokers' predicted WBC levels (8.57×10^3 cells/μl) were 2.10×10^3 cells/μl higher than the predicted levels for never-smokers (6.47×10^3 cells/μl). However, for those aged 60–69 the difference decreased to 1.68×10^3 cells/μl, while for those aged 70–79 the difference decreased again to 1.24×10^3 cells/μl. Finally, for those aged 80 and older smokers' predicted WBC levels (7.92×10^3 cells/μl) were only 0.61×10^3 cells/μl higher than the predicted levels for never-smokers (7.31×10^3 cells/μl), although the difference was still statistically significant (.038).

Finally, when examining trends in HDL by smoking status and age, we found a cross-over effect with age. At younger ages, never-smokers had higher HDL than smokers, while at older ages current smokers had higher HDL than never-smokers. Predicted HDL levels for subjects aged 50–59 were 53.7 mg/dl for never-smokers and 49.7 mg/dl for current smokers; however, for subjects in their sixties, predicted HDL was 53.0 mg/dl for never-smokers, increasing to 50.5 mg/dl for current smokers. For subjects in their seventies, smokers were found to have statistically similar ($p = .781$)

predicted HDL (51.3 mg/dl) to never-smokers (51.7 mg/dl) and finally, for subjects aged eighty and over the predicted HDL of current smokers reached 53.1 mg/dl, while the predicted HDL of never-smokers was 52.3 mg/dl.

4 Discussion

Our findings suggest that differences in mortality risk between current smokers and those who have never smoked are significantly less pronounced at older ages and that smoking did not significantly contribute to mortality risk for individuals who survived to age 80 or older. This phenomenon could be due to variations in susceptibility to physiological stressors within the smoking population—as age increases, the number of smokers in the population decreases, due to the death of frailer individuals. As a result, the subpopulation of extremely long-lived smokers may represent a discrete group of resilient individuals who possess innate characteristics that make them distinct from others in the general population. One such feature that has been suggested is that individuals who survive to the extreme tail end of life expectancy may have higher energy allocation for physiological processes involved in defense and repair mechanisms (Barbieri et al. 2003), and as a result, the negative effects of smoking may be less detrimental for them. Within our sample we found that long-lived smokers did not appear to have detriments in markers of health which have been shown to be affected by cigarette exposure and which were evident in our younger smoker populations. Although younger smokers had significantly elevated levels of inflammation and immune activation in comparison to same-aged never-smokers, long-lived smokers did not appear to differ from never-smokers and even had lower levels than other smokers who were twenty to thirty years younger. Furthermore, we found a crossover for HDL cholesterol when comparing smokers and never-smokers by age—with smokers showing worse health at younger ages and better health at older ages. Finally, both CRP and WBC appeared not to increase with age for smokers, as they did for never-smokers. However, if data for earlier ages had been available for smokers who survive to age eighty, they might have been significantly healthier, with lower levels of inflammation compared to the levels in the general smoking population at ages in the fifties, sixties and seventies. Nevertheless, because frailer smokers make up a larger proportion of the smoking population, the stability of CRP and WBC across the age range may be due to the stronger influence of frailer smokers in increasing the group's predicted values at younger ages. Given the likelihood that those with highest levels of inflammation will die first, they are not contributing to the predicted values at later ages.

The finding that smoking-associated reductions in health were not as pronounced among the oldest-old, in comparison to younger cohorts, is of particular interest given that older subjects had significantly more years of cigarette exposure. One would expect that in a homogenous population, as years of smoking increased, disparities in health between never-smokers and smokers should also increase. However, if

survival is not random, the examination of long-lived smokers presents us with the opportunity to identify characteristics that are important to resiliency.

There are certain limitations in the present study that should be acknowledged. First, the use of cross-sectional physiological and health data prevents us from examining changes or trajectories in these characteristics. Second, the smoking history data available in NHANES did not allow us to calculate pack-years or estimate the magnitude of daily cigarette exposure. Third, top-coding of the age range, at 90, may interfere with our ability to compare late-life survivor groups on the basis of exact chronological age. Fourth, although very few respondents were excluded from our mortality analysis due to missing data, biomarker data were not available for 1,042 persons. However, when we compared mortality models excluding these subjects to models which included the full analytic sample, results were not significantly different. This suggests that if biomarker data were available for all subjects, our findings would remain unchanged. Finally, age cohort and gender patterns in smoking history differ markedly and hinder our ability to interpret differences between age groups or make estimates or predictions of past or future mortality rates.

As a next step, longitudinal studies of long-lived smokers will be useful in facilitating our understanding of the ageing process, resiliency and longevity. While the current study showed that at older ages mortality risks and health profiles of smokers were similar to never-smokers, it needs to be determined whether this sub-population of smokers were also similar to never-smokers at earlier ages or whether they experience different trajectories with age. Furthermore, they may help determine whether smokers with the potential to live to age ninety and above can be detected in middle-age. One way in which this may be possible is by comparing the genetic profiles of long-lived smokers to determine whether hereditary factors such as single nucleotide polymorphisms (SNPs), gene clusters or sub-networks, or gene expression due to differences in methylation patterns of histone modifications are associated with extreme longevity among smoking populations.

Our study is novel in defining a population subgroup that may have low innate frailty. It presents evidence that long-lived smokers may represent a distinct and biologically advantaged group, who are less susceptible to the negative side effects of smoking. Given what we know about the effects of smoking on ageing and mortality, the investigation of long-lived smokers provides a natural experiment to examine the ways in which deterministic and stochastic processes interact to impact the rate of ageing and the susceptibility to death and disease. In moving forward, more research is needed to facilitate our understanding of environmental and genetic mechanisms that influence the degree of degradation with age and to enhance our understanding of factors which influence resiliency and its effect on longevity.

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