ANNALS of Clinical and Translational Neurology
Open Access
ANA American Neurological Association since 1875

RESEARCH ARTICLE

Effect of smoking cessation on the risk of dementia: a longitudinal study

Daein Choi[1,2], Seulggie Choi[1] & Sang Min Park[1,3]

[1]Department of Biomedical Sciences, Seoul National University College of Medicine, Seoul, Korea
[2]Pyeongchang Bongpyeong Public Health Center, Pyeongchang, Korea
[3]Department of Family Medicine, Seoul National University Hospital, Seoul, Korea

Correspondence
Sang Min Park, Department of Family Medicine and Biomedical Sciences, College of Medicine, Seoul National University, 101 Daehak-ro, Jongno-gu, Seoul, Korea. Tel: +82-2-2072-3331; Fax: +82-2-766-3276; E-mail: smpark.snuh@gmail.com

Funding Information
This study was supported by a research fund from the Seoul National University Hospital (Grant No. 04-2018-0370).

Received: 10 May 2018; Revised: 12 July 2018; Accepted: 30 July 2018

doi: 10.1002/acn3.633

Daein Choi and Seulggie Choi are equal contributors

Abstract

Objective: To determine the risk of developing dementia in relation to duration of smoking cessation by using a nationwide health claims database. **Methods**: This cohort study included 46,140 men aged 60 years or older from Korean National Health Insurance System – National Health Screening Cohort, a population-based national health screening program from 2002 to 2013. The changes in smoking habit from a questionnaire during the first (2002 and 2003) and second (2004 and 2005) health examination periods, participants were divided into continual smokers, short-term (less than 4 years) quitters, long-term (4 years or more) quitters, and never smokers. Participants were followed-up for 8 years from January 1, 2006 for the development of overall dementia, Alzheimer's disease, and vascular dementia. **Results**: Compared to continual smokers, long-term quitters and never smokers had decreased risk of overall dementia (hazard ratio, HR 0.86 95% CI, confidence interval 0.75–0.99 and HR: 0.81; 95% CI: 0.71–0.91, respectively). Never smokers had decreased risk of Alzheimer's disease (HR: 0.82; 95% CI: 0.70–0.96) compared to continual smokers. Finally, both long-term quitters (HR: 0.68; 95% CI: 0.48–0.96) and never smokers (HR: 0.71; 95% CI: 0.54–0.95) had decreased risk of vascular dementia compared to continual smokers. **Interpretation**: Smoking was associated with increased risk of dementia. Smokers who quit for a prolonged period of time may benefit from reduced risk of dementia. Therefore, smokers should be encouraged to quit in order to reduce the risk of developing dementia, especially in the elderly population who are already at risk.

Introduction

Cigarette smoking is one of the most important causes of preventable death in the world.[1] At least 14 million cases of serious morbidities are known to attributed by the smoking in the United States,[2] including chronic obstructive pulmonary disease, cardiovascular disease,[3] stroke,[4] and cancer.[5] It is also known that 480,000 deaths are attributable to smoking in the United States alone.[6] However, relatively less is known on the risk of smoking on neurodegenerative disease. Interestingly, early studies funded by the tobacco company have suggested a possible beneficial role of smoking in cognitive function due to the effects of nicotine.[7] Furthermore, several early case–control studies funded by the tobacco industry have reported a preventive effect of smoking on Alzheimer's disease.[8–10] However, since then, a number of cohort studies have shown that smoking was associated with increased risk of dementia.[11] The most recent longitudinal study with a long-term follow-up duration[12] and meta-analysis[13] have also reported smoking as a risk factor for dementia.

As there appears to be a consensus on the risk increasing effect of smoking on dementia,[14,15] it is important to address whether or not smoking habit change, namely smoking cessation, alters the risk of developing dementia next. However, only a few previous studies investigating the association of smoking on dementia evaluated the effect of smoking cessation.[12,13,16] Numerous studies have compared current, former and never smokers, but few if

© 2018 The Authors. *Annals of Clinical and Translational Neurology* published by Wiley Periodicals, Inc on behalf of American Neurological Association. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

any studies have examined duration of smoking cessation. Finally, most studies investigating the effect of smoking on dementia were conducted with Western populations,[13,17] with relatively few studies conducted in Asia. As there are differences in prevalence[18] and type distribution[19] of dementia among Western and Asian populations, the effect of smoking on the risk of dementia might also differ between ethnic groups. Therefore, we aimed to investigate the effect of smoking habit change on the risk of developing dementia in this population-based study using the Korean National Health Insurance System – National Health Screening Cohort (NHIS-HealS).

Methods

Study population

The National Health Insurance Service (NHIS) of Korea provides mandatory health insurance for Korean citizens since the National Health Insurance Act in 1989.[20,21] With an enrollment rate of 97%, the NHIS provides biannual health examinations for all enrollees who turn 40 years old. Using data from the health examinations, the NHIS constructs and provides datasets by a simple random sampling method. The constructed cohort, NHIS-HealS, provides information on sociodemographics, hospital use, examinations, pharmacy visits and other data, which can be used for research purposes. The data used in this study is directly available via the NHIS database registration system. A number of previous studies have used this NHIS database for epidemiological studies, and its validity has been described in detail elsewhere.[22,23]

A total of 51,849 men aged 60 years or older who participated in health examinations between the first (2002 to 2003) and second (2004 to 2005) periods were recruited. Among them, those without information on smoking habit (4744 participants) were excluded. Furthermore, 362 participants who died and 603 participants who were diagnosed with dementia before the index date of January 1, 2006 were excluded. Women were excluded due to extremely low smoking rates in Korea. Ultimately, the final study population consisted of 46,140 participants.

Smoking habit change

The smoking status of the study participants were assessed by a questionnaire during the health examination. Based on the answers to the questionnaire from both the first and second health examinations, the participants were divided into continual smokers, short-term quitters (quitting duration of less than 4 years), long-term quitters (quitting duration of 4 years or longer), and never smokers.[24] Continual smokers were participants who were current smokers during the first and second health examinations. Short-term quitters were defined was those who were current smokers during the first health examination but quitters during the second health examination. Long-term quitters were those who were quitters for both the first and second health examinations. Finally, never smokers were defined as those who were never smokers for both the first and second health examinations.

Assessment of dementia

Hospital use records, including hospitalizations and outpatient visits were used to identify new cases of dementia. Dementia was defined using the codes from the Tenth Revision of International Classification of Diseases (ICD-10) from the World Health Organization. Participants who were hospitalized at least once or visited the outpatient department at least three times with an ICD-10 code pertaining to dementia (F00, F01, F02, F03, G30, G31, and G32) were considered to have developed dementia.[25] Since it is required to fulfill Korean National Health Insurance reimbursement criteria to receive payment in Korea, physicians need to document the evidence for cognitive dysfunction according to strict criteria to submit a valid claim for: (1) Minimal Mental State Examination score ≤ 26 and (2) either a Clinical Dementia Rating ≥ 1 or a Global Deterioration Scale score ≥ 3.[26,27] Among dementia patients, we further categorized patients with Alzheimer's disease (F00 or G30) and vascular dementia (F01). The earliest date of hospital use with an ICD-10 code pertaining to dementia was considered the date of diagnosis for dementia patients.

Covariates

Information on potential confounding covariates was extracted from 2005 and missing values were categorized into a separate group for each covariates. The covariates considered were age, body mass index (<18.5, 18.5–22.9, 23.0–24.9, and ≥25.0 kg/m^2), blood pressure (<120/80, 120/80-139/89, and ≥140/90 mmHg), fasting serum glucose (<100.0, 100.0–125.9, ≥126.0 mg/dL, and missing), total cholesterol (<200.0, 200.0–239.9, ≥240.0 mg/dL, and missing), physical activity (none, 1–2, 3–4, 5–7 times per week, and missing), drinking habit (none, 1–2, ≥3 drinks per week, and missing), and household income (lower half and upper half). Household income was categorized according to each patient's insurance premium status. Finally, Charlson Comorbidity Index (CCI, 0, 1–2, and ≥3), another potential confounding covariate, was extracted from 2002 to 2005. The algorithm for CCI calculation by ICD-10 codes was adapted from a previous study.[28]

 © 2018 The Authors. *Annals of Clinical and Translational Neurology* published by Wiley Periodicals, Inc on behalf of American Neurological Association.

Statistical analysis

All participants were followed-up starting January 1, 2006 and ended at the date of dementia diagnosis, date of death, or December 31, 2013, whichever came first. Taking into account the fact that dementia is a chronic, slowly developing disorder while also trying to minimize the possibility of reverse-causality, we applied a washout-period of 5 years, in which we did not consider new cases of dementia for those diagnosed from January 1, 2006 to December 31, 2010. The risk of developing dementia due to smoking habit change was assessed by calculating the hazard ratios (HRs) and 95% confidence intervals (95% CI) using Cox proportional hazards regression analyses. In all analyses, the continual smoker group was used as the reference group, in which the HR and 95% CI was calculated for the short-term quitter, long-term quitter, and never smoker groups.

Multivariable-adjusted (adjusted for age, household income, physical activity, drinking habit, body mass index, change in body mass index, blood pressure, fasting serum glucose, total cholesterol, and Charlson Comorbidity Index) analyses were conducted for the risk of overall dementia, Alzheimer's disease, and vascular dementia. Furthermore, *P* for trend values were calculated in the order of continual smoker, short-term quitter, long-term quitter, and never smoker, which pertains to decreasing amounts of total tobacco exposure. Stratified, multivariate-adjusted analyses according to subgroups divided by covariates were conducted. Sensitivity analysis was conducted by changing the washout period of dementia cases by 6 years and 7 years. Finally, the association between smoking habit change and dementia among women was determined.

Statistical significance was defined as a p value of less than 0.05 in a two-sided manner. Statistical software SAS 9.3 (SAS Institute, Cary, NC) and STATA 13.0 (StataCorp LP, College Station, TX) were used for data collection and statistical analyses, respectively.

IRB approval

This study was approved by the Seoul National University Hospital Institutional Review Board (IRB number: X-1701/378-902). The IRB waived the requirement for informed consent from the study participants as the NHIS-HealS database is anonymized according to strict confidentiality guidelines.

Results

A total of 46,140 participants were followed up for a mean of 7.11 years, with 328,274 person-years. Table 1 depicts the descriptive characteristics of the study population. The number continual smokers, short-term quitters, long-term quitters, and never smokers were 12,672, 4,175, 9,268, and 20,025 men, respectively. The majority of participants were aged between 60 and 69 years, with the group containing the highest proportion of men aged between 60 and 69 years being continual smokers. Furthermore, compared to other groups, continual smokers tended to have lower body mass index, lower blood pressure, exercise less, drink alcohol more, and have lower household income.

Table 2 shows the effect of smoking habit change on the risk of dementia. A total of 1644 participants were diagnosed with dementia during the follow-up duration. Compared to continual smokers, long-term quitters and never smokers had decreased risk of overall dementia (HR: 0.86; 95% CI: 0.75–0.99 and HR: 0.81; 95% CI: 0.71–0.91, respectively). Furthermore, as the total amount of tobacco exposed decreased in order of continual smokers, short-term quitters, long-term quitters, and never smokers, the risk of developing overall dementia significantly decreased (*P* for trend 0.001). Similarly, never smokers had decreased risk of developing Alzheimer's disease (HR 0.82 95% CI 0.70–0.96) compared to continual smokers. Finally, long-term quitters and never smokers also had decreased risk of vascular dementia (HR: 0.68; 95% CI: 0.48–0.96, HR: 0.71; 95% CI: 0.54–0.95, respectively) compared to continual smokers.

Table 3 shows stratified, multivariate-adjusted analyses according to subgroups divided by covariates for the risk of overall dementia. Never smokers tended to have decreased risk of overall dementia compared to continual smokers, albeit with attenuated results, most likely due to the decreased number of cases upon dividing the study population by subgroups. Similarly, compared to continual smokers, long-term quitters tended to have decreased risk of overall dementia, although most values were not statistically significant.

The results of the sensitivity analyses by changing the duration of washout period to 6 years and 7 years are shown in Table S1. There was a tendency toward decreased risk of overall dementia, Alzheimer's disease, and vascular dementia for long-term quitters and never smokers, albeit with statistical attenuation due to the decreased number of events. Similarly, there was a tendency toward reduced risk of dementia according to decreasing amounts of tobacco exposed after washout periods of 6 and 7 years. In addition, the effect of smoking habit change on the risk of dementia with never smoker being the reference group is shown in Table S2. Compared to never smokers, long-term quitters and short-term quitters was not associated with increased risk of dementia (HR: 1.07; 95% CI: 0.94–1.22, HR: 1.08; 95%

© 2018 The Authors. *Annals of Clinical and Translational Neurology* published by Wiley Periodicals, Inc on behalf of American Neurological Association.

Table 1. Descriptive characteristics of study participants.

	Change in Smoking Status			
	Continual smoker	Short-term quitter (<4 years)	Long-term quitter (≥4 years)	Never smoker
Number of people	12,672	4175	9268	20,025
Age, years, %				
60–69	77.1	74.4	68.2	70.8
70 or older	22.9	25.6	31.9	29.2
Body mass index, kg/m^2, %				
<18.5	5.9	4.6	3.3	2.8
18.5–22.9	46.0	42.1	35.8	35.6
23.0–24.9	25.3	27.0	29.2	28.5
≥25.0	22.9	26.3	31.7	33.1
Blood pressure, mmHg, %				
<120/80	18.9	17.9	16.5	16.1
120/80–139/89	60.4	60.8	62.7	61.3
≥140/90	20.7	21.2	20.9	22.6
Missing	0.0	0.0	0.0	0.0
Fasting serum glucose, mg/dL, %				
<100.0	60.9	59.7	59.1	60.0
100.0–125.9	27.7	28.5	30.0	29.1
≥126.0	11.3	11.7	10.8	10.8
Missing	0.1	0.1	0.1	0.1
Total cholesterol, mg/dL, %				
<200.0	61.1	60.1	60.0	61.5
200.0–239.9	29.0	29.9	29.5	29.2
≥240.0	9.8	9.8	10.3	9.1
Missing	0.1	0.1	0.1	0.1
Physical activity, times per week, %				
None	59.8	58.4	47.2	47.2
1–2	18.8	17.8	20.7	21.5
3–4	7.9	8.4	11.4	11.3
5–7	12.8	12.4	19.1	18.7
Missing	0.7	3.0	1.6	1.3
Drinking habit, drinks per week, %				
None	34.6	56.4	43.6	58.0
1–2	34.6	25.0	33.5	27.4
≥3	30.6	16.9	22.2	14.4
Missing	0.2	1.8	0.7	0.2
Household income, %				
Lower half	51.5	48.1	39.2	39.7
Upper half	47.8	50.9	60.3	59.7
Missing	0.8	1.0	0.6	0.5
Charlson comorbidity index, %				
0	24.5	20.1	19.8	21.8
1–2	48.7	47.0	47.0	46.5
≥3	26.8	33.0	33.3	31.7

CI: 0.90–1.29, respectively), but continual smokers had increased risk of dementia (HR: 1.24; 95% CI: 1.10–1.40). Finally, the association between smoking habit change and dementia among women is shown in Table S3. There was a tendency toward a reduced risk of dementia according to a decreasing amount of tobacco exposure without significant result.

Discussion

In this large-scale longitudinal study, we have shown that prolonged smoking cessation was associated with decreased risk of overall dementia among Korean men. While numerous previous studies[12,13,16] have shown that smoking increases the risk of dementia in Western populations, to the best of our knowledge, this is the first study to evaluate the effects of smoking cessation on the risk of developing dementia in a large Asian population.

Results from most previous studies investigating the association between smoking and dementia are consistent with the findings in this study.[10,12,13,29] A recent meta-analysis of 19 prospective studies and 26,374 participants revealed that current smokers had increased risk of Alzheimer's disease (relative risk, RR: 1.79; 95% CI: 1.43–2.23), vascular dementia (RR: 1.79; 95% CI: 1.28–2.47), and overall dementia (RR: 1.27; 95% CI: 1.02–1.60) compared with never smokers.[13] Furthermore, another previous study studying the effects of smoking on dementia in the Western population revealed that former smokers had decreased risk of dementia compared to current smokers (RR: 1.70; 95% CI: 1.25–2.31).[13] The results from this study support previous studies by showing never smokers had decreased risk of dementia compared to continual smokers. Furthermore, this study demonstrates that smokers who quit for a prolonged period benefit from decreased risk of overall dementia among Korean men.

Previous studies investigating the association between smoking and Alzheimer's disease have been controversial. Few studies have shown that nicotine may actually improve short-term cognitive performance[7,30] and inhibit amyloid formation.[31,32] On the other hand, various other studies have shown that smoking is a risk factor for Alzheimer's disease, namely due to reactive oxygen species produced by smoking.[33–37] Smoking directly delivers reactive oxidant species from the cigarette into the bloodstream, promotes the generation of endogenous reactive oxidant species and causes weakening of antioxidant defense systems.[38,39] Reactive oxygen species caused by smoking can then contribute to cellular damage by oxidizing lipids, proteins, and nucleic acids.[38] Specifically, the brain is particularly susceptible to oxidative stress due to the high proportion of oxidizable polyunsaturated fatty acids in membranes and the high metabolic requirement of oxygen.[40]

In our study, there was a tendency toward decreased risk of Alzheimer's disease upon decreasing amounts of tobacco consumed. The trend toward risk reduction upon decreasing amounts of tobacco implies that the detrimental effects of tobacco on the development of dementia. Therefore, smoking should be considered a risk factor for Alzheimer's disease and smoking cessation should be

 © 2018 The Authors. *Annals of Clinical and Translational Neurology* published by Wiley Periodicals, Inc on behalf of American Neurological Association.

Table 2. Effect of smoking habit change on the risk of developing dementia.

	Change in smoking status				
Dementia type	Continual smoker	Short-term quitter (<4 years)	Long-term quitter (≥4 years)	Never smoker	*p* for trend
Overall dementia					
Number of cases	468	146	342	688	
Person-years	87,040	28,546	63,793	141,263	
HR[1] (95% CI)	1.00 (reference)	0.87 (0.72–1.05)	0.86 (0.75–0.99)	0.81 (0.71–0.91)	0.001
Alzheimer's disease					
Number of cases	294	99	219	451	
Person-years	90,064	29,550	66,483	146,723	
HR[1] (95% CI)	1.00 (reference)	0.92 (0.73–1.16)	0.85 (0.71–1.02)	0.82 (0.70–0.96)	0.010
Vascular dementia					
Number of cases	95	27	53	121	
Person-years	91,327	30,136	67,788	149,094	
HR[1] (95% CI)	1.00 (reference)	0.81 (0.52–1.25)	0.68 (0.48–0.96)	0.71 (0.54–0.95)	0.017

HR, hazard ratio; CI, confidence interval.

[1]Hazard ratio calculated by Cox proportional hazards regression analysis adjusted for age, household income, physical activity, drinking habit, body mass index, change in body mass index, blood pressure, fasting serum glucose, total cholesterol, and Charlson Comorbidity Index.

encouraged in order to reduce the risk of developing Alzheimer's disease.

Smoking is also known to increase the risk of cardiovascular diseases through oxidative damage,[3,39] increased fibrinogen levels[3,41] and induction of a hypercoagulable state.[42] Since cerebrovascular infarction is the key pathophysiological mechanism for vascular dementia, the risk factors of cerebrovascular diseases, which include smoking,[43,44] are also considered to be risk factors of vascular dementia. As smoking cessation reduces the risk of cardiovascular disease due to decreased inflammatory markers and oxidative stress[45–47] upon smoking cessation, similar mechanisms may contribute to the decreased risk of vascular dementia.

There are several limitations to consider upon interpreting the results of our study. First, as Alzheimer's disease is defined as a chronic neurodegenerative disease that usually starts slowly and worsens over time,[48] therefore the follow-up duration of 8 years may not have been enough to fully determine the effects of smoking cessation on Alzheimer's disease. We also did not take into account other neurodegenerative diseases such as Parkinson's disease and amyotrophic lateral sclerosis, which might also be related to smoking. Future studies with a longer follow-up duration, including other possible related neurologic disorders are needed to validate the findings of our results. Second, as the change in smoking habit was not monitored after the second health examination, possible changes in smoking habit were not accounted for. Third, as the smoking status was determined by a questionnaire, it may not reflect the exact smoking status of each participant. Thus, future studies that use biomarkers as a way of determining smoking status are needed to validate our findings. Also, we could not determine smoking duration among smokers, a factor which may alter the effect of smoking on the risk of dementia. Fourth, we were not able to obtain and adjust for the participant's level of education, an important factor upon assessing cognitive function. However, we have adjusted for and conducted subgroup analyses for household income, which could serve as a surrogate marker for education level. Finally, we did not include women in the main analysis, which limits the generalizability of our findings. Therefore, we conducted a separate analysis determining the association between smoking habit change and dementia among women (Table S3). Although there was a tendency toward a decreased risk of dementia according to smoking cessation, we could not obtain significant results since the majority of women were never smokers. Future studies with a large population of women and longer follow-up duration are needed to elucidate the association between smoking habit change and dementia among women.

Despite these limitations, to the best of knowledge, this is the first study to examine the association between smoking cessation and dementia, using an Asian population. We have also shown that smokers who quit for a prolonged period may benefit from decreased risk of dementia. Furthermore, the relatively large study population and wide range of potential confounding covariates also add to the strengths of this study. Finally, the results were consistent across extensive sensitivity and stratified analyses, reinforcing the reliability of our findings.

© 2018 The Authors. *Annals of Clinical and Translational Neurology* published by Wiley Periodicals, Inc on behalf of American Neurological Association.

Table 3. Stratified, multivariate-adjusted analysis according the subgroups divided by covariates for the risk of any dementia.

	Change in Smoking Status			
	Continual smoker	Short-term quitter (<4 years)	Long-term quitter (≥4 years)	Never smoker
Age, years	HR[1] (95% CI)			
60–69	1.00 (reference)	0.84 (0.66–1.08)	0.80 (0.66–0.98)	0.78 (0.66–0.92)
70 or older	1.00 (reference)	0.94 (0.70–1.26)	1.04 (0.84–1.28)	0.93 (0.77–1.13)
BMI, kg/m^2				
<25.0	1.00 (reference)	0.88 (0.74–1.04)	0.92 (0.81–1.04)	0.80 (0.72–0.89)
≥25.0	1.00 (reference)	1.11 (0.75–1.64)	0.91 (0.67–1.24)	1.06 (0.82–1.38)
BMI change, kg/m^2				
≤-1.0	1.00 (reference)	0.58 (0.35–0.97)	0.71 (0.52–0.97)	0.91 (0.71–1.16)
-0.9 ~ +0.9	1.00 (reference)	1.01 (0.80–1.29)	0.93 (0.78–1.12)	0.81 (0.69–0.95)
≥ +1.0	1.00 (reference)	0.76 (0.51–1.14)	0.84 (0.60–1.18)	0.68 (0.50–0.92)
Blood pressure, mmHg				
<140/90	1.00 (reference)	0.81 (0.65–1.01)	0.89 (0.76–1.04)	0.77 (0.67–0.88)
≥140/90	1.00 (reference)	1.10 (0.74–1.61)	0.76 (0.55–1.06)	0.95 (0.73–1.24)
Fasting serum glucose, mg/dL				
<100.0	1.00 (reference)	0.99 (0.77–1.26)	0.93 (0.77–1.12)	0.91 (0.77–1.07)
≥100.0	1.00 (reference)	0.72 (0.53–0.97)	0.77 (0.62–0.96)	0.68 (0.56–0.82)
Total cholesterol, mg/dL				
<200.0	1.00 (reference)	0.93 (0.74–1.18)	0.84 (0.70–0.99)	0.77 (0.66–0.90)
≥200.0	1.00 (reference)	0.78 (0.56–1.08)	0.90 (0.71–1.14)	0.87 (0.71–1.06)
Physical activity, times per week				
None	1.00 (reference)	0.88 (0.70–1.12)	0.86 (0.72–1.03)	0.79 (0.68–0.93)
1 or more	1.00 (reference)	0.87 (0.63–1.20)	0.88 (0.70–1.11)	0.83 (0.68–1.01)
Drinking habit, drinks per week				
None	1.00 (reference)	0.97 (0.74–1.26)	0.92 (0.74–1.15)	0.88 (0.73–1.06)
1 or more	1.00 (reference)	0.80 (0.60–1.06)	0.82 (0.68–0.99)	0.74 (0.62–0.87)
Household income, %				
Lower half	1.00 (reference)	0.86 (0.66–1.12)	0.82 (0.66–1.01)	0.74 (0.62–0.89)
Upper half	1.00 (reference)	0.93 (0.71–1.21)	0.91 (0.75–1.11)	0.88 (0.74–1.04)
Charlson comorbidity index, %				
0	1.00 (reference)	1.11 (0.69–1.81)	1.04 (0.72–1.49)	0.88 (0.64–1.20)
1 or more	1.00 (reference)	0.85 (0.69–1.04)	0.84 (0.72–0.99)	0.80 (0.70–0.92)

BMI, body mass index; HR, hazard ratio; CI, confidence interval.

[1]Hazard ratio calculated by Cox proportional hazards regression analysis adjusted for age, household income, physical activity, drinking habit, body mass index, change in body mass index, blood pressure, fasting serum glucose, total cholesterol, and Charlson Comorbidity Index.

In conclusion, smokers should be encouraged to quit in order to reduce the risk of developing dementia. Smoking should be understood as a risk factor for dementia, especially in the elderly population as our study showed, and proper education regarding the benefit of smoking cessation should be done. Future studies with a longer follow-up duration investigating the effect of smoking cessation on Alzheimer's disease are needed.

Author Contributions

D.C., S.C, and S.M.P. contributed to the conception and design, analysis and interpretation of data, critical revision for important intellectual content, and final approval of the article. D.C., and S.C. contributed to the drafting of the article. S.C. conducted collection and assembly of the data. All authors approved the final copy of the article. S.M.P. is the corresponding author and had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of Interest

None reported.

References

1. Jha P, Chaloupka FJ, Moore J, et al. Tobacco Addiction. In: D. T. Jamison, J. G. Breman, A. R. Measham, G. Alleyne, M. Claeson, D. B. Evans, et al., eds. Disease Control Priorities in Developing Countries. 2nd ed. Washington (DC): Oxford University Press, 2006.

 © 2018 The Authors. *Annals of Clinical and Translational Neurology* published by Wiley Periodicals, Inc on behalf of American Neurological Association.

2. Rostron BL, Chang CM, Pechacek TF. Estimation of cigarette smoking-attributable morbidity in the United States. JAMA Intern Med 2014;174(12):1922–1928.
3. Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: an update. J Am Coll Cardiol 2004;43(10):1731–1737.
4. Wolf PA, D'Agostino RB, Kannel WB, et al. Cigarette smoking as a risk factor for stroke. The framingham study. JAMA. 1988;259(7):1025–1029.
5. Sasco AJ, Secretan MB, Straif K. Tobacco smoking and cancer: a brief review of recent epidemiological evidence. Lung Cancer 2004;45(Suppl 2):S3–S9.
6. Alberg AJ, Shopland DR, Cummings KM. The 2014 Surgeon General's report: commemorating the 50th Anniversary of the 1964 Report of the Advisory Committee to the US Surgeon General and updating the evidence on the health consequences of cigarette smoking. Am J Epidemiol 2014;179(4):403–412.
7. Elrod K, Buccafusco JJ, Jackson WJ. Nicotine enhances delayed matching-to-sample performance by primates. Life Sci 1988;43(3):277–287.
8. Brenner DE, Kukull WA, van Belle G, et al. Relationship between cigarette smoking and Alzheimer's disease in a population-based case-control study. Neurology 1993;43 (2):293–300.
9. Hillier V, Salib E. A case-control study of smoking and Alzheimer's disease. Int J Geriatr Psychiatry 1997;12 (3):295–300.
10. Cataldo JK, Prochaska JJ, Glantz SA. Cigarette smoking is a risk factor for Alzheimer's Disease: an analysis controlling for tobacco industry affiliation. J Alzheimers Dis 2010;19(2):465–480.
11. Almeida OP, Hulse GK, Lawrence D, Flicker L. Smoking as a risk factor for Alzheimer's disease: contrasting evidence from a systematic review of case-control and cohort studies. Addiction 2002;97(1):15–28.
12. Rusanen M, Kivipelto M, Quesenberry CP Jr, et al. Heavy smoking in midlife and long-term risk of Alzheimer disease and vascular dementia. Arch Intern Med 2011;171 (4):333–339.
13. Anstey KJ, von Sanden C, Salim A, O'Kearney R. Smoking as a risk factor for dementia and cognitive decline: a meta-analysis of prospective studies. Am J Epidemiol 2007;166 (4):367–378.
14. Sabayan B, Sorond F. Reducing Risk of Dementia in Older Age. JAMA 2017;317(19):2028.
15. Vos SJB, van Boxtel MPJ, Schiepers OJG, et al. Modifiable Risk Factors for Prevention of Dementia in Midlife, Late Life and the Oldest-Old: validation of the LIBRA Index. J Alzheimers Dis 2017;58(2):537–547.
16. Ott A, Slooter AJ, Hofman A, et al. Smoking and risk of dementia and Alzheimer's disease in a population-based cohort study: the Rotterdam Study. Lancet 1998;351 (9119):1840–1843.
17. Peters R, Poulter R, Warner J, et al. Smoking, dementia and cognitive decline in the elderly, a systematic review. BMC Geriatr 2008;8:36.
18. Ferri CP, Prince M, Brayne C, et al. Global prevalence of dementia: a Delphi consensus study. Lancet 2005;366 (9503):2112–2117.
19. Fratiglioni L, De Ronchi D, Aguero-Torres H. Worldwide prevalence and incidence of dementia. Drugs Aging 1999;15(5):365–375.
20. Lee J, Lee JS, Park SH, et al. Cohort Profile: the National Health Insurance Service-National Sample Cohort (NHIS-NSC), South Korea. Int J Epidemiol 2017;46(2):e15.
21. Cheol Seong S, Kim YY, Khang YH, et al. Data Resource Profile: the National Health Information Database of the National Health Insurance Service in South Korea. Int J Epidemiol 2017;46:799–800.
22. Jee SH, Sull JW, Park J, et al. Body-mass index and mortality in Korean men and women. N Engl J Med 2006;355(8):779–787.
23. Park SM, Yun YH, Kim YA, et al. Prediagnosis Body Mass Index and Risk of Secondary Primary Cancer in Male Cancer Survivors: a Large Cohort Study. J Clin Oncol 2016;34(34):4116–4124.
24. Clair C, Rigotti NA, Porneala B, et al. Association of smoking cessation and weight change with cardiovascular disease among adults with and without diabetes. JAMA 2013;309(10):1014–1021.
25. Hwang D, Kim S, Choi H, et al. Calcium-Channel Blockers and Dementia Risk in Older Adults- National Health Insurance Service - Senior Cohort (2002-2013). Circ J 2016;80(11):2336–2342.
26. Jeong SM, Shin DW, Lee JE, et al. Anemia is associated with incidence of dementia: a national health screening study in Korea involving 37,900 persons. Alzheimers Res Ther 2017;9(1):94.
27. Jungeun K, Jonghyuk L, Ji Hoon J, et al. Study of the Drugs Prescribed on Alzheimer's Disease: from the Insurance Claims Data of Korea National Health Insurance Service. Korean J Clin Pharm 2014;24(4):255–264.
28. Sundararajan V, Henderson T, Perry C, et al. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. J Clin Epidemiol 2004;57(12):1288–1294.
29. Reitz C, den Heijer T, van Duijn C, et al. Relation between smoking and risk of dementia and Alzheimer disease: the Rotterdam Study. Neurology 2007;69(10):998–1005.
30. Sahakian B, Jones G, Levy R, et al. The effects of nicotine on attention, information processing, and short-term memory in patients with dementia of the Alzheimer type. Br J Psychiatry 1989;154:797–800.
31. Zeng H, Zhang Y, Peng L, et al. Nicotine and amyloid formation. Biol Psychiatry 2001;49(3):248–257.

© 2018 The Authors. *Annals of Clinical and Translational Neurology* published by Wiley Periodicals, Inc on behalf of American Neurological Association.

32. Salomon AR, Marcinowski KJ, Friedland RP, Zagorski MG. Nicotine inhibits amyloid formation by the beta-peptide. Biochemistry 1996;35(42):13568–13578.
33. Mondragon-Rodriguez S, Basurto-Islas G, Lee HG, et al. Causes versus effects: the increasing complexities of Alzheimer's disease pathogenesis. Expert Rev Neurother 2010;10(5):683–691.
34. Markesbery WR. The role of oxidative stress in Alzheimer disease. Arch Neurol 1999;56(12):1449–1452.
35. Markesbery WR, Carney JM. Oxidative alterations in Alzheimer's disease. Brain Pathol 1999;9(1):133–146.
36. Kim GH, Kim JE, Rhie SJ, Yoon S. The Role of Oxidative Stress in Neurodegenerative Diseases. Exp Neurobiol 2015;24(4):325–340.
37. Durazzo TC, Mattsson N, Weiner MW, Alzheimer's Disease Neuroimaging I. Smoking and increased Alzheimer's disease risk: a review of potential mechanisms. Alzheimers Dement 2014;10(3 Suppl):S122–S145.
38. Isik B, Ceylan A, Isik R. Oxidative stress in smokers and non-smokers. Inhal Toxicol 2007;19(9):767–769.
39. Burke A, Fitzgerald GA. Oxidative stress and smoking-induced vascular injury. Prog Cardiovasc Dis 2003;46 (1):79–90.
40. Polidori MC, Griffiths HR, Mariani E, Mecocci P. Hallmarks of protein oxidative damage in neurodegenerative diseases: focus on Alzheimer's disease. Amino Acids 2007;32(4):553–559.
41. Kannel WB, Wolf PA, Castelli WP, D'Agostino RB. Fibrinogen and risk of cardiovascular disease. The framingham study. JAMA 1987;258(9):1183–1186.
42. Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes (1). N Engl J Med 1992;326(4):242–250.
43. Gorelick PB. Risk factors for vascular dementia and Alzheimer disease. Stroke 2004;35(11 Suppl 1):2620–2622.
44. Gorelick PB, Brody J, Cohen D, et al. Risk factors for dementia associated with multiple cerebral infarcts. A case-control analysis in predominantly African-American hospital-based patients. Arch Neurol 1993;50(7): 714–720.
45. Critchley JA, Capewell S. Mortality risk reduction associated with smoking cessation in patients with coronary heart disease: a systematic review. JAMA 2003;290(1):86–97.
46. Mohiuddin SM, Mooss AN, Hunter CB, et al. Intensive smoking cessation intervention reduces mortality in high-risk smokers with cardiovascular disease. Chest 2007;131 (2):446–452.
47. Bakhru A, Erlinger TP. Smoking cessation and cardiovascular disease risk factors: results from the Third National Health and Nutrition Examination Survey. PLoS Med 2005;2(6):e160.
48. Burns A, Iliffe S. Alzheimer's disease. BMJ 2009;338:b158.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Sensitivity analysis of the effect of smoking habit change on the risk of developing dementia by excluding events that occurred within the first four and six years, respectively.
Table S2. Effect of smoking habit change on the risk of developing dementia with never smoker being the reference group.
Table S3. Effect of smoking habit change on the risk of developing dementia among women.

 © 2018 The Authors. *Annals of Clinical and Translational Neurology* published by Wiley Periodicals, Inc on behalf of American Neurological Association.