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Biomarker assessment of tobacco smoking exposure and risk of dementia death: pooling of individual-participant data from 14 cohort studies

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Abstract

Background: While there is a suggestion that self-reported tobacco smoking may be a risk factor for dementia, to date, it has not been possible to explore the thresholds at which this exposure elevates risk. Accordingly, our aim was to relate cotinine, a biomarker of tobacco smoking, to risk of dementia death.

Methods: We pooled 14 prospective cohort studies that held data on cotinine (plasma or saliva), covariates, and death records.

Results: In the 33,032 study members (17,107 women) with salivary cotinine data, a mean duration of 8.3 years of follow-up gave rise to 135 deaths ascribed to dementia; while in 15,130 study members (7995 women) with plasma cotinine data, there were 119 dementia deaths during 14.3 years of mortality surveillance. After multiple adjustment, both plasma cotinine (hazard ratio per one standard deviation higher cotinine; 95% confidence interval: 1.29; 1.05, 1.59) and salivary cotinine (1.10; 0.89, 1.36) were positively related to dementia risk, with stronger effects for plasma.

Conclusion: Our finding that plasma cotinine was related to an elevated risk of dementia death warrants testing in studies with measures of disease onset as opposed to just mortality.

What is already known

- In cohort studies, self-reported cigarette smoking reveals a positive relation with dementia risk.
- In the absence of objective measurement of this health behaviour, it has not been possible to explore the thresholds at which this exposure elevates dementia risk.

What this paper adds

- To the best of our knowledge, this is the first study to utilise objective (cotinine) data to examine the smoking–dementia link.

Introduction

It is well documented that dementia is, and will remain for the foreseeable future, a global public health priority.⁽¹⁾ The fiscal, social and health consequences of dementia are profound.⁽¹⁾ In the absence of effective treatments, much research attention has focused on primary prevention via the identification of modifiable risk factors which may be associated with the occurrence of dementia, its progression, and prognosis.⁽²⁾ Position statements and systematic reviews of the literature have suggested a role for selected nutritional factors, physical inactivity, certain somatic medical conditions, and cognitive training, although the evidence base, while voluminous, is inconclusive.⁽²⁾

Cigarette smoking is another plausible modifiable risk factor. Small scale, high resolution studies showing that smokers, relative to their non-smoking counterparts, have a greater degree of brain atrophy, and lower grey matter density in selected areas⁽³⁾ has prompted a series of large, population-based investigations of the link between this health behaviour and dementia risk. While these generally show that cigarette smokers typically experience higher rates of future dementia,^(3, 4) with the evidence being based exclusively on self-reported smoking data it has not been possible to explore the thresholds at which this exposure elevates risk. Utilising objective markers of exposure to direct and indirect cigarette smoking, such as cotinine, would circumvent this problem but we are unaware of any such studies. Accordingly, we carried out a pooling of raw data from 14 longitudinal studies with information on cotinine and dementia.

Methods

We pooled individual-level data from 14 independent, geographically-representative, methodologically near-identical surveys of individuals living in private households conducted between 1994 and 2008 in the UK.⁽⁴⁻⁷⁾ Ethical approval for each survey was granted by local Research Ethics Committees, and study members provided informed consent.

Measurement of cotinine and covariates

In 3 studies taking place before 1998 (Health Survey for England [HSE] 1994, 1996; and Scottish Health Survey [SHS] 1995) the assessment of cotinine was based on a sample of venous blood, whereas salivary cotinine was captured subsequently in 11 studies (HSE [1998-2004, 2007, 2008] and SHS [1996, 2003]). All cotinine assays were performed by the same laboratory using standard gas chromatographic methods with a lower detection limit of 0.1 ng/ml.(8) While plasma cotinine and salivary cotinine are strongly correlated, levels are typically higher in saliva to the extent that the two measures cannot be combined.(9) Our covariates of socioeconomic status, frequency of alcohol consumption, and longstanding illness were self-reported using standard protocols.

Ascertainment of dementia

Study members were linked to national cause of death registers until 15th February 2011 for HSE or 31st December 2009 for SHS. Dementia was denoted by any mention of death from this disorder on certificates, as identified using codes 290.0 to 290.4, 294.9, 331.0 to 331.2 and 331.9 (for ICD-9) and codes F00, F01, F03, F09, G30 and G31 (for ICD-10). In a cohort of Scottish individuals participating in a memory clinic who had gerontologist-confirmed dementia, almost three quarters of those who subsequently died had dementia recorded on their death certificate.(10) This suggests the use of any mention of death from this disorder has sufficient validity for use in population-based studies.

Data analyses

We pooled the data for the 14 studies and fitted Cox proportional hazards models(11) to estimate hazard ratios with accompanying 95% confidence intervals for the association between each of the two indicators of cotinine and dementia death rates. Initially, we adjusted hazard ratios for survey year, sex and age (linear and quadratic). Subsequently, the confounding variables of socioeconomic

status, alcohol intake, and longstanding illness were added to the multivariable model. Throughout our analyses we used calendar period as the time scale. All analyses were computed using SAS (version 9.3).

Results

In the 33,032 study members (17,107 women) with salivary cotinine data, a mean duration of 8.3 years of follow-up gave rise to 135 deaths ascribed to dementia; while in 15,130 study members (7995 women) with plasma cotinine data, there were 119 dementia deaths during 14.3 years of mortality surveillance.

Both plasma cotinine and salivary cotinine were positively related to dementia risk, such that higher levels of exposure were associated with an elevated dementia rates (table 1). The magnitude of these associations were markedly greater for plasma cotinine, with statistical significance apparent in people with a level of >200ng/ml (vs. 0-1.0: age-, sex-, and study year-adjusted hazard ratio; 95% confidence interval: 1.84; 1.02, 3.33). While there was also a suggestion of a dose-response relationship across the plasma cotinine categories (p-value 0.02), active rather than passive smoking appeared to be generating this gradient. Controlling for covariates which included existing physical illness had little impact of the strength of these relationships. Adding self-reported cigarette smoking to the multivariable model, however, essentially eliminated the age- and sex-adjusted relationship between plasma cotinine and dementia (>200.0 vs. 0-1.0ng/ml: 1.16; 0.45, 3.00). By contrast, hazard ratio for current cigarette smoking remained elevated (vs. never smokers: 2.04; 0.83, 5.05) even after adjustment for plasma cotinine, although statistical at conventional levels was not apparent.

In sub-group analyses, we explored the issue of reverse causality such that unmeasured dementia at baseline – there was no cognitive testing in our studies – may have led to an elevation in the

prevalence of cigarette smoking, potentially due to the raised levels of psychological distress seen in people experiencing cognitive impairment.(12) To do so, we dropped dementia deaths within the first 5 years of mortality surveillance and repeated our analyses (Supplemental Table 1). With these exclusions – 24/119 of the dementia deaths in the plasma cotinine analyses and 37/135 of the dementia deaths in the salivary cotinine analyses occurred in the first 5 years of follow-up – the trend and hazard ratios in the plasma cotinine categories has strengthened somewhat while the hazard ratios for salivary cotinine are essentially unchanged.

Discussion

The main finding of this pooling of individual participant data from 14 prospective cohort studies was that plasma cotinine levels were related to a higher dementia risk in a dose-response manner, while the association with salivary cotinine was much weaker. That adjustment for self-reported cigarette smoking eliminated the plasma cotinine–dementia association suggests that our assessment of plasma cotinine provides no additional value for the prediction of this disorder beyond self-reported smoking behaviour.

Study strengths and limitations

The present study has some strengths, including the use of a biomarker of tobacco smoking rather than self-report, and the near full coverage of study members for mortality surveillance. It is also not without its shortcomings. The short half-life of cotinine means that it does have limitations in capturing longer term exposure to smoking. While we have previously demonstrated that dementia death appears to be a valid indicator of dementia in population-based studies,(10) this health outcome does nonetheless combines disease incidence (aetiology) and survival from the disorder (prognosis). Having comprehensive data on dementia incidence, which is problematic to capture except via extensive cognitive testing, would have greater utility when investigating the risk factors for this disorder. Lastly, a low number of dementia deaths meant that we were not able to examine

the association between passive smoking and dementia by exploring cotinine–dementia links in self-declared in non-smokers.

Existing literature and potential mechanisms

While there are, to the best of our knowledge, no studies relating a biomedical marker of exposure to tobacco smoke and dementia risk, several investigators have characterised self-reports of this health behaviour in the context of both active and passive smoking. As described, reviews of direct smoking generally reveal positive relationships with dementia risk.⁽²⁾ In studies which attempt to capture second-hand smoking via self-report there is also evidence of an increased risk of dementia although at rates which, as expected, appear to be lower than those seen in active smokers.⁽¹³⁾ In one of the few studies to have explored the link between biochemical markers of tobacco smoke and cognitive ability, itself a powerful risk factor for dementia, there was evidence that higher levels of salivary cotinine were associated with greater impairment.⁽¹⁴⁾

That the cotinine–dementia gradient was robust to adjustment for selected confounding factors raises the possibility that direct mechanisms may be generating this association. As indicated, imaging studies suggest that, compared with abstainers, smokers have a greater degree of brain atrophy, and lower grey matter density in selected areas.⁽³⁾ Other potential explanations include the observation that smoking exposure has a deleterious influence on the cardiovascular system, including increased coagulation of blood platelets, decreased coronary flow velocity reserves, accelerated atheroma genesis, and endothelial dysfunction.⁽¹⁵⁾ Endothelial dysfunction has been implicated in the reduced clearance of β -amyloid protein which is involved in the pathogenesis of Alzheimer's disease.⁽¹⁶⁾

In conclusion, our finding that plasma cotinine was related to an elevated risk of dementia death warrants testing in studies with measures of disease incidence.

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Table 1. Association of plasma and salivary cotinine with death from dementia: pooling of 14 cohort studies

Smoking status (Cotinine, ng/ml)	Plasma cotinine				Salivary cotinine			
	Number at risk	Dementia cases	Hazard Ratio (95% CI)		Number at risk	Dementia cases	Hazard Ratio (95% CI)	
			Model 1	Model 2			Model 1	Model 2
Non-smokers (0-1.0)	8543	76	1.0 (ref)	1.0 (ref)	21155	93	1.0 (ref)	1.0 (ref)
Passive smokers (1.1-15.0)	2347	16	1.19 (0.69, 2.06)	1.07 (0.62, 1.86)	4223	22	1.26 (0.79, 2.01)	1.23 (0.77, 1.97)
Active smokers, low intensity (15.1-200.0)	1424	13	1.68 (0.93, 3.05)	1.58 (0.87, 2.86)	2119	9	1.51 (0.76, 2.99)	1.47 (0.74, 2.93)
Active smokers, high intensity (>200.0)	2816	14	1.84 (1.02, 3.33)	1.79 (0.98, 3.27)	5535	11	1.19 (0.63, 2.25)	1.14 (0.60, 2.17)
P-value for trend	-	-	0.02	0.03	-	-	0.27	0.35
Per 1 standard deviation higher cotinine ^a	15130	119	1.31 (1.07, 1.61)	1.29 (1.05, 1.59)	33032	135	1.12 (0.91, 1.38)	1.10 (0.89, 1.36)

Model 1 - Hazard ratios are adjusted for age, age squared, sex, survey year.

Model 2 - Hazard ratios are adjusted for age, age squared, sex, survey year, socioeconomic status, frequency of alcohol consumption, longstanding illness.

^aCotinine values were transformed to log (cotinine + 0.5) for this analysis to remove skewness

Supplemental Table 1. Association of plasma and salivary cotinine with death from dementia (excluding deaths in the first 5 years of follow-up): pooling of 14 cohort studies

	Plasma cotinine					Salivary cotinine			
Smoking status (Cotinine, ng/ml)	Number at risk	Dementia cases	Hazard Ratio (95% CI)		Number at risk	Dementia cases	Hazard Ratio (95% CI)		
			Model 1	Model 2			Model 1	Model 2	
Non-smokers (0-1.0)	7924	58	1.0 (ref)	1.0 (ref)	14052	68	1.0 (ref)	1.0 (ref)	
Passive smokers (1.1-15.0)	2197	13	1.29 (0.70, 2.37)	1.17 (0.63, 2.16)	3502	15	1.21 (0.69, 2.12)	1.19 (0.68, 2.10)	
Active smokers, low intensity (15.1-200.0)	1267	12	2.16 (1.15, 4.04)	2.07 (1.10, 3.88)	1522	8	1.81 (0.87, 3.77)	1.79 (0.85, 3.75)	
Active smokers, high intensity (>200.0)	2602	12	2.13 (1.11, 4.08)	2.17 (1.12, 4.19)	4093	7	1.02 (0.46, 2.25)	1.00 (0.45, 2.20)	
P-value for trend	-	-	0.004	0.005	-	-	0.41	0.47	
Per 1 standard deviation higher cotinine ^a	13990	95	1.43 (1.14, 1.78)	1.42 (1.14, 1.78)	23169	98	1.11 (0.87, 1.42)	1.09 (0.85, 1.40)	

Model 1 - Hazard ratios are adjusted for age, age squared, sex, survey year.
Model 2 - Hazard ratios are adjusted for age, age squared, sex, survey year, socioeconomic status, frequency of alcohol consumption, longstanding illness.
^aCotinine values were transformed to log (cotinine + 0.5) for this analysis to remove skewness