The Effect of Smoking on Physical Function in older adults: A Mendelian Randomisation Analysis

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Abstract

Background: Smoking is widely known to be damaging to health. It greatly increases the risk of various cancers, cardiovascular and respiratory diseases, and remains the leading preventable cause of morbidity and mortality in the United Kingdom (UK). The article tested the hypothesis that smoking behaviour (either smoking or non-smoking) is associated with physical function, and assessed inferred causality using genetic predisposition to smoking behaviour as an instrumental variable.

Methods and findings: Data were drawn from the English Longitudinal Study of Ageing (ELSA), waves 1-9 (mean age 65.8 years). Physical function was assessed by means of the body mobility and the activity of daily living (ADL) indices. Polygenic scores for smoking behaviour were used as instrumental variables in a Mendelian randomisation framework. Instrumental variable estimators were used to examine causal effects. Among UK older adults ($n = 29139$), impaired physical function was significantly higher in (current) smokers compared with non-smokers. Relatively to non-smokers, smokers reported a higher level of impairment both in the body mobility index ($\beta = 5.553$; 95% CI 1.029 to 10.077) and in the activities of daily living index ($\beta = 1.908$; 95% CI 0.196 to 3.619).

Conclusions: This study demonstrates smoking behaviour to be a potential causal risk factor for physical function during ageing in the UK population. Accordingly, the benefits of smoking cessations may extend to physical function.

***Keywords*:** Smoking; Physical Function; Polygenic Risk Scores; Instrumental variable; Mendelian Randomisation

What is already known on this subject:

- Previous research suggests that smoking behaviour is damaging to health, and it greatly increases the risk of various cancers, cardiovascular and respiratory diseases, and remains the leading preventable cause of morbidity and mortality in the United Kingdom.
- There is limited evidence showing a decline in physical function in association to smoking behaviour.
- However, the extent to which smoking behaviour and physical function are causally related remains to be determined.

What this study adds:

- The study analyses the relationship between smoking behaviour and physical function, and assesses inferred causality by exploiting genetic predisposition towards smoking behaviour as an instrumental variable.
- The results are adjusted by age, gender, marital status, family size, drinking and sedentary behaviour, education, log of household income, employment status, time, region genetic ancestry effects. Additionally, the study investigates for the potential of pleiotropic effects.
- This study demonstrates smoking behaviour to be a potential causal risk factor for physical function during ageing in the UK population.

How this study might affect research, practice or policy:

- Therapeutic strategies aimed at controlling smoking behaviour could be a converging target to mitigate losses in physical function into ageing.

1. Introduction

According to the World Health Organization (WHO), the tobacco epidemic is one of the biggest public health threats the world has ever faced. It accounts for more than 8 million people a year around the world. More than 7 million of those deaths are the result of direct tobacco use while around 1.2 million are the result of non-smokers being exposed to second-hand smoke (https://www.who.int/health-topics/tobacco#tab=tab_1). The consequence of smoking occurs disproportionately among the elderly because of the long duration of cumulative injury or change that underlies the bulk of tobacco-caused disease.**[1]** Excess absolute rates of disease incidence and mortality due to smoking increase steadily with increasing age and duration of smoking.**[2]**

Physical function may be one of factors affected by smoking behaviour in older adults. Physical function is defined as the ability to perform both basic and instrumental activities of daily living.**[3]** As an older person experiences decline in physical function, s/he encounters increasing difficulty in engaging in the instrumental activities of daily living, and may address these difficulties by avoiding or limiting these activities. Given that this decline may occur gradually, the accompanying changes in physical function may be subtle and not readily apparent until the person is unable to perform any activity at all.**[3]**

While the association between smoking behaviour and physical function decline has been previously reported none of these study were able to assess whether the observed relationship was causal.**[4-10]** The purpose of this study is to fill the gap in the literature and to investigate the association between smoking behaviour and physical function in older adults, and assess inferred causality using genetic predisposition to smoking behaviour as an instrumental variable.**[11]**

2. Data

Study cohort

This study employs data from the English Longitudinal Study of Ageing (ELSA).**[12]** The ELSA is a large-scale longitudinal panel study of people aged 50 and over, and their partners, living in private households in England. The initial sample was drawn from households that had previously responded to the Health Survey for England (HSE) in 1998, 1999 or 2001. To ensure the study remained representative of those aged 50 and over, new cohorts were added at wave 3, and at wave 4. Every two years, the sample has been interviewed to measure changes in their health status, in their economic conditions, and in their social circumstances.

Polygenic risk scores

Importantly for the investigation, ELSA provides polygenic score data for a number of behavioural, emotional and health-related phenotypes.**[13]** Specifically, ELSA participants of European ancestry were genotyped in 2013/14, using the Illumina HumanOmni2.5 Bead-Chips (HumanOmni2.5-4v1, HumanOmni2.5-8v1.3). The genome-wide genotyping was performed at University College London (UCL) Genomics in 2013-2014, funded by the Economic and Social Research Council. Principal components analysis was performed to investigate population structure, and ten principal components were retained to account for any ancestry differences in genetic structures.

In this study, a polygenic score for smoking behaviour is used as the instrumental variable in the Mendelian randomisation analysis. A polygenic score is a weighted sum of cumulative genetic risk for a trait, which aggregates multiple individual loci across the human genome and weights them by

effect sizes from a prior GWAS meta-analysis.**[14]** To ease the interpretation, the polygenic score has been standardised (mean= 0, standard deviation= 1).

Outcome assessments

Physical function is a person's ability to perform normal physical activities of daily living. Two measures of physical function were considered in this study. First, it was considered the body mobility index, which assesses mobility (leg) and arm function.**[15]** For this, participants in the ELSA were asked whether they had difficulty doing any of the following ten activities: (1) walking 100 yards, (2) sitting for two hours, (3) getting up from a chair after sitting long periods, (4) climbing several flight stairs without resting, (5) climbing one flight stairs without resting, (6) stooping, kneeling or crouching, (7) reaching or extending arms above shoulder level, (8) pushing or pulling large objects, (9) lifting or carrying weights over 10 pounds, and (10) picking up a 5p coin from a table. A binary variable for each activity was generated and coded as one if the individual reported to have difficulty in the performance of such activity. Finally, the body mobility index was created by summing up the ten binary variables, and therefore ranges from zero, the least difficulties and best body mobility, to ten, the most difficulties and least body mobility.

Second, it was considered the six-item activities of daily living (ADL) index developed by Katz.**[16]** The ADL index measures the difficulties in performing tasks required for personal self-care and independent living in every-day life. The functional assessment is based on individuals' responses (yes/no) asking if participants experienced difficulties in (1) dressing, (2) walking across a room, (3) bathing or showering, (4) eating, (5) getting out of bed, and (6) using the toilet. The overall score for each individual is calculated by summing across the item-specific responses, and

therefore ranges from zero, the least difficulties, to six, the most difficulties in the activities of daily living.**[17]**

Smoking status

The dependent variable of this study is a binary indicator for whether the individual reports ever being a smoker. Specifically, this was assessed with the question "*Have you ever smoked cigarettes?"* with the response options (1) Yes, (2) No. For our analysis, participants answering (1) were defined as "smokers."

Covariates

A number of covariates are included in the analysis. Age was measured in years and was entered as both a continuous variable as and as a quadratic term to account for potential the non-linear influence of age on smoking behaviour. Gender was coded as binary (male/female). Education was coded as binary taking the value of one for participants who reported having achieved higher education. Marital status was entered as a binary variable (married vs divorced, separated, widowed, never married). Employment status was coded as equal one if the individuals reported being currently working. Household wealth was measured using the log-yearly equivalised disposable real household income deflated using the Consumer Price Index with baseline 2005 = 100. Individuals were classified as drinkers if reported to consume alcohol 5/7 days week, and as sedentary if reported they did not perform any form of physical activity.

Statistical Analysis

To estimate the effect of smoking behaviour on physical function via an instrumental variable the following model is used:

$$S_i = \mu + G_i\pi + \boldsymbol{X_i'}\Omega + \upsilon_i \quad (1)$$

$$P_i = \alpha + \beta\hat{S}_i + \boldsymbol{X_i}'\gamma + \varepsilon_i \quad (2)$$

Where G_i denotes the polygenic score of individual i; S_i is the smoking binary variable that identifies the smokers in the sample, and $\hat{S}_i$ is the smoking variable as predicted from Equation (1). P_i is the dependent variable of the model, namely the physical function of individual i. The term of main interest is β, which measures the causal effect of smoking on physical function. $\boldsymbol{X_i'}$ is a vector of covariates that include age, and its square, gender, marital status, family size, education, log of household income, and employment status. Importantly, the models also includes a set of time and region dummies, as well as a set of ten principal components, to account for the potential confounding effect of genetic ancestry. Finally, υ_i and ε_i are the error terms. All analysis were performed in Stata (v15). The Mendelian randomisation analysis was performed using the linear two-stage least squares estimator, namely ivregress 2sls. The endogeneity test confirms that the regressor of interest, smoking behaviour, is indeed endogenos ($\chi^2 = 6.31; p = 0.0120$).

Characteristics of the sample

The characteristics of the sample of interest are summarised in Table 1. The average score of the body mobility index is 1.95, and the average score of the ADL index is 0.39. Of the total, 14 percent of the sample reports being a (current) smoker, and ever being a smoker; 7 percent of the sample

reports being a regular smoker (>10 cigarettes smoked per day). In terms of sociodemographic characteristics, the average age in the sample was 65.81 years (standard deviation (SD) = 10.38). A total of 54 and 64 percent of the sample are women, and are married, respectively, with an average family size of around 2. 22 of the sample are identified as drinkers and 23 percent are classified as sedentary. Few participants in the sample (15 percent) reported having obtained higher education, and 26 percent are employed. Finally, the (log-equivalised) household income was 5.60 (SD= 0.70).

Table 1: Summary Statistics of Participants characteristics

	Mean	S.D.	Min	Max
Outcome:				
Body Mobility Index [0,10]	1.95	2.59	0	10
ADL Index [0,6]	0.39	1.02	0	6
Smoking Behaviour:				
Smoker [0,1]	0.14	0.35	0	1
Ever Smoker [0,1]	0.14	0.35	0	1
Regular Smoker [0,1]	0.07	0.25	0	1
Cigarettes Smoked per day	1.34	4.95	0	150
Polygenic Score	0.00	1.00	-4	4
Demographics:				
Years of age	65.81	10.38	17	99
Female [0,1]	0.54	0.50	0	1
Married [0,1]	0.64	0.48	0	1
Family Size	2.06	0.91	0	11
Drinker [0,1]	0.22	0.43	0	1
Sedentary [0,1]	0.23	0.42	0	1
Socio-Economic:				
Higher Education	0.15	0.36	0	1
Log HH Income	5.60	0.70	-4	10
Employed [0,1]	0.26	0.44	0	1
Observations	29139			

Source: English Longitudinal Study of Ageing (ELSA), Waves 1-9.
Note: The table reports summary statistics of the main variables of interest.

The Effect of smoking behaviour on physical function

In Table 2, the Mendelian randomisation analysis shows a strong and significant evidence of inferred causality between smoking behaviour and physical function. Columns (1) and (2) report instrumental variable estimates when using as an outcome variable the body mobility index. In Columns (1), instrumental variable estimates are adjusted for age, and its square, gender, marital status, family size, drinking and sedentary behaviour, education, log of household income, and employment status. In Columns (2), the estimates also account for time, region, and genetic ancestry effects. According to the estimates obtained with the instrumental variable approach in Column (2), the preferred specification, smokers report a higher level of impairment in the body mobility index. Specifically, the estimated coefficient implies that smokers experience difficulties in roughly 5 additional activities than their non-smokers counterpart.

Column (3) and (4) report instrumental variable estimates when using as outcome variable the ADL index. Similarly to above, in Columns (1), instrumental variable estimates are adjusted for age, and its square, gender, marital status, family size, drinking and sedentary behaviour, education, log of household income, and employment status. In Columns (2), the estimates also account for time, region, and genetic ancestry effects. Consistently to above, the instrumental variable estimates suggest that smokers experience a significantly higher level of impairment in their activities of daily living. Specifically, the estimated coefficient in Column (4) implies that smokers experience difficulties in 2 additional activities of daily living than their non-smoker counterpart.

Table 2: The Effect of Smoking Behaviour on Physical Function

	(1) **Body Mobility Index**	(2) **Body Mobility Index**	(3) **ADL Index**	(4) **ADL Index**
Smoker [0,1]	5.304 [0.799,9.808]	5.553 [1.029,10.077]	1.657 [0.043,3.270]	1.908 [0.196,3.619]
Covariates:				
Years of Age	0.198 [-0.020,0.417]	0.004 [-0.058,0.066]	0.049 [-0.029,0.128]	-0.007 [-0.031,0.017]
Years of Age Sq.	-0.001 [-0.003,0.000]	0.000 [-0.000,0.001]	-0.000 [-0.001,0.000]	0.000 [-0.000,0.000]
Female [0,1]	0.645 [0.486,0.804]	0.642 [0.495,0.788]	0.016 [-0.040,0.073]	0.021 [-0.035,0.076]
Married [0,1]	-0.338 [-0.449,-0.226]	-0.238 [-0.316,-0.161]	-0.118 [-0.159,-0.077]	-0.086 [-0.117,-0.056]
Family Size	0.055 [-0.009,0.119]	0.029 [-0.021,0.079]	0.025 [0.001,0.049]	0.017 [-0.002,0.037]
Higher Education	-0.083 [-0.213,0.048]	-0.120 [-0.219,-0.021]	0.007 [-0.040,0.055]	-0.002 [-0.040,0.037]
Log HH Income	0.189 [-0.097,0.475]	-0.088 [-0.140,-0.035]	0.101 [-0.001,0.204]	0.016 [-0.004,0.035]
Employed [0,1]	-0.606 [-0.696,-0.515]	-0.626 [-0.704,-0.547]	-0.184 [-0.215,-0.153]	-0.191 [-0.219,-0.162]
Observations	29178	29171	29179	29172

Source: English Longitudinal Study of Ageing (ELSA), Waves 1-9.

Note: The table reports instrumental variable (IV) estimates of the effect of smoking behaviour on physical function. In Columns (1) and (2) the outcome variable is the body mobility index [0,10], while in Columns (3) and (4) the outcome variable is the activities of daily living index [0,6]. In Column (1) and (3), the regression model includes the full set of covariates, namely age, and its square, gender, marital status, family size, drinking and sedentary behaviour, education, log of household income, and employment status. In Columns (2) and (4), the regression model adds in time fixed effects (FE), region fixed effects (FE), and the principal components to account for genetic ancestry effects. 95% confidence limits are reported in squared brackets.

Sensitivity Analysis

Table 3 explicitly investigates for the potential of pleiotropic effects. In this case, pleiotropic effects are any other effects that may be caused by the polygenic score, other than smoking behaviour, that may be related with the outcome of interest. To address this concern, Table 3 reports the results of running a series of multivariate regression models of the smoking polygenic scores on key psychosocial factors and lifestyle behaviours that could potentially be linked to physical function, namely: (*i*) Quality of life, as measured by the Control, Autonomy, Self-Realization and Pleasure (CASP) 19;**[18]** (*ii*) Mental health, as measured by the Centre for Epidemiological Studies – Depression (CES-D) index;**[19]** (*iii*) Memory Index, as measured by the word listing test;[18] (*iv*) Executive function, as measured by the verbal fluency test;**[20]** and finally (*v*) Drinking behaviour, defined as weather an individual reported drinking daily. The results in Table 3 reports that the estimated coefficients are all statistically indistinguishable from 0. This is consistent with the idea of no pleiotropic effects.

Table 3: Effect of the Polygenic Score on Different Outcomes

	(1) Quality of Life	(2) CES Depression	(3) Memory Index	(4) Executive Function	(5) Drinker [0,1]
Polygenic Score	0.033 [-0.068,0.134]	0.014 [-0.007,0.034]	0.006 [-0.032,0.045]	-0.008 [-0.034,0.019]	-0.000 [-0.005,0.004]
Covariates:					
Years of Age	0.599 [0.463,0.735]	-0.062 [-0.091,-0.033]	0.073 [0.020,0.127]	0.055 [0.021,0.089]	0.005 [-0.001,0.011]
Years of Age Sq.	-0.005 [-0.006,-0.004]	0.000 [0.000,0.001]	-0.002 [-0.002,-0.001]	-0.001 [-0.001,-0.001]	-0.000 [-0.000,0.000]
Female [0,1]	0.854 [0.663,1.046]	0.371 [0.332,0.410]	0.982 [0.910,1.054]	-0.001 [-0.051,0.050]	-0.094 [-0.103,-0.085]
Married [0,1]	1.776 [1.514,2.038]	-0.451 [-0.505,-0.396]	0.033 [-0.063,0.129]	0.005 [-0.061,0.071]	0.024 [0.013,0.035]
Family Size	-0.637 [-0.797,-0.476]	0.005 [-0.029,0.038]	-0.054 [-0.113,0.005]	-0.013 [-0.052,0.026]	-0.020 [-0.027,-0.014]
Higher Education	0.655 [0.411,0.900]	-0.096 [-0.145,-0.047]	1.113 [1.015,1.212]	0.645 [0.578,0.712]	0.141 [0.127,0.155]
Log HH Income	1.695 [1.515,1.874]	-0.210 [-0.245,-0.175]	0.502 [0.439,0.565]	0.320 [0.276,0.363]	0.081 [0.073,0.090]
Employed [0,1]	0.338 [0.071,0.605]	-0.199 [-0.253,-0.145]	-0.256 [-0.358,-0.155]	-0.086 [-0.157,-0.016]	-0.036 [-0.049,-0.023]
Observations	27125	28915	29089	25641	37548

Source: English Longitudinal Study of Ageing (ELSA), Waves 1-9.

Note: The table reports estimates of the effect of the polygenic score (PGS) on different key factors and lifestyle behaviours that can be potentially linked to early retirement, namely: (1) Quality of life, as measured by the Control, Autonomy, Self-Realization and Pleasure (CASP) 19; (2) Mental health, as measured by the Center for Epidemiological Studies – Depression (CES-D) index; (3) Memory Index, as measured by the word listing test; (4) Executive function, as measured by the verbal fluency test; and finally (5) Drinking behaviour, defined as whether an individual reported drinking daily. 95% confidence limits are reported in squared brackets.

3. Conclusions

The present study was conducted among a sample of older adults from the English Longitudinal Study of Ageing (ELSA) participating in Waves 1-9. To the best of the author's knowledge, this is a novel study using a Mendelian randomisation framework to investigate the inferred causal nature of smoking behaviour and physical function.

After adjusting for age, sex, marital status, family size, drinking and sedentary behaviour, education, log of household income, employment status, region and time effects, and ten ancestry-specific principal component, current smokers reported a significantly higher level of impairment than their non-smokers counterpart.

The main strength of this study is that it contributes to an important, yet limited, literature examining smoking behaviour and physical function in the context of genetics. Importantly, the use of genetic data allows to employ genetic predisposition to smoking behaviour (polygenic score) as an instrumental variable in a Mendelian randomisation framework, which is a very powerful tool to account for confounding and reverse causation. The critical assumption to be satisfied for the validity of a Mendelian randomisation is exclusion restriction. In this case, this assumption entails that the smoking behaviour polygenic score should not have any effect on any other variables that may be related to the outcome of interest (i.e. pleiotropic effects). Accordingly, several tests were performed that provide compelling evidence on the validity of the Mendelian randomisation analysis. However, the potential violation of the independence and exclusion restriction assumptions cannot be completely ruled out. Thus, the inferred causality between smoking behaviour and physical function should be interpreted with caution.

Impairment in physical function due to aging and diseases decrease human mobility, independence, and quality of life. Findings in this study underscore the potential benefits of smoking cessation and its role in maintaining body mobility during aging. Thus, therapeutic strategies aimed at controlling smoking behaviour could be a converging target to mitigate losses in physical function.

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