Pulmonary Function and Risk of Alzheimer Dementia
Two-Sample Mendelian Randomization Study

To the Editor:

Dementia is a major growing global public health problem.1 Alzheimer disease (AD) risk is thought to be raised in the presence of relatively few environmental and genetic factors that include lower educational attainment, hypertension, obesity, diabetes mellitus, cigarette smoking, and the APOE e4 allele.2 Recent findings also suggest that impaired pulmonary function is associated consistently with approximately 40% elevation in later dementia risk.3 Although there is mechanistic evidence to support this—including hypoxia from extended suboptimal ventilator function4—crucially, given the observational nature of these studies, it is unclear whether this relationship is causal. An obstacle to drawing causal inference from such studies is the perennial problem of confounding, that characteristics of people with poorer pulmonary function differ from the unexposed in various ways that may explain the association. Investigators attempt to include as many relevant covariates as possible, but the possibility of confounding by unmeasured or imprecisely quantified factors is universal. Mendelian randomization (MR) has been seen as a possible remedy to this problem5 and has been extended to two-sample MR where genetic associations for the exposure and outcome are obtained from independent samples.6 Accordingly, for the first time to our knowledge, we present a two-sample MR study to clarify whether the observed association between poorer pulmonary function and subsequent AD is causal.

Methods

We ran a two-sample MR using summary data from the UKBiobank/SpiroMeta Consortium Genome-Wide Association Study (GWAS) comprising 400,102 individuals.7 We derived two genetic instruments for lung function: FEV1 (liters) and FVC (liters). Of the 279 single nucleotide polymorphisms (SNPs) associated with lung function, but not smoking, only those related to the relevant trait with \( P < 5 \times 10^{-8} \) and the same direction of effect in UKBiobank and SpiroMeta were used as genetic instruments. In addition, we included a more exploratory measure: the FEV1/FVC ratio, which has been used in the diagnosis of COPD whereby lower values are more suggestive of this condition.8 For the outcome, we used summary data from the most recent GWAS that included 21,982 people with AD and 41,944 control subjects.9 The models used the TwoSampleMR R package.10 Because this study used publicly available data, no ethical approval was required.

Results

Table 1 shows the relationship between lung function and subsequent AD risk. There was no evidence of a causal effect of poorer lung function, using FEV1 or FVC, on AD risk (both \( P > .35 \)). However, each SD increase in FEV1/FVC ratio (indicating superior lung function) was associated with an increased AD risk (OR, 1.12; 95% CI, 1.02 - 1.23; \( P = .016 \)). The MR Egger intercept for the latter indicates little horizontal pleiotropy (\( \beta = 0.0002; P = .96 \)) and the inverse-variance weighted Q-value (177.7; \( P = .08 \)) suggests no substantial heterogeneity. Using the weighted median method gave a similar result (OR, 1.15; 95% CI, 1.00-1.31; \( P = .048 \)).

Discussion

We found that the observed association between lower pulmonary function and AD risk was not supported as being causal. Thus, it is possible that the original relationship resulted from confounding by one or more unmeasured or poorly measured confounders. Multiple candidates exist that include an adverse intrauterine environment that led to reduced maximal lung function, exposure to environmental factors (eg, tobacco smoke, atmospheric pollution) that affected lung function and development and socioeconomic factors (poverty, educational failure, and less-advantaged social class). In our systematic review and meta-analysis, most of the included studies took account of smoking and
cardiovascular disease risk factors; slightly fewer included height. Socioeconomic position was accounted for variably, and there was little coverage of the whole life course in terms of all included covariables.

The FEV1/FVC ratio has not been examined routinely in relation to dementia risk. However, we found a link, albeit a weak one, between higher pulmonary function captured by this measure and increased AD risk. This may possibly be explained by survivor bias, with participants with poorer pulmonary function dying before they reach late life; however, a false-positive result must also be considered.

MR uses genetic variants that are allocated randomly at conception and therefore are generally independent of confounders that may otherwise bias an association when observational methods are used as proxies for environmental exposures. This assumes that genetic variants are (1) associated with the exposure, (2) only associated with the outcome of interest via their effect on the exposure, and (3) independent of confounders. It also relies on the exposure being measured accurately in the GWAS from which the instrument is derived. Pulmonary function was measured accurately with rigorous quality control in both UKBiobank (87.2% participants) and the individual studies of the SpiroMeta consortium. Pathway analysis suggested biologic plausibility for the SNPs used as instruments, with enrichment of genes relating to extracellular matrix organization and ciliogenesis. Furthermore, a genetic risk score comprising all 279 lung function SNPs predicted COPD. It is unlikely that collider bias due to smoking and height adjustment in the lung function GWAS explains the observed association, because SNPs associated with smoking behavior were excluded, and a sensitivity analysis that excluded the 12 SNPs included in our instrument which were associated with height in UKBiobank did not affect our conclusions.

The AD GWAS included 46 case-control studies from four consortia; rates of APOE e4 carriage are not reported. These studies used various methods of ascertaining dementia, with multiple diagnostic criteria being applied. Some studies used clinical diagnoses, and some identified Alzheimer-type pathology after death. This variation is likely to affect the applicability of the GWAS findings in our analysis.

In contrast to the instrumental AD variable used here, most observational studies use a more general category of “dementia.” This lack of clarity is common, and the multiple diseases that cause the dementia syndrome (eg, AD, cerebrovascular disease, Lewy body disease, and Fronto-Temporal Lobar Degenerative syndromes) frequently are conflated. Depending on the methods used, clarifying an individual’s precise diagnosis can be challenging. For example, death certificates frequently record only the broad dementia syndrome. Thus, although we can conclude that there is no causal link between impaired pulmonary function and AD, our study sheds less light on potential links with other types of dementia. It is plausible that there may be a different relationship between pulmonary function and vascular dementia, for instance.

Tom C. Russ, PhD, MRCPsych
Sarah E. Harris, PhD
Edinburgh, UK
G. David Batty, DSc
London, UK

AFFILIATIONS: From the Alzheimer Scotland Dementia Research Centre (T. C. Russ and G. D. Batty), University of Edinburgh; Edinburgh Dementia Prevention Group (T. C. Russ), University of Edinburgh; Division of Psychiatry (T. C. Russ), Centre for Clinical Brain Sciences, University of Edinburgh; Lothian Birth Cohorts, Department of Psychology (T. C. Russ and S. E. Harris), University of Edinburgh; UCL Research Department of Epidemiology & Public Health (G. D. Batty), University College London.

FINANCIAL/NONFINANCIAL DISCLOSURES: None declared.

CORRESPONDENCE TO: Tom C. Russ, PhD, MRCPsych; email: T.C. Russ@ed.ac.uk

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DOI: https://doi.org/10.1016/j.chest.2020.11.056
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