



Childhood infectious diseases and old age cognitive functioning: a nationally representative sample of community-dwelling older adults

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ABSTRACT

Background: Cumulative evidence suggests that health-related risk factors during midlife and old-age are associated with cognitive impairment. However, studies are needed to clarify the association between early-life risk factors and impaired cognitive functioning to increment existing knowledge.

Objective: To examine the association between childhood infectious diseases and late-life cognitive functioning in a nationally representative sample of older adults.

Participants: Eligible respondents were 2994 community-dwelling individuals aged 65–85.

Measurements: Cognitive functioning was assessed using the Mini-Mental State Examination (MMSE). Childhood infectious diseases (i.e. chicken pox, measles, and mumps) were self-reported. The study covariates were age, sex, highest educational level achieved, smoking status, body mass index, and depression. The primary statistical analysis examined the association between the number of childhood infectious diseases and total MMSE scores, accounting for all study covariates. Regression models of progressive complexity were examined for parsimony. The robustness of the primary results was tested in 17 sensitivity analyses.

Results: The most parsimonious model was a linear adjusted model (Bayesian Information Criterion = 12646.09). Late-life cognitive functioning significantly improved as the number of childhood infectious diseases increased ($\beta = 0.18$; 95% CI = 0.11, 0.26; $p < 0.001$). This effect was not significantly attenuated in all sensitivity analyses.

Conclusion: The current study results are consistent with prior ecological findings indicating that some childhood infectious diseases are associated with better cognitive functioning in old-age. This points to an early-life modifiable risk factor associated with older-life cognitive functioning. Our results may reflect selective mortality and/or beneficial effects via hormetic processes.

Key words: cognition, childhood illness, epidemiology

Introduction

Impaired cognitive functioning among community-dwelling older adults is estimated to have a prevalence of 18.3% in the UK (Rait *et al.*, 2005), ranging between 8.7% and 22.2% in the United States (Plassman *et al.*, 2008; Langa *et al.*, 2008). Impaired cognitive functioning is associated with increased risks of Alzheimer's disease (Bäckman *et al.*, 2005) and mortality (Langa *et al.*, 2008). The identification

of risk factors and preventative strategies are primary objectives in research on impaired cognitive functioning in older adults (Brayne, 2007; Treichler and Jeste, 2019). Indeed, general health-related risk factors have been identified during midlife and old age (Launer, 2005; Launer, 2007; Kaufman and Perales-Puchalt, 2019; Lee *et al.*, 2019; Shaaban *et al.*, 2019; Tu *et al.*, 2020; Walker *et al.*, 2019). Nonetheless, a recent shift has seen studies that examine the role of early-life risk factors to increment current knowledge of risk factors (Grainger *et al.*, 2019; Launer, 2007; Whalley *et al.*, 2006; Williamson and Leroy, 2019).

Few observational studies have examined the association between health in early-life and late-life cognition. Two studies found that retrospective reports of better global childhood health were

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associated with improved cognitive functioning in old age (Luo and Waite, 2005; Yi *et al.*, 2007). Three others studies reported a null association (Barnes *et al.*, 2012; Yount, 2016; Zhang *et al.*, 2018). A single study examined the association between childhood infectious diseases and late-life cognitive functioning and showed mixed disease effects (Case and Paxson, 2009). This study used an ecological design to examine childhood health based on region-level historical data and linked it with performance on cognitive tests during adulthood. Ecological studies are valuable for assessing the global disease burden, yet may not accurately reflect the true association for a given group (Lilienfeld, 1983; Piantadosi *et al.*, 1988). In addition, ecological studies raise concerns of the ecological fallacy (Robinson, 1950), whereby lower and higher levels of abstraction are not interchangeable (i.e. implying individual-level characteristics from collective ones may be erroneous).

Competing views exist concerning the long-term impact of childhood infectious diseases. Exposure to childhood infectious diseases has been shown to be associated with both negative (Case and Paxson, 2009; Dalman *et al.*, 2008) and positive health outcomes in later life (Alexander *et al.*, 2000; Amirian *et al.*, 2016; Case and Paxson, 2009). Negative outcomes may be explained via direct effects of pathogens and indirect effects of inflammatory response (Khandaker *et al.*, 2012). Positive outcomes may be attributed to mild stress-induced repeated stimulation of protective mechanisms in cells and organisms which has a wide range of health-promoting and life span-extending effects (Rattan, 2008), and/or selective mortality.

The current study aims to examine the direction of the association between common childhood infectious diseases and late-life cognitive functioning in a nationally representative sample of community-dwelling older adults.

Methods

Design and data source

The current study cohort was based on a nationally representative sample of community-dwelling individuals aged 65 and over from the Republic of Ireland. Data were obtained from the Irish Longitudinal Study on Ageing (Kenny, 2018). This large-scale, nationally representative, aging study was conducted in Ireland. The current data were derived from interviews, undertaken between January 2016 and December 2016. The response rate was 62.0%. The study was approved by the Faculty of Health Sciences Research Ethics Committee in Trinity College Dublin. Further details of sampling and

study design have been described elsewhere (Whelan and Savva, 2013).

Participants

Eligible respondents for this study included community-dwelling individuals aged 65–85 ($N = 3434$). People with known or suspected dementia were not recruited. A subsample of people who did not have any information on past illnesses of any sort were removed ($N = 440$). Therefore, the final sample was 2994 people.

Cognitive functioning

Cognitive functioning was assessed with the Mini-Mental State Examination (MMSE) (Folstein *et al.*, 1975). The MMSE is one of the most widely used research and screening measures of cognitive functioning in aging populations (Folstein *et al.*, 1975, 1983). It is easy to administer, available in over 15 languages (Steis and Schrauf, 2009), and has high levels of acceptability by health professionals and researchers as a diagnostic instrument (Nieuwenhuis-Mark, 2010). The scale has 20 items to assess orientation, recall, attention, calculation, language, and visuospatial abilities. It is divided into two sections, the first of which requires vocal responses only and covers orientation, memory, and attention; the maximum score is 21. The second part tests cognitive abilities to name, follow verbal and written commands, write a sentence spontaneously, and copy a polygon; the maximum score is nine. The maximum overall score is 30, with higher scores representing better cognitive functioning (Folstein *et al.*, 1983). Questions were asked and scored immediately. The test was not timed. The tester was instructed first to make the individual comfortable, to establish rapport, to praise successes, and to avoid pressing on items which the individual finds difficult.

In the current study, MMSE scores were computed, based on the original instructions (Folstein *et al.*, 1975) for each of the five subscales: orientation, registration, attention and calculation, recall, and language. Total scores were computed as well. For the primary analysis, the total test scores were not dichotomized into categories of impaired cognitive functioning and intact cognitive functioning because dichotomizing leads to information lost, increased risk of a false positive and may seriously underestimate the extent of variation in outcome such that individuals close to but on opposite sides of the cut point are characterized very differently rather than similarly (Altman and Royston, 2006). However, for robustness, when recomputing the sensitivity analysis, the total test scores were

dichotomized into categories of impaired and intact cognitive functioning.

Childhood infectious diseases

The childhood infectious diseases selected for this study were chickenpox, measles, and mumps. These were chosen because they are viral diseases, infection with which are followed by an enduring immunity (Simpson, 1952) and were common at the time of our sample's childhood years due to recurrent outbreaks (London and Yorke, 1973). Childhood infectious diseases were assessed self-reported by asking participant if they have had chicken pox, measles, and mumps in childhood. Responses were classified as "yes" (score of 1), "no" (score of 0), or "don't know" (coded as missing values). A total number of childhood infectious diseases score was computed for each person as the sum of the reported diseases of chicken pox, measles, and mumps. The total score ranged from 0 (having had no diseases) to 3 (having had all three diseases).

Covariates

The following covariates were included in the analyses to adjust for potential confounding, model effect modification and to define subgroups of particular interest with possible differential effects on cognitive functioning. The covariates considered (and entered in the following order) were demographics, metabolic, and psychiatric. Demographic covariates were age at the time of data collection and sex (van der Flier and Scheltens, 2005), highest education achieved [primary or none, secondary, third, or higher (Solfrizzi *et al.*, 2004; Tervo *et al.*, 2004; Tyas *et al.*, 2007)], and smoking status at the time of data collection [classified as smoker or non-smoker (Swan and Lessov-Schlaggar, 2007)]. The metabolic covariate was body mass index categories [0–25, 25–30, 30–40, 40+ (Atti *et al.*, 2008)]. The psychiatric variable was depression (Butters *et al.*, 2008) as measured by the Composite International Diagnostic Interview (Robins *et al.*, 1988). This established instrument is widely used for assessing a clinical diagnosis of major depression in epidemiological and clinical studies. Respondents received binary scores depending on whether they had fulfilled criteria for a major depressive episode in the last 12 months or not.

Analytic approach

First, missing values were examined, and the data were imputed accordingly using MICE (Multivariate Imputation by Chained Equations; van Buuren and Groothuis-Oudshoorn, 2010) in R package for

multivariate imputation by chained equations. Second, sample characteristics were computed.

Third, the primary statistical analysis tested the association between the total MMSE scores as a function of the number of childhood infectious diseases using regression models. The assumptions of the regression models were tested. Visual inspection of residual figures was performed in order to reveal deviations from homoscedasticity or normality. An inspection for normality of error terms followed using a histogram and probability plots of the residuals. Independence of the error term was examined through a scatter plot of residuals by the predicted values to show that no discernible association existed. Next, multiple regression analysis models were computed. Regression models were computed in ascending complexity and tested without adjustment and adjusted for confounding of age at the time of data collection, sex, highest education achieved, smoking status, body mass index, and depression. Models were numbered as follows. The first model accounted for a linear effect of the number of childhood infectious diseases on MMSE scores (model 1 hereafter). The second model accounted for a linear effect of the number of childhood infectious diseases, age, sex, education level, smoking status, body mass index, and depression on MMSE scores (model 2 hereafter). The third model accounted for a quadratic effect of the number of childhood infectious diseases on MMSE scores (model 3 hereafter). The fourth model accounted for a quadratic effect of the number of childhood infectious diseases, age, sex, education level, smoking status, body mass index, and depression on MMSE scores (model 4 hereafter). The fifth model accounted for a cubic effect of the number of childhood infectious diseases on MMSE scores (model 5 hereafter). The sixth model accounted for a cubic effect of the number of childhood infectious diseases, age, sex, education level, smoking status, body mass index, and depression on MMSE scores (model 6 hereafter).

Fourth, the six models were compared for parsimony based on the Bayesian Information Criterion (BIC) for model selection (Schwarz, 1978), similar to prior research (Rotstein *et al.*, 2018). Lower BIC values represent more parsimonious models and so are a better fit to the data. The best fitting model was then chosen based on the lowest BIC score and plotted using the ggplot2 library (Wickham, 2011). All analyses were computed in R (R Core Team, 2018).

Fifth, the robustness of the primary results was tested in 17 sensitivity analyses. The most parsimonious regression model was recomputed in subgroups

Table 1. Sample characteristics

	M (SD)/N (%)
Total Mini-Mental State Examination score (0–30)	28.37 (2.14)
History of chicken pox (score of 1)	2029 (67.8%)
History of measles (score of 1)	2684 (89.7%)
History of mumps (score of 1)	1866 (62.3%)
Total number of childhood infectious diseases (0–3)	2.20 (0.95)
Age (65–85 years)	73.50 (6.18)
Sex (male)	1372 (45.8%)
Education	Primary/none: 906 (30.3%) Secondary: 1119 (37.4%) Third/higher: 969 (32.4%)
Smoking status (smoker)	265 (8.85%)
Body mass index	0–24.99: 1001 (33.4%) 25–29.99: 1334 (44.6%) 30–39.99: 628 (21.0%) 40 +: 31 (1.0%)
Depression (a major depressive episode in the last 12 months)	99 (3.3%)

with differential effects on cognitive functioning. First, the most parsimonious model was recomputed without sex as a covariate for females then males, since females are at greater risk for impaired cognitive functioning (van der Flier and Scheltens, 2005). Second, the most parsimonious model was recomputed for persons aged 65–75 then aged 75–85, since cognitive functioning is related to age (van der Flier and Scheltens, 2005). Third, the most parsimonious model was computed for each of the three diseases (i.e. chicken pox, measles, and mumps) separately to show their individual effect on cognitive functioning. Fourth, the most parsimonious model was computed using a saturated model in which dummy variables for one, two, or three childhood infectious diseases were entered as covariates. Fifth, the most parsimonious model was computed for each of the MMSE subscales (i.e. orientation, registration, attention and calculation, recall, and language) separately. Sixth, the most parsimonious model was computed without education to account for effects of mediation. Seventh, possible methodological confounders were considered. Although dichotomizing may be problematic (Altman and Royston, 2006), for robustness and because dichotomous models have increased clinical lure, the most parsimonious model was recomputed dichotomized to account for intact cognitive functioning versus impaired cognitive functioning. Impaired

cognitive functioning was defined using a cutoff score of 1.5 standard deviations below the mean score of the MMSE (Palmer *et al.*, 2002). Additionally, the most parsimonious model was recomputed for observed data with missing values and compared to the primary analysis based on imputed data (Sterne *et al.*, 2009).

Results

Data imputation and sample characteristics

The data were imputed using multiple imputations because simulation studies showed the technique to be robust even if the data are not missing at random (Sinharay *et al.*, 2001). The analytic sample consisted of 2994 older adults. The sample had a mean age of 73.50 (SD = 6.18) and 54.2% ($N = 1,622$) were female. The average MMSE score was 28.37 (SD = 2.14). Most of the participants had a history of measles (89.7%; $N = 2,684$), chicken pox (67.8%; $N = 2,029$), and/or mumps (62.3%; $N = 1,866$). See Table 1 for all sample characteristics.

Primary statistical analysis: cognitive functioning and the number of childhood infectious diseases

Comparison of the six regression models showed that model 2 was the most parsimonious (BIC = 12646.09; see supplementary Table S1 for comparison of BIC values for all regression models published as supplementary material online attached to the electronic version of this paper at <https://doi.org/10.1017/S1041610220001404>). This model accounted for the linear effect of the number of childhood infectious diseases on MMSE scores (Figure 1), adjusted for age, sex, education level, smoking status, body mass index, and depression. Late-life cognitive functioning improved as the number of childhood infectious diseases increased. Each disease incremented the MMSE score by 0.18. For two diseases, the MMSE total score increased by 0.36. Having had three diseases increased the MMSE score by 0.54. See Table 2 for model statistics.

Sensitivity analyses

Model 2, accounting for the linear effect of the number of childhood infectious diseases, age, education level, smoking status, body mass index, and depression on MMSE scores, was recomputed for all sensitivity analyses. A significant effect of childhood infectious diseases was found for males ($N = 1372$), females ($N = 1622$), persons aged 65–75 ($N = 1828$), persons aged 75–85 ($N = 1166$), each of

Table 2. Model 2 statistics

Variable	Coefficient	95% CI	P-value
Age	-0.09	-0.10 ; -0.07	<0.001
Sex (female)	0.05	0.09 ; -0.20	0.47
Education (secondary)	0.79	0.61 ; 0.96	<0.001
Education (third/higher)	1.20	1.02 ; 1.38	<0.001
Smoking (smoker)	-0.53	-0.78 ; -0.28	<0.001
BMI (25-29.99)	0.10	-0.07 ; 0.26	0.24
BMI (30-39.99)	-0.02	-0.22 ; 0.18	0.85
BMI (40+)	-0.35	-1.06 ; 0.36	0.33
Depression	-0.32	-0.72 ; 0.08	0.11
No. diseases	0.18	0.11 ; 0.26	<0.001

Note. Model 2 is the linear effect of the number of childhood infectious diseases, age, sex, education level, smoking status, body mass index, and depression on Mini-Mental State Examination scores.

Sex reference group = male.

Education reference group = primary/none.

Smoking status reference group = non-smoker.

Body mass index reference group = 0–24.99.

Depression reference group = not having had a major depressive episode in the last 12 months.

Abbreviations: BMI = Body Mass Index; No. diseases = the number of childhood infectious diseases.

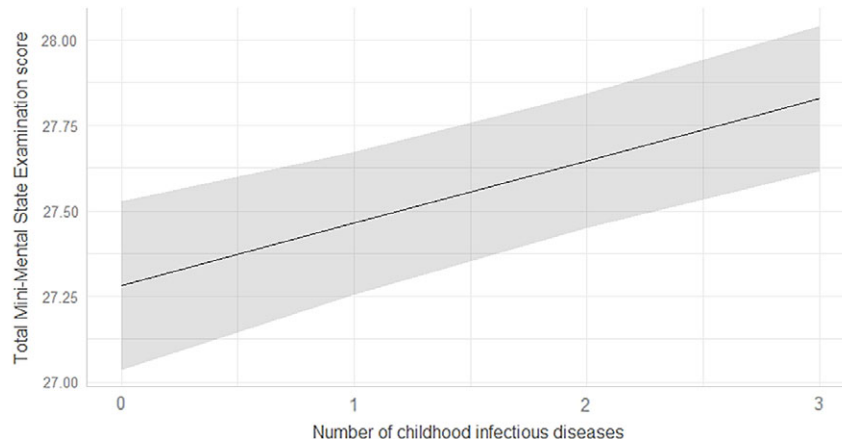


Figure 1. The linear adjusted effect of the number of childhood infectious diseases on Mini-Mental State Examination scores.

Note. For this adjusted model, having had one disease increases the Mini-Mental State Examination score by 0.18, all other covariates equal. Having had two diseases increases the Mini-Mental State Examination total score by 0.36, all other covariates equal. Having had three diseases increases the score by 0.54, all other covariates equal.

the childhood infectious diseases separately (chicken pox, measles, and mumps), a saturated model (in which the effect size increased as the number of childhood infectious diseases increased), each sub-scale of the MMSE separately, a dichotomized regression model (intact cognitive functioning vs. impaired

cognitive functioning), a model without education, and observed data with missing values (in which 191 people were excluded due to missingness; $N=2803$). See supplementary Tables S2–S17 for model statistics (published as supplementary material online attached to the electronic version of this paper).

Discussion

The current study examined the association between childhood infectious diseases and old age cognitive functioning, among community-dwelling older adults, using data from a representative national sample. The primary results show that late-life cognitive functioning improved as the number of childhood infectious diseases increased. Specifically, for each additional disease, there was an improvement in cognition reflecting a 0.18 MMSE total point increase. The primary result was not statistically significantly attenuated in a series of sensitivity analyses, including four subgroups with potentially differential cognitive functioning, two methodological confounders, two alternative models, each infectious disease and each MMSE subscale examined. The strongest effects were found among females and among those aged 75–85 years.

The current study results are consistent with prior ecological findings showing that some childhood infectious diseases (i.e. influenza) are associated with better cognitive functioning (i.e. successful counting) in old age (Case and Paxson, 2009). The literature provides related examples of early-life infectious diseases having a protective effect on health in later life. For instance, the varicella zoster virus that causes chickenpox is consistently reported to have an inverse association with glioma (Amirian *et al.*, 2016). Similarly, measles and/or combined childhood infections (chicken pox, measles, mumps, pertussis, and rubella) were found protective for Hodgkin's disease (Alexander *et al.*, 2000).

Consistent with prior studies that have reported positive long-term health effects of childhood infectious diseases, our results contribute to identifying modifiable risk factors positively related to older-life cognitive functioning. Tentative explanations of our results are (I) selective mortality; and/or (II) that low levels of exposure to harmful agents may have beneficial effects via hormetic processes (Rattan, 2008). Future studies may identify possible mechanisms.

The current study has several limitations. First, selective mortality may have occurred, biasing the current study results. Second, our results are restricted to chickenpox, measles, and mumps. Future research is warranted to ascertain the effects of other childhood infectious diseases on cognitive functioning in old age. Third, childhood infectious diseases were assessed through self-reports which are less reliable than testing for serum antibodies (Mortimer, 1978). Specifically, higher rates of prevalence for actual mumps antibodies are expected since one person in three who contracts mumps does not present any symptoms (Mortimer, 1978). Still,

prior evidence has suggested that these assessments of childhood health have reasonably good reliability and validity (Haas, 2007). In addition, past epidemiological studies have found similar prevalence rates as those reported in the current study for chickenpox, measles, and self-reported mumps (Mortimer, 1978; Pollock and Golding, 1993; Stocks, 1928). Nonetheless, it should be noted that a selection bias may have occurred as respondents with better cognitive function may have recalled their childhood experience of infectious diseases more accurately. Fourth, the MMSE relies on an interviewer administration and rating which may introduce further biases. Although the interviewer is given specific instructions for administration, differences resulting from the skill and style of the interviewer in eliciting answers and in scoring the answers given by the subject exist (Bowie *et al.*, 1999). Fifth, the sample did not include individuals with verified diagnoses of dementia or mild cognitive decline. Future studies may focus on individuals with and without dementia to extend the current findings.

Conclusions

In summary, despite its limitations, the current study draws on a large representative sample and is the first to examine the individual and cumulative effects of common childhood infectious diseases (chickenpox, measles, and mumps) on late-life cognitive functioning. The study results show a consistent positive association between the number of childhood infectious diseases and late-life cognitive functioning. Childhood infectious diseases may be a future direction for modifiable risk factors related to older-life cognitive functioning.

Conflicts of interest

None.

Description of authors' role

Both authors designed the study, conducted the statistical analyses, interpreted the data, and prepared the manuscript.

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Based on data collected through the Irish Longitudinal study on Ageing. Accessed via the Irish Social Science Data Archive -www.ucd.ie/issda.

Supplementary material

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