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Longitudinal association between pulmonary function and incident cognitive decline : Results of the SONIC cohort study

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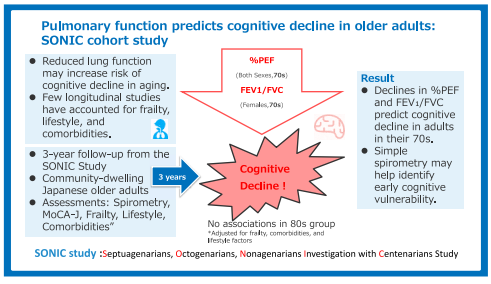
HIGHLIGHTS

- Examined if baseline spirometry-based pulmonary function links to cognitive decline.
- MoCA-J scores reduced among adults in their **80s** but were stable in those in their **70s**.
- Reduced %PEF was associated with **incident cognitive decline** only in participants in their **70s**.
- Reduced FEV1/FVC ratio was associated with increased **risk of cognitive decline** in females in their **70s**.
- Simple pulmonary measures may help identify those at risk.

GRAPHICAL ABSTRACT



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ABSTRACT

Reduced pulmonary function may contribute to cognitive decline in older adults; however, few longitudinal studies adjust for frailty, lifestyle, and comorbidities. This study examined whether baseline spirometry predicts 3-year cognitive decline in community-dwelling older Japanese adults. Data were derived from the SONIC Study, a longitudinal cohort of older Japanese adults. This 3-year follow-up included community-dwelling adults in their 70 s and 80 s, stratified by age and sex. Baseline and follow-up assessed anthropometry, physical frailty indicators (grip strength and gait speed), cognition (Montreal Cognitive Assessment, Japanese version [MoCA-J]) and pulmonary function (percent vital capacity [%VC], percent forced vital capacity [%FVC], percent forced expiratory volume in one second [%FEV_1], forced expiratory volume in one second / forced vital capacity ratio [FEV_1/FVC], and percent peak expiratory flow [%PEF]). Associations with mild cognitive decline were examined using logistic regression, adjusted for comorbidities, health behaviors, and frailty. Most pulmonary function measures markedly decreased over 3 years, whereas the FEV_1/FVC ratio remained stable. MoCA-J scores markedly declined among adults in their 80 s but remained stable in those in their 70 s. Reduced %PEF was

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markedly associated with cognitive decline only in participants in their 70 s, in males and females. Additionally, reduced FEV_1/FVC ratio was associated with increased cognitive decline in females in their 70 s. No significant associations were found in participants in their 80 s. In older adults, declines in %PEF and FEV_1/FVC ratio increased cognitive decline in the 70 s age group, with sex differences noted. Simple pulmonary measures may help identify those at risk.

1. Introduction

Dementia is one of the most urgent global public health challenges in ageing societies (World Health Organization, 2021). In Japan, dementia cases are projected to reach approximately seven million by 2025, accounting for one in five adults aged 65 years and older (Chen et al., 2024). By 2060, this proportion is expected to rise to one in six (Ministry of Health & Welfare, 2019) Globally, approximately 35.6 million people had dementia in 2012, with cases projected to nearly double by 2030 and triple by 2050 (World Health Organization, 2012). These trends highlight the urgent need for proactive dementia prevention strategies in Japan and worldwide.

Recent studies suggest that dementia incidence may be stabilizing or even declining in some countries, including Japan, possibly owing to improved education and healthier lifestyles (Satake et al., 2017) However, prevalence trends differ across regions, indicating diverse socioeconomic and environmental influences (Livingston et al., 2017; Satake et al., 2017).

Dementia pathogenesis is multifactorial and complex (Zhang et al., 2024). Vascular dysfunction, including chronic cerebral hypoperfusion, endothelial injury, and blood–brain barrier disruption, contributes to Alzheimer's disease and vascular dementia. Age-related mechanisms such as cellular senescence, oxidative stress, and mitochondrial dysfunction accelerate cognitive decline (Mattson & Magnus, 2006; Zlokovic, 2011). Environmental exposures (e.g., toxins, traumatic brain injury), neurodegenerative processes (e.g., abnormal protein aggregation), and chronic inflammation may also play important roles (Livingston et al., 2020). Arterial stiffness and pulse wave-induced vascular damage may contribute, although evidence remains limited (O'Rourke & Safar, 2005).

Emerging research suggests that pulmonary function may be linked to dementia risk (Tachibana et al., 2024; Li et al., 2023). Chronic hypoxia and pulmonary diseases such as chronic obstructive pulmonary disease reduce oxygen delivery to the brain, promoting neurodegeneration and cognitive impairment (Schou et al., 2012).. Moreover, reduced peak expiratory flow (PEF) has been linked to elevated dementia risk.(Tachibana et al., 2024). Sleep-disordered breathing, including obstructive sleep apnea, is associated with impaired pulmonary function and cognitive decline, although not directly assessed in this study (Blackwell et al., 2014). Prospective cohort studies have shown that reduced lung volumes, such as vital capacity, are associated with long-term cognitive decline(Vasilopoulos et al., 2015).. Furthermore, smoking is a major contributing factor to pulmonary decline and may affect cognitive function through its association with respiratory diseases (Oelsner et al., 2020).

Although reduced muscle strength and sarcopenia are also important determinants of frailty and cognitive outcomes among older adults in Japan (Tabara et al., 2025)., respiratory muscles and peripheral skeletal muscles do not necessarily decline in a parallel manner. The respiratory system is influenced not only by general age-related muscle loss but also by pulmonary mechanics, thoracic compliance, and neural respiratory control. Accordingly, respiratory function should be regarded as a distinct physiological domain rather than a simple reflection of generalized muscle strength. Understanding how pulmonary function relates to cognitive decline may thus provide new insights into mechanisms of brain vulnerability that differ from those linked to overall sarcopenia.

Therefore, examining the relationship between pulmonary function and cognitive decline, while accounting for smoking status is of particular importance.

Despite these findings, most prior studies used cross-sectional designs, limiting causal inference (Tachibana et al., 2024). In addition, some research focused on clinical populations with pre-existing diseases rather than healthy community-dwelling older adults. Longitudinal studies evaluating respiratory function as a predictor of cognitive decline in the general aging population remain scarce.

Moreover, previous studies have not sufficiently examined whether the association between pulmonary and cognitive function differs by age group or sex. Considering these gaps, the present study aimed to explore potential age- and sex-specific patterns in the relationship between pulmonary function and cognitive decline in community-dwelling older adults.

To address this gap, we conducted a longitudinal analysis using data from the SONIC Study (Septuagenarians, Octogenarians, Nonagenarians Investigation with Centenarians), a large Japanese cohort of community-dwelling older adults (Kamide et al., 2025). We examined whether baseline spirometry-based pulmonary function was associated with cognitive decline over a 3-year follow-up period. In addition, we evaluated whether age-related physical frailty, measured by grip strength and 1-minute walk test, modified this association.

2. Methods

2.1. Study design and population

This longitudinal cohort study was conducted using data from the SONIC Study, a nationwide prospective cohort of community-dwelling older adults in Japan (Iinuma et al., 2020; Kamide et al., 2025). Participants in the 70 s cohort were assessed at baseline in 2013 at age 73 years (±1 year), and those in the 80 s cohort in 2014 at age 83 years (±1 year). Each group underwent a follow-up assessment 3 years later. Initially, 449 individuals in their 70 s and 448 in their 80 s were enrolled (n = 897). Exclusion criteria included missing or outlier data on cognitive or pulmonary function tests, prior dementia diagnosis, missing physical frailty indicator data, or loss to 3-year follow-up. After exclusions, 396 participants remained (219 in their 70 s and 175 in their 80 s) (Fig. 1). These participants were included in all longitudinal and stratified logistic regression analyses.

Eligible participants were community-dwelling adults aged 70 years or older, randomly selected using the Basic Resident Registry in four Japanese regions (urban and rural areas in the Kansai and Kanto regions). Further details on sampling methodology and study protocol have been described elsewhere (Iinuma et al., 2020; Kamide et al., 2025).

The SONIC study was approved by the Institutional Review Boards of the Osaka University Graduate School of Medicine, Dentistry, and Human Sciences, and the Tokyo Metropolitan Institute of Gerontology (approval numbers: 266, H22-E9, 22,018, and 38). Written informed consent was obtained from all participants prior to their participation in the study.

2.2. Cognitive assessment

Cognitive function was assessed using the Japanese version of the Montreal Cognitive Assessment (MoCA-J), validated for detecting mild cognitive impairment in Japanese older adults (Fujiwara et al., 2010). Cognitive decline was defined as a decline of two or more points in the

MoCA-J score over the 3-year follow-up period (Marcucci et al., 2023; Tan et al., 2017).

2.3. Pulmonary function

Pulmonary function was evaluated by trained technicians at baseline using standard electronic spirometry (SP-370; Fukuda Denshi, Tokyo, Japan). The following spirometry indices were used as primary exposures:

- Percent predicted vital capacity (%VC)
- Percent predicted forced vital capacity (%FVC)
- Percent predicted forced expiratory volume in one second (%FEV_1)
- Forced expiratory volume in one second to forced vital capacity ratio (FEV_1/FVC)
- Percent predicted peak expiratory flow (%PEF)

Measurements were standardized using age, sex, and height-adjusted reference values based on Japanese normative data (Japanese Respiratory Society, 2023).

Pulmonary function was defined as abnormal when any of the following criteria were met VC<80 %, FEV_1/FVC <70 %, or PEF <80 % (Test, 2025).

2.4. Grip strength

Handgrip strength was measured as an indicator of physical frailty using a digital dynamometer (YD-100; Yagami Ltd., Japan). Measurements were conducted in a seated position, using the mean of two trials with the dominant hand. Low grip strength was defined as <26 kg for men and <18 kg for women (Cruz-Jentoft et al., 2019).

2.5. Gait speed

Gait speed was assessed using a 2.44-meter (8-foot) walk test. This distance was selected because it is the standard distance used in the Short Physical Performance Battery (SPPB) and in large-scale international cohort studies of older adults (e.g., Health ABC Study, NHATS), ensuring international comparability and feasibility even in limited testing spaces. Participants were instructed to walk at their usual pace, and gait speed was calculated by dividing 2.44 m by the time taken to walk the distance. The test was conducted once per participant.Gait speed < 1.0 m/s was defined as frailty according to the Asian Working Group for Sarcopenia (AWGS) 2019 criteria (Cruz-Jentoft et al., 2019)..

2.6. Covariates

Demographic, lifestyle, and health-related covariates were obtained via structured interviews and medical history. Variables included age, sex, years of education, smoking and alcohol consumption, and presence of comorbidities (hypertension, diabetes, dyslipidemia, cardiovascular disease) (Prince et al., 2015). Smoking status included current and former smokers, while alcohol consumption referred exclusively to current drinking. Smoking was categorized in this manner because it can cause permanent structural lung damage, which may affect pulmonary function even after cessation (Oelsner et al., 2020).

2.7. Statistical analysis

Descriptive statistics were used to summarize baseline and follow-up characteristics. Continuous variables are expressed as means with standard deviations [SD] or medians with interquartile ranges [IQR], as appropriate. Paired *t*-tests were used for normally distributed variables, and Wilcoxon signed-rank test for non-normal distributed data within-group baseline vs. 3-year follow-up comparisons (Tables 1 and 2).

Changes in cognitive performance from baseline to the 3-year follow-up were analyzed using the Wilcoxon signed-rank test for within-group comparisons, as the MoCA-J scores were not normally distributed.

Participants were stratified by age group (70 s and 80 s) and by baseline pulmonary function or smoking status.

Pulmonary function impairment was defined according to standard spirometry parameters as follows: %VC ≤ 80 %, FEV_1/FVC < 70 %, %

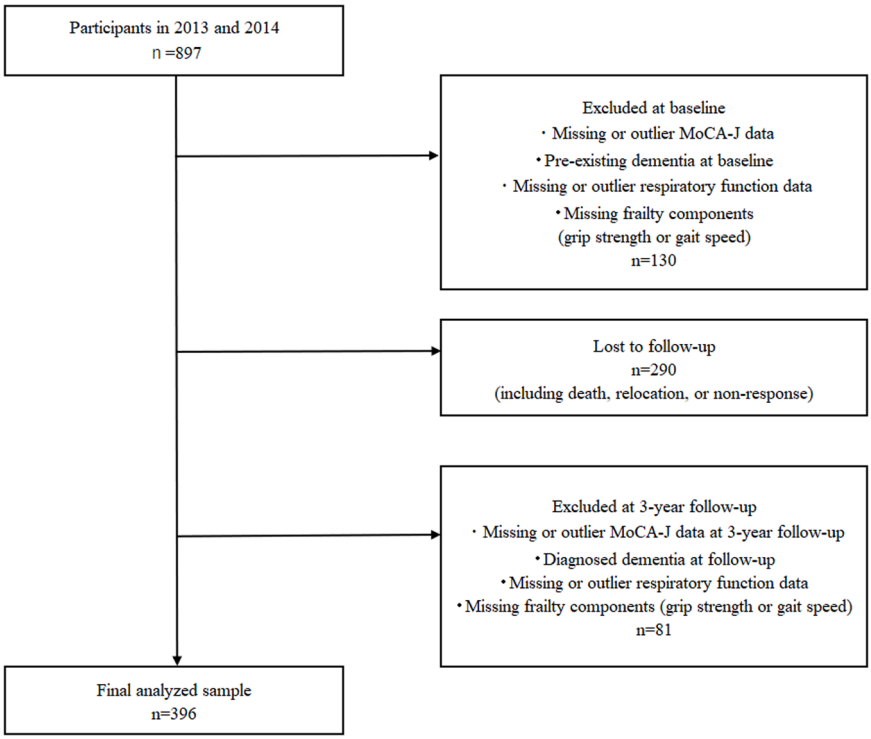

Fig. 1. Flow of participants through the study.

Table 1
Baseline and 3-year follow-up characteristics of adults stratified by age group (70 s and 80 s) and sex.

Variable	Sex	70s Baseline	70s 3 years later	*P-Value*	80s Baseline	80s 3 years later	*P-Value*
Height (cm)	**Male ($n = 218$) 70s ($n = 125$) 80s ($n = 93$)**	163.9[5.9]	163.3[6.0]	<0.01**	159.7 [5.8]	159.1 [5.6]	<0.01**
Weight (kg)		62.9[9.2]	62.0[9.2]	<0.01**	59.6 [7.9]	59.8 [8.2]	0.008
BMI (kg/m^2)		23.4[2.8]	23.2[2.8]	0.106	23.0 [21.5–25.2]	23.0 [21.0–24.8]	0.186
MoCA-J (point)		24.0[22–26]	23.4[22–26]	0.911	23.0 [21–26]	23.0 [21–25]	0.954
Grip (kg)		31.5[5.9]	31.5[6]	0.638	27.0 [5.8]	25.5 [5.3]	<0.01**
%VC (%)		137.0 [120.5–156.0]	95.3[85.7–159.6]	<0.01**	137.3 [122.2–152.8]	96.3 [88.5–107.3]	<0.01**
%FVC (%)		127.0 [109.5–144.3]	90.0[80.4–102.5]	<0.01**	126.1 [100.5–144.4]	97.7 [79.0–100.3]	<0.01**
%FEV$_1$ (%)		127.0 [106.0–141.9]	90.7[77.0–104.2]	<0.01**	126.9 [106.0–147.5]	95.7 [77.2–106.0]	<0.01**
FEV$_1$/FVC (%)		78.3[73.8–84.8]	78.8[74.1–82.7]	0.641	79.4 [10.2]	79.1 [10.2]	0.633
%PEF (%)		112.0[84.1–132.0]	82.8[59.6–98.4]	<0.01**	105.5 [79.9–139.4]	87.1 [60.1–104.1]	<0.01**
Height (cm)	**Female ($n = 178$) 70s ($n = 96$) 80s ($n = 82$)**	151.2[5.6]	150.6[5.6]	0.204	146.4 [5.4]	145.4 [5.6]	<0.01**
Weight (kg)		51.0[7.6]	50.8[7.8]	0.023*	46.8 [7.0]	45.9 [6.6]	<0.01**
BMI (kg/m^2)		22.3[3.2]	22.4[3.3]	0.368	21.5 [19.3–24.2]	21.3 [19.5–23.7]	0.041*
MoCA-J (point)		24.8[23–22]	24.0[22–26]	0.201	23.0 [21–26]	22.0 [20–25]	0.003**
Grip (kg)		19.2[4.1]	19.6[4.6]	0.366	16.8 [4.6]	16.4 [4.0]	0.241
%VC (%)		142.5 [126.0–158.3]	97.3[89.6–110.7]	<0.01**	145.2 [131.6–159.3]	103.8 [89.3–115.8]	<0.01**
%FVC (%)		137.0 [123.0–152.3]	97.4[89.1–110.7]	<0.01**	144.8 [125.6–158.7]	99.2 [84.6–113.4]	<0.01**
%FEV$_1$ (%)		140.1 [125.0–158.0]	103.0 [92.3–116.9]	<0.01**	155.8 [131.0–180.1]	109.7 [94.2–124.8]	<0.01**
FEV$_1$/FVC (%)		81.3[75.5–87.2]	82.0[77.2–85.9]	<0.01**	83.0 [77.5–87.5]	81.9 [77.3–87.8]	<0.01**
%PEF (%)		112.5[85.8–131.5]	85.5[65.1–100.7]	<0.01**	110.5 [63.6–126.2]	75.4 [54.5–91.8]	<0.01**

*Note. Data are shown as the mean [SD] or median [IQR] as appropriate. P-values were derived from paired t-tests or Wilcoxon signed-rank tests. %FEV$_1$, percent forced expiratory volume in 1 s; %FVC, percent forced vital capacity; MoCA-J, Japanese version of the Montreal Cognitive Assessment; %PEF, percent peak expiratory flow; %VC, percent vital capacity. *$p < 0.05$, **$p < 0.01$.*

Table 2
Comparison of medical history, lifestyle habits, and frailty by age group (70 s and 80 s) and sex.

	Male ($n = 218$)			**Female ($n = 178$)**		
	70s Baseline ($n = 125$)	**80s Baseline ($n = 93$)**	***P-Value***	**70s Baseline ($n = 96$)**	**80s Baseline ($n = 82$)**	***P-Value***
Medical history						
Hypertension	95 [76.0]	74 [79.6]	0.532	58 [60.4]	63 [76.8]	0.019**
Diabetes mellitus	25 [20.0]	19 [20.4]	0.938	4 [4.2]	22 [26.8]	<0.01**
Dyslipidemia	62 [49.6]	46 [49.5]	0.984	36 [37.5]	55 [67.1]	<0.01**
Coronary heart disease	28 [22.4]	20 [21.5]	0.875	14 [14.6]	16 [19.5]	0.381
Stroke	10 [8.0]	3 [3.2]	0.141	5 [5.2]	5 [6.1]	1.000
Healthy habits						
Current and former smoking	85 [69.7]	70 [75.3]	0.365	3 [60.0]	3 [40.0]	1.000
Current alcohol consumption	89 [73.0]	60 [65.2]	0.223	19 [19.8]	11 [14.3]	0.342
Frailty indicators						
Grip frail	35 [28.0]	62 [66.7]	<0.01**	33 [34.4]	53 [64.6]	<0.01**
Gait speed frail	48 [38.4]	48 [51.6]	0.052	32 [33.3]	51 [62.2]	<0.01**

Note. Values are presented as number [%].
***Grip frail:** defined as handgrip strength <26 kg for male and 18 kg for female, based on the Asian Working Group for Sarcopenia (AWGS) 2019 criteria.*
***Gait speed frail:** defined as gait speed below 1.0 m/s, based on the AWGS 2019 criteria.*
*p-values were calculated using chi-squared test (or Fisher's exact test where appropriate) *$p < 0.05$, **$p < 0.01$.*

PEF ≤ 80 %, both reduced FEV$_1$/FVC and %PEF.

Comparisons of MoCA-J scores between baseline and 3-year follow-up within each subgroup (e.g., normal, reduced %PEF, reduced FEV$_1$/FVC, and smoking status) are summarized (Table 3).

Logistic regression analyses were performed to examine the associations between cognitive decline (defined as $a \geq 2$-point decrease in the MoCA-J score) and potential predictors of pulmonary function. Two models were constructed. Model 1 was adjusted for medical history (hypertension, diabetes mellitus, dyslipidemia, coronary heart disease, and stroke) and healthy habits (current or former smoking and current alcohol consumption). Model 2 was further adjusted for frailty indicators (grip weakness and slow gait speed).

All covariates were simultaneously entered into the models using a forced-entry (enter) method, rather than a stepwise selection procedure. Multicollinearity among pulmonary function variables (%VC, %FVC, % FEV$_1$, FEV$_1$/FVC, and %PEF) was checked using variance inflation factors (VIFs), all of which were within acceptable limits (< 2.0). Analyses were stratified by sex and age group (70 s and 80 s) to explore potential effect modification (Tables 4).

All analyses were conducted using IBM SPSS Statistics version 29 (IBM Corp., Armonk, NY, USA). Statistical significance was set at $p <$ 0.05.

3. Results

3.1. Baseline and follow-up characteristics

In total, 396 community-dwelling older adults were included (218

Table 3
Changes in MoCA-J Scores from Baseline to 3-Year Follow-up by Respiratory Function and Smoking Status in 70 s and 80 s Age Groups.

Age Group	Group	Baseline	3-year follow-up	*P-Value*
70s	Normal ($n = 155$)	25.0	24.0	0.969
	Reduced FEV_1/FVC ($n = 35$)	24.0	24.0	0.273
	Reduced FEV_1/FVC and %PEF ($n = 20$)	24.0	24.0	0.497
	Reduced %PEF ($n = 51$)	24.0	23.0	0.047*
	Reduced %VC ($n = 2$)	19.5	22.0	0.655
	Current and Former Smoking ($n = 88$)	24.0	24.0	0.284
	No Smoking ($n = 127$)	25.0	24.0	0.116
80s	Normal ($n = 113$)	24.0	22.0	<0.001**
	No Smoking ($n = 102$)	23.0	22.0	<0.001**
	Current and Former Smoking ($n = 72$)	23.0	22.0	<0.001**
	Reduced %VC ($n = 3$)	25.0	19.0	0.286
	Reduced FEV_1/FVC ($n = 24$)	22.0	21.0	0.027*
	Reduced FEV_1/FVC and %PEF ($n = 15$)	21.0	21.0	0.284
	Reduced %PEF ($n = 53$)	22.0	20.0	<0.001**

*Note: Normal, %VC ≤80 %, FEV_1/FVC ≤70 %, %PEF ≤80 %, and both FEV_1/FVC and %PEF reduced groups were defined based on spirometry parameters at baseline. Data are presented as mean values. p-values were calculated using the Wilcoxon signed-rank test for within-group comparisons between baseline and 3-year follow-up. $p < 0.05$, **p** < 0.01 were considered statistically significant.*
Abbreviations: VC, vital capacity; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow.

males and 178 females), with mean baseline ages of 73 ± 1 years (70 s group) and 83 ± 1 years (80 s group). As shown in Table 1, mean weight significantly decreased over the 3-year follow-up in both age groups, height significantly decreased in all subgroups except females in their 70 s, and the BMI remained stable. Detailed baseline and follow-up characteristics are provided in the supplementary material ($p < 0.01$).

3.2. Comparison by age group and sex

Table 2 presents medical history, lifestyle habits, and frailty indicators stratified by age group and sex. Among females, hypertension, diabetes mellitus, and dyslipidemia was significantly more prevalent in the 80 s group than in the 70 s group ($p < 0.05$), with no significant differences in coronary heart disease or stroke. Smoking status and alcohol consumption did not significantly differ by age group; however, overall, additional analysis (not shown in the table) indicated that females had significantly lower rates than did males ($p < 0.05$). Grip strength and gait speed frailty were more prevalent in the 80 s group ($p < 0.05$).

3.3. Longitudinal changes in cognitive function by pulmonary function and smoking status

Table 3 illustrates the 3-year changes in MoCA-J scores stratified by pulmonary function and smoking status. In the 70 s group, participants with reduced PEF showed a significant decline in MoCA-J scores ($p < 0.05$), while scores in the normal pulmonary function group remained stable. In the 80 s group, participants with reduced PEF or lower FEV_1/FVC ratio showed greater declines than did those with normal function ($p < 0.05$). No significant changes were observed within smoking status subgroups in either age group.

3.4. Association between pulmonary function and cognitive decline

Table 4 shows the multivariate logistic regression analyses examining the association between abnormal pulmonary function and 3-year incidence of cognitive decline, defined as $a \geq 2$-point decrease in the MoCA-J score. After adjusting for age, lifestyle-related diseases, and health behaviors (Model 1), a reduced FEV_1/FVC ratio (<70 %) was significantly associated with an increased risk of incident cognitive decline only among females in their 70 s (adjusted OR = 4.2, 95 % CI = 1.02–17.51, $p = 0.046$). However, this association was attenuated and became non-significant after additional adjustment for frailty indicators (grip weakness and slow gait speed) in Model 2 (adjusted OR = 3.9, 95 % CI = 0.93–16.56, $p = 0.063$). In contrast, reduced %PEF (<80 %) consistently predicted incident cognitive decline in both males and females in their 70 s. In Model 1, the adjusted odds ratios were 3.5 (95 % CI = 1.31–9.19, $p = 0.012$) for males and 3.7 (95 % CI = 1.12–12.04, $p = 0.032$) for females. These associations remained statistically significant after further adjustment for frailty (Model 2), with adjusted ORs of 3.5 (95 % CI = 1.30–9.63, $p = 0.013$) for males and 3.5 (95 % CI = 1.07–11.50, $p = 0.039$) for females. No significant associations were observed among participants in their 80 s, although a similar direction of effect was seen for both %PEF and FEV_1/FVC ratio. These results suggest that reduced expiratory flow, particularly %PEF, may be a sensitive marker of cognitive vulnerability in the younger-old population, independent of age, chronic diseases, lifestyle habits, and frailty status.

Table 4
Multivariate logistic regression for 3-year incidence of cognitive decline with abnormal pulmonary function.

	Crude		*Adjusted OR Model 1*		*Adjusted OR Model 2*	
	OR (95%CI)	***P-Value***	**OR (95%CI)**	***P-Value***	**OR (95%CI)**	***P-Value***
FEV_1/FVC ratio<70 (No: 0, Yes: 1)						
70s Male	1.4 (0.55–3.57)	0.476	2.2 (0.77–6.11)	0.142	2.0 (0.69–5.76)	0.202
70s Female	2.1 (0.72–6.26)	0.173	4.2 (1.02–17.51)	0.046*	3.9 (0.93–16.56)	0.063
80s Male	2.7 (0.79–8.93)	0.113	2.9 (0.74–11.59)	0.124	2.9 (0.58–4.67)	0.129
80s Female	0.5 (0.12–2.14)	0.360	0.5 (0.11–2.60)	0.432	0.5 (0.11–2.60)	0.446
%PEF (%) <80 (No: 0, Yes: 1)						
70s Male	1.9 (0.84–4.28)	0.127	3.5 (1.31–9.19)	0.012*	3.5 (1.30–9.63)	0.013*
70s Female	1.1 (0.48–2.65)	0.782	3.7 (1.12–12.04)	0.032*	3.5 (1.07–11.50)	0.039*
80s Male	1.8 (0.67–4.58)	0.254	1.7 (0.62–4.63)	0.306	1.7 (0.584–4.67)	0.444
80s Female	1.2 (0.51–2.95)	0.647	1.2 (0.47–3.07)	0.705	1.073 (0.40–2.91)	0.891

Note. Cognitive decline was defined as $a \geq 2$-point decrease in the MoCA-J score over the 3-year follow-up (Yes = 1, No = 0).
Model 1 was adjusted for medical history (hypertension, diabetes mellitus, dyslipidemia, coronary heart disease, and stroke) and healthy habits (current or former smoking and current alcohol consumption).
Model 2 was adjusted for medical history (hypertension, diabetes mellitus, dyslipidemia, coronary heart disease, and stroke), healthy habits (current or former smoking and current alcohol consumption), and frailty indicators (grip weakness and slow gait speed).
For women in their 80 s, participants with a history of stroke (n = 5) or current/former smoking (n = 3) were excluded from the multivariate analysis due to the small sample size.
*OR = odds ratio; CI = confidence interval; MoCA-J = Japanese version of the Montreal Cognitive Assessment; %PEF = percent peak expiratory flow; FEV_1/FVC = forced expiratory volume in 1 s / forced vital capacity. *p < 0.05, *p < 0.01.*

4. Discussion

Maintaining both respiratory and cognitive functions is essential for extending healthy life expectancy in rapidly aging societies (Ksinan et al., 2024). From a public health perspective, identifying respiratory markers that are associated with subsequent cognitive decline may help guide community-based screening and preventive strategies for older adults. However, the most informative pulmonary function indicators for detecting early cognitive changes remain unclear (Duggan et al., 2020).

PEF may reflect not only airway caliber but also respiratory muscle strength, neuromuscular coordination, and overall physical resilience. Therefore, a decline in PEF could serve as an early marker of global physiological vulnerability, which may partly explain its consistent association with cognitive decline.

These findings indicate that expiratory flow capacity (%PEF) may reflect broader age-related physiological decline encompassing respiratory muscle strength, overall muscular performance, and physical frailty, rather than airway obstruction alone. The attenuation of associations after adjusting for frailty suggests that frailty may partly mediate the relationship between ventilatory impairment and cognitive decline. This interpretation aligns with previous findings that respiratory function, muscle strength, and cognition are interrelated components of late-life physiological resilience (Kim, 2018; Cui et al., 2021).

The observed association between lower %PEF and cognitive decline in the younger-old group (70 s) but not in those aged 80 and older may be influenced by survivor bias, where individuals with severe respiratory or cognitive impairments are less likely to survive to advanced age, resulting in a healthier analytic sample among the oldest participants. In older age, multiple comorbidities, polypharmacy, and advanced neurodegenerative changes may further dilute the relative contribution of pulmonary function to cognition. These patterns underscore the importance of maintaining respiratory function and preventing frailty from earlier stages of aging. This interpretation is further supported by our Supplementary Table 2, which showed that participants lost to follow-up—especially in their 80s—had lower baseline pulmonary function (%VC, %FEV_1, and %PEF) and poorer cognitive scores compared with completers. These differences indicate that selective attrition of more vulnerable individuals may have contributed to the reduced variability in pulmonary function among the oldest participants, making age-related associations with cognitive decline more difficult to detect (Kelfve et al., 2013).

While smoking status was not directly associated with cognitive decline, its detrimental impact on pulmonary function is well established (GOLD, 2023). Thus, smoking may exert indirect effects on cognition through chronic respiratory impairment. Sex-specific factors—including differences in airway size, thoracic biomechanics, and hormonal influences—may also contribute to variations in the pulmonary–cognition link (Somayaji & Chalmers, 2022; Vilor-Tejedor et al., 2024; Milne et al., 2024). In particular, post-menopausal inflammatory changes and more pronounced age-related declines in muscle mass among women may amplify the cognitive impact of mild airflow limitation (Somayaji & Chalmers, 2022; Vilor-Tejedor et al., 2024; Milne et al., 2024). The attenuation of the association between FEV_1/FVC and cognitive decline after adjustment for frailty in our study supports a partially mediated pathway through physical vulnerability in women.

Overall, our findings suggest that simple spirometry-derived indicators such as %PEF and FEV_1/FVC could be useful in identifying individuals at risk of cognitive decline in community settings. However, causal pathways remain to be clarified. Future studies incorporating longitudinal mediation or structural modeling, as well as physiological assessments (e.g., hypoxemia monitoring, inflammatory biomarkers, and respiratory muscle testing), are warranted to better understand the mechanisms linking respiratory and cognitive aging.

Some limitations of this study warrant consideration. First, the study population comprised relatively healthy, community-dwelling Japanese older adults (mean age 73 ± 1 years, and 83 ± 1 years in some analyses), excluding frailer or institutionalized individuals, which may introduce survivor bias and limit generalizability (Kelfve et al., 2013). As shown in Supplementary Table 2, participants who were lost to follow-up exhibited significantly lower pulmonary (%FVC, %FEV_1, %PEF) and cognitive (MoCA-J) function than those who completed the 3-year follow-up. This pattern was particularly evident among men in their 70 s and 80 s and among women in their 80 s, who showed significantly lower MoCA-J scores and %VC. These findings suggest that individuals with concurrent pulmonary and cognitive decline (pulmonary–cognitive comorbidity) were more likely to drop out or die, resulting in a relatively healthy and homogeneous analytic sample. Consequently, this selective attrition and "healthy survivor" effect may have attenuated or obscured associations in the oldest cohort, and the findings should be interpreted with caution when generalizing to frailer elderly populations.

Second, although the MoCA-J is a validated global cognitive screening tool, it may not detect subtle domain-specific impairments such as executive dysfunction or processing speed deficits that are relevant in early cognitive decline (Ciolek & Lee, 2020). In this study, cognitive decline was defined as $a \geq$ 2-point reduction in MoCA-J score over 3 years, consistent with prior literature (Nasreddine et al., 2005; Rossetti et al., 2011; Tachibana et al., 2024).

However, this cutoff may not equally represent clinically meaningful change across all subgroups, and the limited longitudinal sensitivity of the MoCA-J may have contributed to the absence of significant associations in some strata. In addition, self-reported data on health behaviors and medical history may be subject to recall bias, and residual confounding by unmeasured factors—such as nutritional status, sleep quality, occupational exposure, and lifelong activity—cannot be excluded.

Third, the relationships among pulmonary function, frailty, and cognitive decline are likely to be reciprocal rather than unidirectional, as suggested by recent evidence (Chen et al., 2024; Cui et al., 2021).

Decline in pulmonary function may promote frailty through reduced physical activity, while progressing frailty can further exacerbate ventilatory limitations, creating a feedback loop that contributes to cognitive vulnerability.

Although the present analyses could not statistically test these multidirectional pathways, future research using structural equation modeling or longitudinal mediation analysis is warranted to clarify these interdependent relationships.

Finally, because multiple subgroup analyses and several pulmonary parameters were examined without formal correction for multiple comparisons, the possibility of Type I error cannot be ruled out. However, this study was designed as an exploratory investigation to identify which aspects of pulmonary function are most strongly associated with cognitive decline across age and sex groups. While this exploratory approach may increase the likelihood of false-positive findings, it provides valuable hypotheses for future confirmatory and interventional research.

In addition, as shown in Supplementary Table 3, a post hoc power analysis for logistic regression revealed that the achieved statistical power ($1-\beta$) across subgroups ranged from 0.63 to 0.82. The smallest subgroup (80 s female) demonstrated slightly low power (0.63), whereas other subgroups reached moderate to adequate levels (0.69–0.82). These results suggest that some non-significant associations, particularly among older or smaller subgroups, may have been due to limited statistical power rather than the absence of true effects.

However, this study also has notable strengths, including its longitudinal design, standardized pulmonary function testing, and adjustment for multiple relevant covariates. In particular, the SONIC cohort uniquely includes long-term longitudinal data stratified by age groups among community-dwelling older adults, allowing the examination of age-specific physiological changes characteristic of late life. This design provides valuable insights into how aging processes differentially influence the association between pulmonary and cognitive functions.

Despite the limitations, the present findings suggest that simple pulmonary function measures such as %PEF and FEV_1/FVC ratio may be useful indicators for identifying older adults at higher risk of cognitive decline. These measures are easily obtainable in clinical and community settings and may help in early risk stratification. However, this study does not establish causality or the preventive efficacy of improving pulmonary function. Instead, the results highlight the potential importance of maintaining respiratory health and preventing frailty as complementary targets for preserving cognitive function in late life. Because frailty and pulmonary function likely interact reciprocally, interventions focusing solely on lung function may not be sufficient. Integrated strategies that address both respiratory and physical resilience—while accounting for sex-specific vulnerabilities—may ultimately prove most effective for maintaining cognitive health in aging populations.

5. Conclusion

This three-year longitudinal study of community-dwelling older Japanese adults demonstrated that declines in several pulmonary function parameters—particularly %PEF and the FEV_1/FVC ratio—were associated with increased risk cognitive decline, with some sex-specific patterns observed.

These findings suggest that reduced expiratory flow capacity may reflect a broader age-related physiological decline encompassing respiratory muscle strength and physical frailty, rather than representing a direct causal pathway.

Maintaining respiratory health and preventing frailty may play complementary roles in preserving cognitive function in aging populations; however, the observational nature of this study precludes causal inference. Future research with larger, more sociodemographically diverse cohorts and longer follow-up periods, incorporating detailed assessments of respiratory muscle strength, physical activity, and frailty, is warranted to confirm these associations and clarify underlying mechanisms.

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Declaration of generative AI use

During the preparation of this work, the authors used ChatGPT (OpenAI) to assist with English phrasing. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

CRediT authorship contribution statement

Yuka Tachibana: Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Keigo Kobayashi:** Software, Project administration, Methodology, Investigation, Conceptualization. **Mai Kabayama:** Project administration, Investigation, Funding acquisition. **Michiko Kido:** Investigation. **Yuya Akagi:** Software, Project administration, Methodology, Investigation. **Hiroshi Akasaka:** Writing – review & editing, Methodology, Investigation. **Yoshio Iwashima:** Investigation. **Saori Yasumoto:** Project administration, Investigation. **Yukie Masui:** Project administration, Investigation. **Kazunori Ikebe:** Investigation. **Takumi Hirata:** Writing – review & editing, Investigation. **Yasumichi Arai:** Investigation. **Yasuyuki Gondo:** Resources, Project administration, Investigation, Funding acquisition. **Koichi Yamamoto:** Investigation. **Kei Kamide:** Writing – review & editing, Methodology, Investigation, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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References

Blackwell, T., Yaffe, K., Laffan, A., Ancoli-Israel, S., Redline, S., Ensrud, K. E., Song, Y., Stone, K. L., & Osteoporotic Fractures in Men (MrOS) Study Group. (2014). Associations of objectively and subjectively measured sleep quality with subsequent cognitive decline in older community-dwelling men: The MrOS Sleep Study. *Sleep, 37*, 655–663. https://doi.org/10.5665/sleep.3562

Chen, L.-M., Inoue, M., & Buckley, N. (2024a). Case studies on community care in Japan: Considerations for mitigating social isolation and loneliness in older adults with dementia. *Frontiers in Public Health, 12*, Article 1411217. https://doi.org/10.3389/fpubh.2024.1411217

Chen, X., Yu, Z., Liu, Y., Zhao, Y., Li, S., & Wang, L. (2024b). Chronic obstructive pulmonary disease as a risk factor for cognitive impairment: A systematic review and meta-analysis. *BMJ Open Respiratory Research, 11*(1), Article e001709. https://doi.org/10.1136/bmjresp-2023-001709

Ciolek, C. H., & Lee, S. Y. (2020). Cognitive issues in the older adult. In D. Avers, & R. A. Wong (Eds.), *Guccione's geriatric physical therapy* (4th ed, pp. 425–452). Mosby.

Cruz-Jentoft, A. J., Bahat, G., & Bauer, J. (2019). Sarcopenia: Revised European consensus on definition and diagnosis. *Age and Ageing, 48*, 16–31. https://doi.org/10.1093/ageing/afy169

Cui, M., Zhang, S., Liu, Y., Gang, X., & Wang, G. (2021). Grip strength and the risk of cognitive decline and dementia: A systematic review and meta-analysis of longitudinal cohort studies. *Frontiers in Aging Neuroscience, 13*, Article 625551. https://doi.org/10.3389/fnagi.2021.625551

Duggan, E. C., Graham, R. B., Piccinin, A. M., Jenkins, N. D., Clouston, S., Muniz-Terrera, G., & Hofer, S. M. (2020). Systematic review of pulmonary function and cognition in aging. *Journals of Gerontology: Series B, 75*, 937–952. https://doi.org/10.1093/geronb/gby128

Fujiwara, Y., Suzuki, H., Yasunaga, M., Sugiyama, M., Ijuin, M., Sakuma, N., Inagaki, H., Iwasa, H., Ura, C., Yatomi, N., Ishii, K., Tokumaru, A. M., Homma, A., Nasreddine, Z., & Shinkai, S. (2010). Brief screening tool for mild cognitive impairment in older Japanese: Validation of the Japanese version of the Montreal Cognitive Assessment. *Geriatrics and Gerontology International, 10*, 225–232. https://doi.org/10.1111/j.1447-0594.2010.00585.x

Global Initiative for Chronic Obstructive Lung Disease (GOLD). (2023). *Pocket guide to copd diagnosis, management, and prevention*. https://goldcopd.org/wp-content/uploads/2023/03/POCKET-GUIDE-GOLD-2023-ver-1.2-17Feb2023_WMV.pdf.

Iinuma, T., Arai, Y., & Fukumoto, M. (2020). Comprehensive geriatric assessment of community-dwelling older adults in the SONIC study: Study design and preliminary findings. *Geriatrics and Gerontology International, 20*(Suppl. 2), 15–22. https://doi.org/10.1111/ggi.13933

Japanese Respiratory Society. (2023). *Guidelines for standardization of pulmonary function tests (2023 Revised Edition)*.

Kamide, K., Ikebe, K., Masui, Y., Nakagawa, T., Kabayama, M., Akasaka, H., Mameno, T., Murotani, Y., Ogawa, M., Yasumoto, S., Yamamoto, K., Hirata, T., Arai, Y., Gondo, Y., & S.O.N.I.C. Study Group. (2025). Multidimensional insights about healthy aging from the cohort study for community-dwelling older adults: The SONIC study. *Geriatrics and Gerontology International, 25*, 346–355. https://doi.org/10.1111/ggi.70003

Kelfve, S., Thorslund, M., & Lennartsson, C. (2013). Sampling and non-response bias on health outcomes in surveys of the oldest old. *European Journal of Ageing, 10*, 237–245. https://doi.org/10.1007/s10433-013-0275-7

Kim, N.-S. (2018). Correlation between grip strength and pulmonary function and respiratory muscle strength in stroke patients over 50 years of age. *Journal of Exercise Rehabilitation, 14*, 1017–1023. https://doi.org/10.12965/jer.1836444.222

Ksinan, A. J., Dalecká, A., Court, T., Pikhart, H., & Bobák, M. (2024). Pulmonary function and trajectories of cognitive decline in aging population. *Experimental Gerontology, 189*, Article 112386. https://doi.org/10.1016/j.exger.2024.112386

Li, Q. Y., Li, X. M., Hu, H. Y., Ma, Y. H., Ou, Y. N., Wang, A. Y., Tan, L., & Yu, J. T. (2023). Associations of lung function decline with risks of cognitive impairment and dementia: A meta-analysis and systematic review. *Journal of Alzheimer's Disease, 92*, 853–873. https://doi.org/10.3233/JAD-221136

Livingston, G., Sommerlad, A., Orgeta, V., Costafreda, S. G., Huntley, J., Ames, D., … Mukadam, N. (2017). Dementia prevention, intervention, and care. *The Lancet, 390*, 2673–2734. https://doi.org/10.1016/S0140-6736(17)31363-6

Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., Banerjee, S., … Mukadam, N. (2020). Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *The Lancet, 396*, 413–446. https://doi.org/10.1016/S0140-6736(20)30367-6

Marcucci, M., Thirumala, P., Mrkobrada, M., & Devereaux, P. J. (2023). Association of a ≥2-point decrease of MoCA 1 year after noncardiac surgery with patient-important outcomes: A secondary analysis of the NeuroVISION cohort study. *Neurology, 100*(17 Suppl. 2), 1884. https://doi.org/10.1212/WNL.0000000000202174

Mattson, M. P., & Magnus, T. (2006). Ageing and neuronal vulnerability. *Nature Reviews Neuroscience, 7*, 278–294. https://doi.org/10.1038/nrn1886

Milne, K. M., Mitchell, R. A., Ferguson, O. N., Hind, A. S., & Guenette, J. A. (2024). Sex differences in COPD: From biological mechanisms to therapeutic considerations. *Frontiers in Medicine, 11*, Article 1289259. https://doi.org/10.3389/fmed.2024.1289259

Ministry of Health, Labour and Welfare. (2019). *Comprehensive strategy to accelerate dementia measures*. https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000208970.html.

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., … Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society, 53*(4), 695–699. https://doi.org/10.1111/j.1532-5415.2005.53221.x

Oelsner, E. C., Balte, P. P., Bhatt, S. P., Cassano, P. A., Couper, D., Folsom, A. R., … Yende, S. (2020). Lung function decline in former smokers and low-intensity current smokers: A secondary data analysis of the NHLBI Pooled Cohorts Study. *The Lancet Respiratory Medicine, 8*, 34–44. https://doi.org/10.1016/S2213-2600(19)30276-0

O'Rourke, M. F., & Safar, M. E. (2005). Relationship between aortic stiffening and microvascular disease in brain and kidney. *Hypertension, 46*, 200–204. https://doi.org/10.1161/01.HYP.0000168052.00426.65

Prince, M. J., Wu, F., Guo, Y., Gutierrez Robledo, L. M., O'Donnell, M., Sullivan, R., & Yusuf, S. (2015). The burden of disease in older people and implications for health policy and practice. *The Lancet, 385*, 549–562. https://doi.org/10.1016/S0140-6736(14)61347-7

Pulmonary function test. (2025). *Physiopedia.* https://www.physio-pedia.com/Pulmonary_Function_Test.

Rossetti, H. C., Lacritz, L. H., Cullum, C. M., & Weiner, M. F. (2011). Normative data for the Montreal Cognitive Assessment (MoCA) in a population-based sample. *Neurology, 77*(13), 1272–1275. https://doi.org/10.1212/WNL.0b013e318230208a

Satake, S., Shimada, H., Yamada, M., Kim, H., Yoshida, H., Gondo, Y., … Arai, H. (2017). Prevalence of frailty among community-dwellers and outpatients in Japan. *Geriatrics and Gerontology International, 17*, 2629–2634. https://doi.org/10.1111/ggi.13129

Schou, L., Østergaard, B., Rasmussen, L. S., Rydahl-Hansen, S., & Phanareth, K. (2012). Cognitive dysfunction in patients with chronic obstructive pulmonary disease: A systematic review. *Respiratory Medicine, 106*, 1071–1081. https://doi.org/10.1016/j.rmed.2012.03.013

Somayaji, R., & Chalmers, J. D. (2022). Just breathe: A review of sex and gender in chronic lung disease. *European Respiratory Review, 31*, Article 210111. https://doi.org/10.1183/16000617.0111-2021

Tabara, Y., Matsumoto, T., Murase, K., Kawaguchi, T., Setoh, K., Wakamura, T., … Matsuda, F. (2025). Descriptive epidemiology and prognostic significance of diaphragm thickness in the general population. *Journal of Cachexia, Sarcopenia and Muscle, 16*(1), 1–12. https://doi.org/10.1002/jcsm.13690

Tachibana, Y., Godai, K., Kabayama, M., Akagi, Y., Kido, M., Hosokawa, M., … Kamide, K. (2024). Relationship between respiratory function assessed by spirometry and mild cognitive impairment among community-dwelling older adults. *Geriatrics and Gerontology International, 24*, 1001–1007. https://doi.org/10.1111/ggi.14962

Tan, H. H., Xu, J., Teoh, H. L., Chan, B. P. L., Seet, R. C. S., Venketasubramanian, N., … Dong, Y. (2017). Decline in changing Montreal Cognitive Assessment (MoCA) scores is associated with post-stroke cognitive decline. *PLOS One, 12*, Article e0173291. https://doi.org/10.1371/journal.pone.0173291

Vasilopoulos, T., Kremen, W. S., Grant, M. D., Panizzon, M. S., Xian, H., Toomey, R., Lyons, M. J., Jacobson, K. C., & Franz, C. E. (2015). Cognitive ability at age 20 predicts pulmonary function 35 years later. *Journal of Epidemiology and Community Health, 69*, 261–265. https://doi.org/10.1136/jech-2014-204143

Vilor-Tejedor, N., Rodríguez-Fernández, B., Genius, P., Fernández-Bonet, A., González-Escalante, A., Brugulat-Serrat, A., … Gispert, J.D. (2024). Sex-specific neuroinflammatory responses to air pollution mediate cognitive performance in cognitively unimpaired individuals at risk of Alzheimer's disease. *medRxiv*. https://doi.org/10.1101/2024.08.09.24311733.

World Health Organization. (2012). *Dementia: A public health priority*. https://www.who.int/publications/i/item/dementia-a-public-health-priority.

World Health Organization. (2021). *Global status report on the public health response to dementia*. https://www.who.int/publications/i/item/9789240033245.

Zhang, J., Zhang, Y., Wang, J., Xia, Y., Zhang, J., & Chen, L. (2024). Recent advances in Alzheimer's disease: Mechanisms, clinical trials and drug development strategies. *Signal Transduction and Targeted Therapy, 9*, 211. https://doi.org/10.1038/s41392-024-01911-3

Zlokovic, B. V. (2011). Neurovascular pathways to neurodegeneration in Alzheimer's disease. *Nature Reviews Neuroscience, 12*, 723–738. https://doi.org/10.1038/nrn3114