

Community-level Educational Attainment and Dementia: A 6-year Longitudinal Multilevel Study in Japan

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Abstract

Background:

Understanding of the association between community-level socioeconomic status and dementia is insufficient. We examined the contextual effect of community-level prevalence of lower educational attainment on the risk of dementia incidence. This work further explored the potential differences in associations for urban and non-urban areas.

Methods:

We analyzed a six-year prospective cohort data from the Japan Gerontological Evaluation Study, a nationwide survey between 2010 and 2012 of 49,888 (23,339 men and 26,549 women) physically and cognitively independent individuals aged ≥ 65 years from 346 communities at 16 municipalities in seven prefectures. Dementia incidence was assessed through the public long-term care insurance system by the Ministry of Health, Labor, and Welfare in Japan. Educational years were dichotomized as ≤ 9 years and ≥ 10 years. We classified urban and non-urban areas using a Functional Urban Area defined by the European Union (EU) and Organisation for Economic Co-operation and Development (OECD). We performed a two-level (community- and individual-level) multilevel survival analysis to calculate hazard ratios (HRs) and 95% confidence intervals (CIs).

Results:

The cumulative incidence of dementia during the follow-up period was 10.3%. The mean proportion of educational attainment with ≤ 9 years was 41.1% (range, 4.7%–88.4%). Higher prevalence of community-level lower educational attainment had a significant association with a higher risk of dementia incidence (HR, 1.03; 95% CI, 1.00–1.06, estimated by 10 percentage points of lower educational attainment) post adjusting for individual-level educational years, age, sex, income, residential years, disease, alcohol, smoking, social isolation, and population density. The association was significant in non-urban areas (HR, 1.05; 95% CI, 1.00–1.10).

Conclusions:

Older people living in communities with a higher prevalence of less educational attainment among their age demographic tended to develop dementia more often than those living in areas with a lower prevalence of less educational attainment after adjusting for individual-level educational attainment and covariates. In particular, the association was more pronounced in non-urban areas than in urban areas. Securing education for adolescence as a life course and population approach could thus be crucial to prevent dementia later in life among all older people living in non-urban areas.

Background

Dementia is a major global health issue due to rapid population aging worldwide, with over 50 million people being affected. The total number of people with dementia will reach 82 million in 2030 and 152 million in 2050 [1]. Mostly, half of the new 10 million dementia cases occur in Asia [2]. Dementia not only affects an individual's personal life, family, and career but also adds to high medical and social care costs [3].

A recent review reported that 40% of dementia cases are preventable, although there is currently no cure. The following 12 risk factors for dementia should be focused on: less education in early life, hearing loss, traumatic brain injury, hypertension, alcohol consumption, and obesity in midlife, smoking, depression, social isolation, physical inactivity, air pollution, and diabetes in late life. The second-highest percentage of these risk factors is less education [4]. A systematic review showed that lower education was associated with an increased risk for cognitive decline or dementia [5]. Recently, understanding the association between community-level, rather than individual-level, socioeconomic status (SES) and dementia and cognitive impairment is emphasized. For example, we can examine how community-level inequality of income affects individual-level dementia incidence after adjusting for individual-level SES. A systematic review found that lower community-level SES was associated with worse cognition [6]. Another review identified that living in urban areas was likely to reduce cognitive decline risk when compared to those in rural areas [7]. On the other hand, a recent US study showed that the prevalence of dementia declined more significantly among adults living in rural areas than those in urban areas over the past few decades as a result of improving educational attainment [8].

However, earlier studies might have four limitations relating to their research design. First, most were cross-sectional studies [6]. Second, the sample sizes in these studies were often limited to a few thousand participants [6]. Third, it was not common to adjust for confounding factors such as residential years [6, 9]. Fourth, exploring the relationship between community-level educational attainment and dementia among urban and rural older adults was insufficient [7, 8]. Overcoming the limitations of the aforementioned studies, this longitudinal study with large sample size data aimed to examine whether older populations living in communities with a higher proportion of lower educational attainment have the risk of dementia incidence when compared to those living in communities with a lower proportion of less education after controlling for individual-level educational years. We performed community- and individual-level multilevel analyses to investigate the contextual effect of community-level educational attainment on developing dementia among older individuals after adjusting for sufficient confounding factors. This work further explored the potential differences in associations for urban and non-urban areas.

Methods

Participants

This research was a six-year prospective longitudinal study with a large sample size data acquired from the Japan Gerontological Evaluation Study (JAGES). One objective of the JAGES is to identify social and behavioral factors associated with dementia onset among physically and cognitively independent individuals aged ≥ 65 years [10, 11]. A baseline mail self-reported questionnaire survey was administered from August 2010 to January 2012. In the study, 95,827 older people were chosen by random sampling from 16 municipalities in seven prefectures in Japan, including urban and non-urban areas. Among 62,426 respondents (response rate: 65.1%), 56,687 participants had valid information on ID number, sex, and age (valid response rate: 59.2%). To control for community-level educational attainment with a ≤ 9 years variable, we excluded 2,666 respondents who lived in communities with less than 30 respondents and whose information regarding the extent of educational attainment and residence was unknown. Excluding these respondents resulted in 54,021 respondents living in 346 areas primarily defined by the school district. Of the 56,687 valid participants, 54,554 (96.2%) respondents were successfully linked to the records of dementia incidence during a six-year follow-up term. A total of 49,888 participants (23,339 men and 26,549 women) were available for the present multilevel survival analyses (Figure 1). This sample size was determined after excluding survey respondents without information on the community-level variable (the extent of educational attainment) and those with limitations in basic activities of daily living, such as walking, bathing, and toileting, to ensure that the sample was both functionally and cognitively independent. Our research protocol and informed consent method were approved by the Human Subjects Committees of Nihon Fukushi University (no. 10-5) and the Chiba University Faculty of Medicine (no. 2493).

Measures

Dependent Variable

Our outcome was dementia incidence based on the public long-term care insurance records managed by the municipalities. The Ministry of Health, Labor, and Welfare (MHLW) in Japan established the Degree of Independency in Daily Lives of Demented Individuals [12]. In this system, a certification system in each local government sent personal investigators to applicants' homes to assess their nursing care eligibility (e.g., a home-helper). The investigators evaluated physical function, daily life ability, cognitive function, mental and behavioral disorders, adaptation to social life, and special medical treatment within 14 days [13, 14]. Following the assessment, the investigators classified the applicants into eight ranks on a dementia scale according to their cognitive disability (Supplementary Table S1) [14, 15]. The dementia scale was highly correlated with the Mini Mental State Examination (Spearman rank correlation $\rho = -0.74$) [16]. Moreover, another study showed that this dementia scale was a good indicator that reflects dementia diagnosis [17]. According to the MHLW, we defined rank II or above as dementia incidence showing some symptoms, behaviors, or communication problems during their daily lives [14, 18].

Community- and Individual-level Independent Variables

Participants were queried the following on educational attainment: "How many years of formal education have you had?" Answer choices included <6 , 6–9, 10–12, and ≥ 13 years. Educational attainment was

dichotomized, separating those with ≤ 9 years of education and those with ≥ 10 years [19]. The cut-off point of educational attainment was set to 9 years because this has been the amount of compulsory education in Japan since 1947 [20]. We aggregated individual-level educational attainment by the community as the community-level independent variable.

Covariates

The following variables reported to be risk factors for dementia were evaluated as potential confounders in this study [4, 6]. Data of age at baseline and sex were distributed based on the municipalities. Age was categorized into five groups: 65–69, 70–74, 75–79, 80–84, and ≥ 85 years. As community-level covariates, the inhabitable area's population density in the participants' residential school districts was divided into quartiles ($\geq 10,100$, 7900–10,099, 3280–7899, or < 3280 persons per square kilometer) [21]. We calculated an equivalized household income by dividing household income by the number of household members' square root. The income per year was categorized into three groups (≤ 1.99 , 2–3.99, or ≥ 4 million yen) [18]. Years of residence were classified as seven groups (< 5 , 5–9, 10–19, 20–29, 30–39, 40–49, or ≥ 50 years). Current medical treatment for those diseases known to raise the risk of dementia (stroke, hypertension, diabetes, and/or hearing loss) [4] was collected with yes/no answer choices. Health behaviors covered alcohol consumption (non, past, or current) and smoking status (non, past, or current). The definition of social isolation is social contact with other people less than once monthly [4]. We queried household members living with the participants and the frequency of seeing friends/acquaintances. In our study, socially isolated people were defined as those who live alone and meet with others less than monthly [21]. The individual-level covariates with missing data were assigned to a “missing” category. Therefore, participants with missing data on the covariates were included in the analysis.

Classification of Urban and Non-Urban Areas

We used the European Union (EU) and Organisation for Economic Co-operation and Development (OECD) definition of a Functional Urban Area (FUA). An FUA is a combination of multiple municipalities and consists of a city and its surroundings with less densely populated local units that are part of the commuting areas. FUAs are an excellent tool for comparing SES among cities [22]. FUAs are classified into the following four urban areas: 1) small urban areas with populations below 200,000; 2) medium-sized urban areas with populations from 200,000–500,000; 3) metropolitan areas with populations from 500,000 to 1.5 million; and 4) large metropolitan areas with populations above 1.5 million [23]. In this study, the cut-off point of urban areas was set at a population with 500,000. Therefore, metropolitan areas and large metropolitan areas were categorized as “urban areas,” and other areas were “non-urban areas” [24]. As a result, “urban areas” included five municipalities, and “non-urban areas” covered 11 municipalities.

Statistical Analyses

We performed a multilevel survival analysis incorporating both individual- and community-level factors. As recent research has reported that community-level factors had different impacts on urban and non-urban areas, we modeled urban and non-urban areas separately [8]. We calculated the hazard ratio (HR) and confidence interval (CI) for developing dementia during the follow-up term. The HR of community-level educational attainment was estimated as a 10 percentage point difference in aggregated educational attainment. Both community- and individual-level educational attainment and cross-level interaction terms were included in the crude model. In Model 1, the community-level covariate (population density) and individual-level covariates (age, sex, income, years of residence, stroke, hypertension, diabetes, hearing loss, drinking status, smoking status, and social isolation) were added. The significance level was set at less than 5% for all analyses. We used STATA/MP 16.1 (Stata Corp., College Station, TX) for all statistical analyses.

Results

The 49,888 participants in this study contributed to 263,419 person-years. In the study, 5,130 cases (10.3%) acquired dementia during the follow-up period. The incidence per 1000 person-years was found to be 19.5 people. Table 1 describes all respondents' demographics and socioeconomic characteristics and those stratified by urban and non-urban areas. Overall, the majority of participants in non-urban areas had educational attainment of ≤ 9 years; equivalized income of ≤ 1.99 million yen; and were current drinkers. The proportion of educational attainment with ≤ 9 years was calculated for each community. The mean (SD) and the ranges were 41.1% (17.5%) and 4.7–88.4% (Table 2).

Table 3 shows the results of the multilevel survival analyses for incident dementia. According to the analysis for all participants, Model 1—including the community-level covariate and individual-level covariates and community-level higher prevalence of lower educational attainment—demonstrated a significant relationship with a higher risk of dementia (HR, 1.03; 95% CI, 1.00–1.06), estimated by 10 percentage points of increment of a proportion of educational attainment in a community area. Individual-level educational attainment showed a significant association with a high likelihood of developing dementia (HR, 1.08; 95% CI, 1.01–1.16 in Model 1). There were no significant cross-level interaction terms in any models.

In Model 1, for the non-urban area participants, community-level higher prevalence of lower educational attainment demonstrated a statistically significant relationship with a higher risk of dementia (HR, 1.05; 95% CI, 1.00–1.10). We found a statistically significant cross-level interaction term (HR, 0.94; 95% CI, 0.88–0.999 in the crude model). This indicated that individuals with lower educational attainment declined 6% in dementia incidence, estimated by 10 percentage points of increment of a proportion of educational attainment in a community area. According to the analysis, for the participants in urban areas, the HRs of community-level higher prevalence of lower educational attainment were not significant in any of the models. In urban areas, individual-level educational attainment showed a significant relationship with a high likelihood of developing dementia (HR, 1.52; 95% CI, 1.40–1.65 in Crude Model). The significance disappeared in Model 1.

Discussion

This is the first study to find the contextual effects of community-level prevalence of less educational attainment and developing dementia among older people using data based on a longitudinal and large-scale sample. Older adults living in communities with a higher prevalence of less educational attainment among their age demographic tended to develop dementia more often than those living in areas with a lower prevalence of less educational attainment after adjusting for individual-level educational attainment and covariates. In particular, the association was more pronounced in non-urban areas than in urban areas.

Our results support the systematic review showing consistent evidence of an association between lower community-level SES, such as the proportion with no high school degree and worse cognition, after controlling for personal SES factors. A few longitudinal studies included in the review showed that community-level SES was significantly associated with cognitive decline. The proposed mediator between lower community-level SES and worse cognition may be social isolation [6]. In addition, previous studies have recommended that years of residence [6, 9] be included as potentially confounding factors. In our models, possible mediators and confounding factors, such as the abovementioned, were fully adjusted to overcome the existing studies' limitations. The current study was a longitudinal study with 50,000 participants, although the systematic review mainly included cross-sectional and small-sized studies of less than 10,000 [6]. Therefore, our study design was more robust than those of prior studies.

We found a contextual worse effect of community-level lower educational attainment on dementia incidence. People living in lower SES communities may heavily depend on community-level resources rather than individual-level ones due to the limitation of individual-level resources [25]. This means resources in the communities may affect the quality of life and health. Some disadvantages of lower SES communities (places with poor access, few bus lines, old-age income subsidies, and neighborhood organizations) were associated with lower cognitive decline [25, 26]. Moreover, previous studies have found that lower food store availability and lower sidewalk installation were associated with increased dementia incidence [14, 27]. Therefore, in the current study, lacking the physical and social resources in lower SES communities may increase dementia incidence when compared to higher SES communities.

Bridging social capital, which indicates a connection between different groups or SES levels, may be less developed in lower SES communities than in higher SES communities due to limited local resources. Therefore, the spreading of actions and information among people in lower SES communities may be inactive [28]. For example, people living in communities with stronger bridging of social capital may quickly acquire health or dementia prevention information through various local human networks. This idea is called "social contagion" [28, 29]. Moreover, the informal social control concept shows that people with higher social capital tend to work harder to maintain social order. These people ask people with unhealthy lifestyles, who include people with a lower SES, to change their health behaviors. In addition, people with unhealthy lifestyles can observe correct health behaviors and imitate their actions through community networks [28, 29]. Therefore, improving bridging of social capital among older adults with a

lower SES may result in a decline in the risk of dementia due to the effects of social contagion and informal social control.

On the other hand, there is strong bonding social capital in communities with a higher proportion of lower SES because people with a lower SES survive and help those with similar SES levels. Bonding social capital is associated with more psychological disorders [28]. This association may lead to raising the risk of dementia. In addition, because local resources are limited in lower SES communities when compared to higher SES communities, we may observe negative aspects of social capital, such as excessive demands on members, which leads to increased pain for a few limited, reliable members, and the exclusion of newcomers are residents with shorter years of residence [28]. The negative aspects of social capital may contribute to a higher risk of dementia. Development of human and economic resources, such as training community leaders and volunteer expenses, is simultaneously required in communities with more vital bonding social capital to reduce the negative impacts on social capital [28].

Our study is consistent with review articles that found that people living in urban centers tended to develop dementia less than those in rural areas [7, 30]. Although there was an unequal distribution or a lack of resources related to better cognitive function (health clinics, bookstores, and libraries) due to the deficit of educated consumer demand or taxes for such resources in lower education communities [26], this may more easily happen in non-urban areas than in urban areas. Similarly, people living in lower education communities, especially non-urban areas, may be disproportionately exposed to chronic and stressful life conditions that generate hazards, such as decreased employment opportunities or income. This situation results in a lack of social resources (social clubs and neighborhood organizations) and safe physical resources, including gyms [26]. In the current study, few resources in non-urban areas may increase dementia incidence when compared to urban areas.

A systematic review with a meta-analysis concluded that early life rural living was strongly associated with a risk of Alzheimer's disease [30]. In addition, previous studies have mentioned that rural areas had educational inequality, such as more insufficient educational opportunities and less quality of education [7, 31]. Although some children left rural areas and proceeded to higher grade schools in urban areas [31], many participants in the current study may live in the same rural areas where they received education for a long time [32]. A consequence of educational disadvantage in rural areas may cause an increase in the risk of dementia later in life [32], although we did not clarify the quality of education or the childhood residential areas in our study. On the other hand, a US study reported that cognitive decline was more significant among adults living in rural areas than those in urban areas during the past few decades. This resulted in a narrowing of the rural-urban disparities due to increasing education between 1910-1940 [8]. The same trend may occur in Japan in the future as compulsory education was extended from six to nine years in 1947 [20].

This study has some limitations. First, we did not identify transfers of residential areas, including urban to non-urban or non-urban to urban. In addition, we did not clarify the childhood residential areas among participants. However, we adjusted for years of residence to overcome the limitations of prior studies [6,

9]. Second, we did not consider the quality of education. However, the majority of SES indicators in the existing studies were educational years [6]. Third, the data on some potentially community-level confounding factors, such as accessibility of local services, were lacking, although population density was taken into account.

Conclusions

Older people living in communities with a higher prevalence of less educational attainment among their age demographic tended to develop dementia more often than those living in areas with a lower prevalence of less educational attainment after adjusting for individual-level educational attainment and covariates. In particular, the association was more pronounced in non-urban areas than in urban areas. Securing education for adolescence as a life course and population approach could thus be crucial to prevent dementia later in life among all older people living in non-urban areas.

List Of Abbreviations

CI: Confidence interval

EU: European Union

FUA: Functional Urban Area

HR: Hazard ratio

JAGES: Japan Gerontological Evaluation Study

MHLW: Ministry of Health, Labor, and Welfare

OECD: Organisation for Economic Co-operation and Development

SES: Socioeconomic status

Declarations

Ethics approval and consent to participate

The research protocol of JAGES and informed consent method were approved by the Human Subjects Committees of Nihon Fukushi University (no. 10-5) and the Chiba University Faculty of Medicine (no. 2493). We obtained written consent from the participants.

Consent for publication: Not applicable

Availability of data and materials

Data are from the JAGES study. All enquiries are to be addressed at the data management committee via e-mail: dataadmin.ml@jages.net. All JAGES datasets have ethical or legal restrictions for public deposition due to inclusion of sensitive information from the human participants. Following the regulation of local governments that cooperated on our survey, the JAGES data management committee has imposed the restrictions upon the data.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

TTa: conception, design, analysis and interpretation of the data, and writing the article; TTs: conception, design, interpretation of the data, and critical revision of the article; MH: conception, design, and critical revision of the article; YM: conception, design, and critical revision of the article; TO: critical revision of the article; and KK: conception, design, critical revision of the article, and principal investigator for the JAGES project. All authors read and approved the final draft submitted.

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Tables

Table 1. Descriptive statistics of all individual-level variables

	Urban		Non-Urban		Total	
<i>Individual-level variables</i>	n	%	n	%	n	%
Total	29,515	59.2%	20,373	40.8%	49,888	100.0%
Dementia onset						
No dementia	26,685	90.4%	18,073	88.7%	44,758	89.7%
Dementia	2,830	9.6%	2,300	11.3%	5,130	10.3%
Educational attainment (year)						
≤9	12,554	42.5%	12,113	59.5%	24,667	49.4%
≥10	16,961	57.5%	8,260	40.5%	25,221	50.6%
Sex						
Male	14,051	47.6%	9,288	45.6%	23,339	46.8%
Female	15,464	52.4%	11,085	54.4%	26,549	53.2%
Age						
65–69	8,381	28.4%	5,638	27.7%	14,019	28.1%
70–74	9,290	31.5%	5,833	28.6%	15,123	30.3%
75–79	6,713	22.7%	4,611	22.6%	11,324	22.7%
80–84	3,566	12.1%	2,861	14.0%	6,427	12.9%
≥85	1,565	5.3%	1,430	7.0%	2,995	6.0%
Disease status in treatment						
Stroke: no	28,647	97.1%	19,682	96.6%	48,329	96.9%
Stroke: yes	325	1.1%	286	1.4%	611	1.2%
Hypertension: no	17,393	58.9%	11,728	57.6%	29,121	58.4%
Hypertension: yes	11,579	39.2%	8,240	40.4%	19,819	39.7%
Diabetes: no	25,217	85.4%	17,543	86.1%	42,760	85.7%
Diabetes: yes	3,755	12.7%	2,425	11.9%	6,180	12.4%
Hearing loss: no	27,016	91.5%	18,295	89.8%	45,311	90.8%
Hearing loss: yes	1,956	6.6%	1,673	8.2%	3,629	7.3%
Data Missing	543	1.8%	405	2.0%	948	1.9%
Social isolation						

No	28,457	96.4%	19,753	97.0%	48,210	96.6%
Yes	623	2.1%	298	1.5%	921	1.8%
Data Missing	435	1.5%	322	1.6%	757	1.5%
Drinking status						
Non	10,092	34.2%	6,000	29.5%	16,092	32.3%
Past	997	3.4%	648	3.2%	1,645	3.3%
Current	16,647	56.4%	12,565	61.7%	29,212	58.6%
Data Missing	1,779	6.0%	1,160	5.7%	2,939	5.9%
Smoking status						
Non	15,533	52.6%	11,301	55.5%	26,834	53.8%
Past	8,169	27.7%	4,861	23.9%	13,030	26.1%
Current	3,093	10.5%	2,005	9.8%	5,098	10.2%
Data Missing	2,720	9.2%	2,206	10.8%	4,926	9.9%
Equalized income (million yen)						
≤1.99	11,008	37.3%	9,179	45.1%	20,187	40.5%
2–3.99	10,418	35.3%	5,663	27.8%	16,081	32.2%
≥4	3,219	10.9%	1,561	7.7%	4,780	9.6%
Data Missing	4,870	16.5%	3,970	19.5%	8,840	17.7%
Years of residence(year)						
<5	368	1.2%	467	2.3%	835	1.7%
5–9	419	1.4%	589	2.9%	1,008	2.0%
10–19	1,037	3.5%	1,138	5.6%	2,175	4.4%
20–29	1,395	4.7%	1,105	5.4%	2,500	5.0%
30–39	2,640	8.9%	1,709	8.4%	4,349	8.7%
40–49	5,523	18.7%	2,816	13.8%	8,339	16.7%
≥50	17,796	60.3%	12,233	60.0%	30,029	60.2%
Data Missing	337	1.1%	316	1.6%	653	1.3%

Table 2. Descriptive statistics of community-level variables

<i>Community-level Variables</i>	n	%	n	%	n	%
Total	292	84.4%	54	15.6%	346	100.0%
Proportion of Educational attainment						
Mean (SD)		41.1%	17.5%	(SD)		
(Min-Max)		(4.7%–88.4%)				
Population density (persons per square km of inhabitable area)						
Highest quartile ($\geq 10,100$)		86				
Second quartile (7900–10,099)		87				
Third quartile (3280–7899)		86				
Lowest quartile (< 3280)		87				

Table 3 Results of multilevel survival analysis for developing dementia (participants nested in 346 community areas)

	Crude		*	Model 1		*
	HR	95%CI		HR	95%CI	
All participants (N=49,888)						
Community-level educational attainment ^a	1.04	(1.01-1.06)	*	1.03	(1.00-1.06)	*
Individual-level educational attainment ^b	1.55	(1.44-1.66)	*	1.08	(1.01-1.16)	*
Cross-level interaction	0.97	(0.93-1.01)		0.99	(0.95-1.02)	
Non-Urban (n=20,373)						
Community-level educational attainment ^a	1.07	(1.02-1.12)	*	1.05	(1.00-1.10)	*
Individual-level educational attainment ^b	1.67	(1.44-1.93)	*	1.07	(0.93-1.24)	
Cross-level interaction	0.94	(0.88-0.999)	*	0.99	(0.93-1.05)	
Urban (n=29,515)						
Community-level educational attainment ^a	1.00	(0.97-1.04)		1.02	(0.98-1.05)	
Individual-level educational attainment ^b	1.52	(1.40-1.65)	*	1.08	(0.998-1.18)	
Cross-level interaction	0.97	(0.91-1.03)		0.99	(0.93-1.04)	

Notes: HR: hazard ratio; CI; confidence interval

^aHR for 10 percentage point increment of proportion of educational attainment in a community area.

^bHR for educational attainment less than 9 yr.

Model 1: crude model + age + sex + community-level covariate (population density) + individual-level covariates (income, years of residence, stroke, hypertension, diabetes, hearing loss, drinking status, smoking status, and social isolation).

*:p < 0.05

Figures

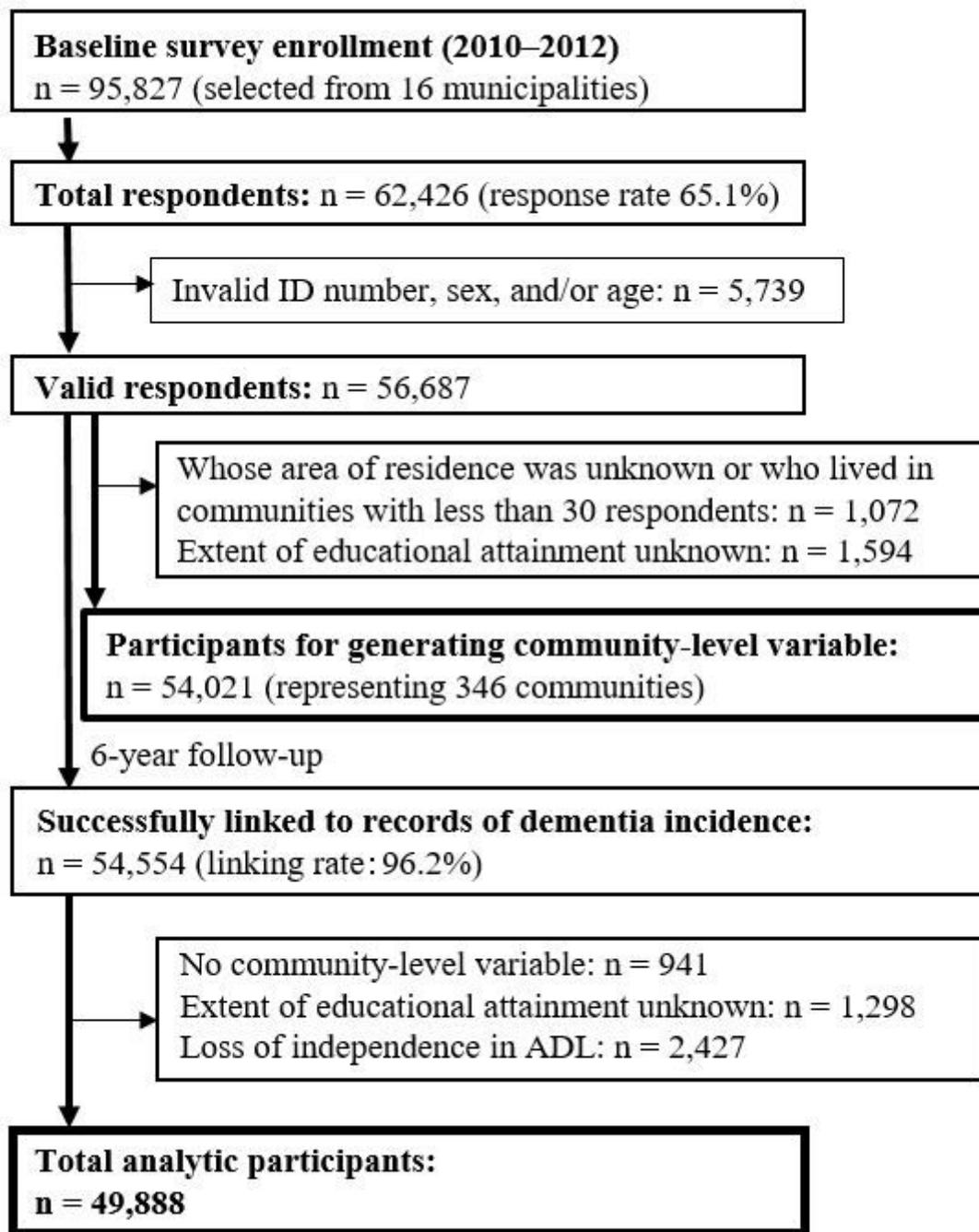


Figure 1

Flow of participants in the cohort study.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryTableS1.docx](#)