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ORIGINAL ARTICLE

An Alzheimer's dementia cumulative risk model in a sample of general population over 65: Public health implications

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Abstract
Background and objectives: With the population ageing, the identification of modifiable risk factors for dementia represents a public health priority. Co-occurrence of risk factors in the same individual is more frequent than an isolated appearance and may create synergistic effects, with an increased risk of negative outcomes such as dementia and mortality. We aim to study the cumulative risk of incident Alzheimer's Dementia (AD) in a community sample aged >65 (n= 3044).
Methods: To this end, we will examine the impact on the risk of AD of the co-occurrence of variables that have previously been shown to increase risk: age, gender, education, marital status, depression, anxiety, body mass index (BMI) and hearing loss.
Results: The most frequent number of co-occurring risk factors was 3. We found a cumulative increased risk of both death and AD by the confluence of 2 or more risk factors. Using a competing risk regression model, each increase in a co-occurring risk factor was associated with a significant increase in the risk of incident AD of more than two-fold. By the analysis of the Population Attributable Fractions (PAF) of AD due to several risk factors, we found that if 4 or more co-occurring risk factors could be eliminated from the population, the prevalence of AD would be reduced by approximately 38%.

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Conclusion: Our study offers an estimate of the impact that preventive interventions could have if the number of modifiable risk factors of AD at a population level.

Introduction

All dementias, with dementia due to Alzheimer's Dementia (AD) as the most common type, constitute significant economic and social burdens and are a global public health priority.[1] The disease has been on the rise with increasing life expectancy,[2] and the absolute number of people with dementia is expected to considerably increase in the future.[3,4] With currently no effective treatment options available,[5] the development of risk management programs through the identification of modifiable risk factors has become a scientific priority[6] with the potential to prevent around 35% of dementia cases by individually preventing these factors.[7]

Previous studies have predominantly explored the individual impact of these risk factors on dementia, even though the isolated occurrence is uncommon whereas the simultaneous presence of several risk factors in the same individual is the most frequent scenario.[8] To address this problem, different multifactorial dementia risk scales,[9] and some clinical trials focusing on prevention by acting on multiple risk factors have been conducted,[10] yet there is still a need to better understand how these risk factors co-occur and their impact on the population.

Finally, when studying multifactorial risk factors for dementia, the competing risk of death should also be considered. Since the main risk factor for Alzheimer's Dementia is older age, this is also directly related to a higher risk of death. Thus, not taking into account the risk of death could lead to biased risk estimates.[11]

The present study aimed to estimate the impact on the individual risk of AD associated with the exposure to one or several risk factors, based on data from our previous study (an AD score risk that includes age, gender, education level, marital status, depression and anxiety, BMI, and hearing loss as risk factors),[12] and to observe the effect that their aggregation has on the prevalence of dementia in the general population. To do this, we calculated a gradient risk score according to the number of risk factors present and accounting for the competing risk of death. Then, for each level of this gradient, we calculated the Population Attributable Fraction (PAF). PAF is a widely used measure of the potential influence of risk prevention strategies and is useful for clinicians and policymakers.

Materials and methods

Sample and procedure

We used data from the Zaragoza Dementia and Depression (ZARADEMP) project, a longitudinal, population-based study intended to document the incidence and risk factors of somatic and psychiatric diseases in adults aged ≥55 years.[13] The sample was drawn from Spanish official census lists, included community-dwelling and institutionalised individuals (nursing homes, hospices, or any other care resources) and was stratified with proportional allocation by age and sex. The refusal rate was 20.5%, and 4803 individuals finally participated at baseline (starting in 1994). A two-phase screening procedure was implemented in the baseline (Wave I) and the two follow-up waves (Waves II and III) were completed for this study. This two-phase screening involved a first standardised clinical interview with a lay interviewer and a subsequent interview with a research psychiatrist if required. Validated, Spanish versions of international instruments were used for the assessment: the Mini-Mental Status Examination (MMSE); the Geriatric Mental State-B (GMS-B); the Automated Geriatric Examination for Computer Assisted Taxonomy (AGECAT)[14]; the History and Aetiology Schedule (HAS) (medical and psychiatric history data); the Katz's Index for basic activities of daily living (bADL's) and the Lawton and Brody scale for instrumental activities (iADL's); and the European Studies of Dementia (EURODEM) Risk Factors Questionnaire (for medical conditions). A more detailed account of the methods, along with data on the baseline sample and an account of the prevalence of risk factors, has been reported previously.[12,15–17] To allow comparison with the existing literature, we focused on participants aged 65 years and older.[12]

The Ethics Committee of the University of Zaragoza and the "Fondo de Investigacion Sanitaria" (FIS) approved the study, according to Spanish Law, and principles of written informed consent, privacy, and confidentiality have been maintained throughout the project.

Alzheimer's Dementia assessment and diagnosis

At the end of the baseline assessment, identified cases of dementia and subcases of dementia (GMS—criteria) were excluded for the follow-up waves (II and III). Incident dementia (including subtypes) was initially diagnosed at follow-up by a psychiatrist and the final AD DSM-IV diagnosis was made by consensus that required the agreement of at least three psychiatrists in a four-member panel. The validity of this diagnostic process has also been shown.[18] To document the accuracy of the panel, some detected cases were invited to a hospital diagnostic work-up, and NINCDS-ADRDA criteria were applied to diagnose AD. Agreement on the diagnosis of dementia and type of dementia was reached in 95.8% and 87.5% of the cases, respectively. For the purposes of our study, cases of mixed dementia were excluded, so only cases of Alzheimer's disease without other comorbid dementias were included.

ZARADEMP Alzheimer dementia risk index

The *ZARADEMP Alzheimer Dementia Risk Index* predicts an individual's risk of developing AD within 5 years based on selected risk factors easily accessible in primary care settings: age, sex, education, marital status, depression,

anxiety, BMI, and hearing loss.[12] The diagnoses of anxiety and depression were based on the GMS-AGECAT system, considering "cases" with a cut-off point of ≥3 confidence levels, which has demonstrated good sensitivity and specificity for the diagnosis of those cases of depression that require clinical intervention.[19]

Number of risk factors measurement

Each risk factor in the *ZARADEMP Alzheimer's Dementia Risk Index* was categorized as present (1) or absent (0) and a new variable was generated as the total number of risk factors present. Factors included (see Table 1): being older than 85 years, female, illiterate or formerly married (divorced, separated or widowed), having depression, anxiety, hearing impairment (or need of hearing aids), and not being overweight or obese (this includes normal body mass index (BMI) and underweight). These factors have been selected since they were shown to increase the individual risk of Alzheimer's Dementia in previous work, where they are explained in detail.[12]

Statistical analysis

To investigate the impact of the individual as well as aggregated risk factors for AD, we followed different steps.[12]

Table 1 Risk factors included in ZARADEMP Alzheimer Dementia Risk Index.

Risk factor	Value
Sociodemographic characteristics	
Age	
65 — 74	0
75 — 84	0
Over 85	1
Sex	
Male	0
Female	1
Education (years)	
Secondary or higher	0
Primary	0
Illiterate	1
Marital status	
Single	0
Married/in couple	0
Formerly married	1
Psychological risk factors	
Depression	
No case	0
Case	1
Anxiety	
No case	0
Case	1
Behavioural risk factors	
BMI	
Overweight/Obesity	0
Normal/Underweight	1
Medical risk factors	
Hearing loss	
No case	0
Case	1

First, we constructed cumulative incidence function (CIF) curves[20] for the number of risk factors to estimate the probability of incident AD. The cumulative incidence function approach (CIF) was used to display the risk of patients experiencing the event of interest (i.e., AD), taking into account the competing event (death) as time progressed.[20] Then, we test for equality of the CIF for each number of risk factors.[21] In the second step, we aimed to estimate the effect of baseline predictors on the cumulative incidence function by using the Fine and Gray[22] regression model. This model estimates a subdistribution hazard and it is considered a modified Cox proportional hazards model, allowing for competing risks to be taken into account.[23] Then, multivariate models were estimated to calculate the risk of developing AD over time. We confirmed the assumption of proportional hazards through the Therneau and Grambsch test.[24] In a third step, we estimated the fraction of population AD incidence attributable to each number of risk factors. The PAF estimates the proportion of AD risk that would be avoided if the condition (number of risk factors in this particular case) was prevented. To estimate the PAF)of AD due to the number of risk factors, the following calculation was performed: $[px(SHR - 1)/(1 + px(HR - 1))] \times 100$, where p represents the proportion of subjects who were exposed to each number of risk factors and SHR represents the subdistribution hazard ratio in the multivariate model.[25]

All p-values were two-tailed, and we used bootstrap resampling using the Kalbfleisch and Prentice method[26] to compute all confidence intervals (CIs) at the 95% level. Statistical analyses were conducted using *R* software,[27] with the *epiR* package to analyse epidemiologic data, and *cmprsk* the and *timereg* packages for survival analyses.

Results

The total number of co-occurring risk factors ranged from 0 to 7 (Tables 1 and 2), with a median of 3 risk factors. The most frequent number of co-occurring risk factors was 3 (n=1021), followed by 4 (n=887). Of the total sample, 2.8% (n=85) of the subjects developed AD, while 21.6% (n=650) died. Table 3 provides the prevalence of each of the risk factors included in the ZARADEMP Alzheimer Dementia Risk Index. All risk factors showed a progressively higher prevalence in the group with 4 or more risk factors, with the exception of marital status "married/in couple". Notably, the risk factor "age", defined in our study as being 85 years or older, appears to have a higher increase in prevalence in the groups with more risk factors, compared to having between 75 and 85 years of age, or being younger than 75 years of age.

According to this competing risk regression model, each increment in a co-occurring risk factor was associated with a significant increase in the risk of incident AD of more than two-fold (SHR: 2.19; 95% CI: 1.85-2.60; $p<0.001$, data not shown). Table 3 shows that taking into account the competing risk of death, the risk of AD increased as the number of co-occurring risk factors also increased. Using our scale, a 77-year-old male, with a primary school education, divorced, suffering from depression, being overweight and without hearing loss would have 2 risk factors in total and 8-fold risk of Alzheimer's Dementia. Conversely, an 86-year-old female, widowed, with a high school education, without

Table 2 Associations between the number of co-occurring risk factors at baseline and according to follow-up status.

No. of co-occurring risk factors at baseline	Follow-up status			Competing risk regression model	
	No AD *n* (%)	Incident AD *n* (%)	Deaths *n* (%)	SHR (95% CI)[a]	p-value
0 (*n*=12)	10 (83.3%)	0 (0%)	2 (16.7%)	reference	-
1 (*n*=140)	125 (89.3%)	0 (0%)	15 (10.7%)	0.83 (0.47-1.46)	0.480
2 (*n*=577)	480 (83.2%)	3 (0.5%)	94 (16.3%)	8.05 (2.29-28.22)	<0.001
3 (*n*=1021)	822 (80.5%)	15 (1.4%)	184 (18.1%)	9.10 (4.32-19.16)	<0.001
4 (*n*=887)	621 (70.0%)	37 (4.2%)	229 (25.8%)	10.17(5.33-19.42)	<0.001
5 (*n*=314)	184 (58.6%)	23 (7.3%)	107 (34.1%)	10.74 (5.41-21.32)	<0.001
6 (*n*=50)	29 (58.0%)	4 (8.0%)	17 (34.0%)	10.83 (3.47-33.75)	<0.001
7 (*n*=6)	1 (16.7%)	3 (50.0%)	2 (33.3%)	12.79 (4.02-40.65)	<0.001
p-value[a]		<0.001		<0.001	

Data are given as number (%).
Notes: AD: Alzheimer's Dementia; CI: Confidence Interval; SHR: Subdistribution Hazard Ratio.
[a] p-values from "normal approximation" of linear trend $\chi 2$ test with 1 *df*. PAF: Population-attributable fraction.

hearing loss, at a normal weight and suffering from anxiety, would have 5 risk factors and a 10.7-fold risk of Alzheimer's Dementia in the next 5 years.

Lastly, PAF estimates ranged from 0.9% (95% CI: 0% - 4.9%) for one risk factor to 38.1% (95% CI: 36.3% - 39.0%) for 4 or more risk factors (Table 4). This means that approximately 38% of the population's AD prevalence is due to the co-occurrence of 4 or more concurrent risk factors.

Discussion

In this study, we examined the effect of the co-occurrence of multiple risk factors and provided data on the potential prevention of Alzheimer's Dementia (AD) based on the reduction of these risk factors. We found a frequent co-occurrence of risk factors in our sample of subjects older than 65 years, with most individuals of the sample having 3

Table 3 Prevalence of the included risk factors.

Variables	1 risk factor(*n* = 140)	2 risk factors(*n* = 577)	3 risk factors (*n* = 1,021)	4+ risk factors (*n* = 1,257)
Sociodemographic characteristics				
Age (*n*,%)				
75-84	4 (2.9%)	62 (10.7%)	260 (25.5%)	571 (45.4%)
Over 85	3 (2.1%)	15 (2.6%)	124 (12.1%)	404 (32.1%)
Sex (*n*,%)				
Female	16 (11.4%)	79 (13.7%)	584 (57.2%)	1,006 (80.0%)
Education (years) (*n*,%)				
Primary	19 (13.6%)	390 (67.6%)	799 (78.3%)	1,058 (84.2%)
x Illiterate	2 (1.4%)	32 (5.5%)	80 (7.8%)	150 (11.9%)
Marital status				
Married/in couple	84 (60.0%)	453 (78.5%)	676 (66.2%)	490 (39.0%)
Formerly married	5 (3.6%)	50 (8.7%)	246 (24.1%)	720 (57.3%)
Psychological risk factors				
Depression (*n*,%)				
Case	1 (0.7%)	2 (0.3%)	31 (3.0%)	329 (26.2%)
Anxiety (*n*,%)				
Case	0 (0.0%)	2 (0.3%)	6 (0.6%)	62 (4.9%)
Behavioural risk factors				
BMI (*n*,%)				
Normal/Underweight	6 (4.3%)	68 (11.8%)	257 (25.2%)	647 (51.5%)
Medical risk factors				
Hearing loss (*n*,%)				
Case	0 (0.0%)	1 (0.2%)	0 (0.0%)	23 (1.8%)

We observed that, as the number of co-occurring risk factors increased, participants were more likely to develop AD or die (Table 2). A significantly higher probability of death compared to the probability of AD was observed for all number of co-occurring risk factors (*p*-<0.001).

Table 4 Influence of the number of concurrent risk factors on AD incidence across 5 years, based on competing risk multivariable model.

No. of co-occurring risk factors at baseline	% PAF (95% CI)
1 (*n*=140)	0.9 (0-4.9)
2 (*n*=577)	16.8 (15.9-17.7)
3 (*n*=1021)	30.2 (28.4-31.1)
4+ (*n*=1257)	38.1(36.3-39.0)

Notes: PAF: Population attributable fraction; CI: Confidence Interval.

or 4. Additionally, we observed a cumulative increased risk of both mortality and AD by the confluence of 2 or more risk factors. Using a competing risk regression model, each increment in a co-occurring risk factor was associated with a significant increase in the risk of incident AD of more than two-fold. On the other side, we estimated that *approximately 38% of the population's AD prevalence is due to the co-occurrence of 4 or more risk factors*.

To our knowledge, only three studies have previously examined the impact of the co-occurrence of various risk factors on the risk of AD.[28–30] Compared to our results, they found smaller risks for AD associated with a greater number of risk factors (HR= 3.5[28] and 2.6[29]). These three studies were mainly focused on vascular risk factors, which represent a small fraction of the risk factors currently identified.[31] In addition, they did not include age as a risk factor, which in our case is the main risk factor in the risk score.[12] Similar to our findings, Luchsinger et al.[28] and Qiu et al.[29] reported a gradual increment in the risk of AD as the number of risk factors increased. Conversely, in a study by Rönnemaa et al.[30], the authors did not find this gradual increment, probably due to the inclusion of different risk factors such as hypercholesterolemia or overweight (which in our study was identified as a protective factor), or the fact that they only focused on men. It is worth mentioning that none of these previous studies took into account the competing risk of death in their risk estimation. This gradual increment in the risk associated with the co-occurrence of several factors has also been reported for global dementia in a meta-analysis conducted in 2019.[32] The authors reported, based on a total of 18 studies, a pooled relative risk for AD of 1.20 for one factor, 1.65 for two and 2.21 for three or more. Again, our estimates appear to be higher than that reported by the meta-analysis, and this could be explained by the inclusion of a greater number of risk factors or the control of competing risks of death.

To our knowledge, this is the first study to provide PAF estimates for the co-occurrence of risk factors of AD based on a large population-based cohort study. A previous study on the risk of all-type dementia[33] showed an estimate of the PAF due to modifiable risk factors of 40%, which is similar to the one reported here. However, the factors used to calculate the PAF were different in this study, and they included older subjects in a narrow age range. Similarly, Norton et al.[34] provided the first estimate of PAF for AD of 31.4% related to several modifiable risk factors. They calculated PAF using relative risks of AD for these risk factors estimated from several meta-analyses and their prevalence and co-occurrence according to official UK surveys. The literature provides similar estimates based on PAF for AD: 45.2%, 48.4%, 30.5% and 33% in countries such as Italy,[35] Australia,[36] Germany[37] or the Netherlands,[38] respectively. These studies used a different methodological approach, included different variables as risk factors, and different estimates of AD risk and prevalence for each variable. This, as well as the inherent variability of different populations and settings, could explain the wide variability of the estimates. However, our PAF estimate was congruent with the expected variability reported in the literature. Additionally, and similar to the Rolandi et al. study,[33] we considered other non-modifiable risk factors (age and sex) and controlled for the competing risk of death, which would result in a more realistic and modest estimation of PAF for AD.

Even though physical health conditions, such as obesity, hypertension, diabetes mellitus and dyslipidaemia have been recognized by the WHO as targets for risk reduction of dementia[39] and are included in previous studies regarding the cumulative risk of dementia[33,40] or AD,[28–30] their effect could be age-dependent and more efficient when applying on middle-aged adults.[40] In fact, in our sample of subjects older than 55 years, we did not find a significantly increased risk of AD for diabetes, or vascular conditions and found a decrease in AD risk for overweighted subjects.[12]

Our study has several limitations. First, we analysed data from a cohort study with limited data collection, thus some variables that have been previously found to be related to an increased risk of AD have not been included in this study. For example, ApoE4 (one of the main risk factors for dementia[33]), living alone,[41] physical inactivity[42] or cognitive engagement[43] (included as targets for risk reduction of dementia by the WHO Guidelines;[39]) have been shown to be related to a higher risk of AD. Conversely, we included other potential risk factors, such as hearing loss, affective disorders, physical[44] and cognitive[45] activity. Anxiety, for example, has also been linked to sedentary behaviour[46] and it is directly related to social isolation.[47] Hearing loss has also been associated with social isolation.[48] Furthermore, this study is based on a risk calculation generated from a single cohort study, which limits the generalizability of the results and their application to global prevention strategies.[49] Furthermore, the initial exclusion from the risk score of certain risk factors, such as cardiovascular risk factors or drug use, as no relationship with AD was observed in our study, has prevented us from studying their effect when they co-occur with other risk factors. Nevertheless, most of the included factors in our model have been consistently recognized as risk factors for dementia and AD[12,31,42] and our PAF estimate is similar to previous studies about dementia[33] or in line with the observed variability regarding AD.[34–38]

Finally, we were unable to study the influence of the different combination patterns on the joint effects of the risk factors and, even though we analysed a considerable number of risk factors for AD, this number was not enough to analyse their clustering. This would be of interest since risk factors are often grouped in the form of specific clusters or lifestyle patterns[50] that have shown a different influence on cognitive function[51] and different levels of risk for dementia and/or AD.[52] Related to this, there is growing interest in addressing multiple health-related behaviours by cluster analysis, as opposed to single risk factors, to increase the

efficacy and efficiency of interventions in the general population.[50] In this sense, some socio-demographical factors included in our study, such as low education or having lost a marital partner, may be associated with unhealthy lifestyle clusters.[50] Psychological factors, such as anxiety and depression, could also be associated with harmful behaviours such as smoking[50] or physical inactivity[46,53] and with low cognitive engagement.[53] Additionally, clinical factors such as hearing loss are thought to decrease physical activity[44] and cognitive engagement[45] and increase social isolation.[48] Tobacco or alcohol use was analysed as an independent variable in our sample and was not associated with a significantly increased risk of AD.[12]

Some strengths of this study are the inclusion of a wider array of variables in the study of the effect of the co-occurrence of various risk factors on the incidence of AD, and the estimation of the potential impact of minimizing the number of co-occurrent risk factors on the prevalence of AD using population-based data. Additionally, the use of competing risk models allowed us to control for the risk of death, this being especially important in the case of AD.[11] Other similar studies[33,54] have also controlled for the risk of death when calculating the risk of dementia, but to the best of the authors' knowledge, this is the first study to calculate the risk of AD and PAF taking into account the risk of death.

Conclusions

Our findings of an increased risk of death associated with a higher number of risk factors support the importance of considering risk factors co-occurrence when analysing the risk associated with AD. The majority of these risk factors are modifiable; thus this can help design more precise preventive strategies. Additionally, the risk factors of AD evaluated in our study can be easily assessed by clinicians in their routine practice and do not require expensive medical tests; thus they can provide health advice or targeted interventions for individual patients according to their cumulative risk of AD.[55] Finally, an optimal preventive intervention for dementia could be obtained by targeting multiple risk behaviours at the same time, rather than individual factors.[39,50] In this sense, future studies focusing on how different health-related behaviours are clustered in older adults and how this might impact the risk of AD are needed.[50]

Author contributions

J. B.-N. participated in the study conceptualization and design, project administration, methodology, investigation, data curation, analysis and interpretation of data, writing-original draft preparation, writing-review and editing and visualization. P. G.-G. participated in the data curation, investigation, writing-review and editing, supervision and visualization. B.O. participated in the methodology, writing-review and editing, visualization and supervision. C. D.-L.-C. participated in visualization and funding acquisition. R. L.-A. participated in the study conceptualization and methodology, software, validation and visualization. A. L. participated in supervision, resources, investigation, project administration and funding acquisition. J. S. participated in the study conceptualization, methodology, software, validation, formal analysis, investigation, data curation, writing-review and editing, visualization, supervision and funding acquisition. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the CEIC Aragón (protocol code CP16/2012, 19 September 2012)

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

Data supporting this study is available on reasonable demand.

Conflict of Interest

We declare that Dr. Gracia-García has received financial support to attend scientific meetings from Servier, Pfizer, Lundbeck, Nutrición Médica, Esteve and Angelini. Dr. de la Cámara has received financial support to attend scientific meetings from Janssen-Cilag, Almirall, Eli Lilly, Lundbeck, Rovi, Esteve, Novartis and AstraZeneca. None of these activities is related to the current project. For the remaining authors, no conflicts of interest were declared. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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