RESEARCH ARTICLE

Nutritional status, survival and mortality in Alzheimer patients - a cross-sectional study [version 1; peer review: 1 approved with reservations, 1 not approved]

Elizama de Gregorio ¹, Dayanna Hartmann Cambruzzi Mendes ^{2,3},
Luan Henrique Patrzyk ², Luana Felski²,
Guilherme Barroso Langoni de Freitas ², Anne Karine Bosetto ¹,
Bárbara Luisa Fermينو², Maria Vaitsa Loch Haskel², Flávia Ivanski ²,
Juliana Sartori Bonini ², Camila Diedrich⁴,
Weber Cláudio Francisco Nunes da Silva⁵

¹Biological Sciences Department, Federal University of Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil

²Pharmacy Department, Midwest State University, Guarapuava, Paraná, Brazil

³Pharmacy Department, Federal Institute of Paraná, Palmas, Paraná, Brazil

⁴Chemistry Department, Federal Technological University of Paraná, Pato Branco, Paraná, Brazil

⁵Laboratory of Neuropsychopharmacology, Pharmacy department, Midwest State University, Guarapuava, Paraná, Brazil

V1 First published: 01 Feb 2018, 7:137
<https://doi.org/10.12688/f1000research.12984.1>
Latest published: 01 Feb 2018, 7:137
<https://doi.org/10.12688/f1000research.12984.1>

Abstract

Introduction: Dementia is a common health problem in elderly people, Alzheimer disease (AD) being the most prevalent. AD can be considered as a cause of death and must be registered on the death certificate of the patients. However, most of the time, the main cause of death registered is not related to AD, but as an underlying or contributing cause. For example, individuals who have AD and die from myocardium infarction. This study aimed to analyze if nutritional status was associated with survival and mortality for AD, and if AD was reported as actual cause of death on the death certificate

Methods: The study was carried out as a cross-sectional study with elderly citizens of the community registered in the National Health System (SUS), with cognitive, nutritional, biochemical and hematological evaluations of 30 AD patients in Guarapuava, Paraná state, Brazil.

Results: Significant differences were not observed between live and dead patients when evaluated considering the methods applied. Only 22% of the death certificates stated death due to AD. The patient's cause of death showed a strong relation to respiratory issues; potential explanations based on immunological, biochemical and comorbidity were not confirmed on this study.

Conclusions: AD was not declared as the cause of death in the

Open Peer Review

Approval Status ? X

	1	2
version 1
01 Feb 2018	view	view

1. **Robert Stewart** , King's College London, London, UK

2. **Irving E Vega**, Michigan State University, Grand Rapids, USA

Any reports and responses or comments on the article can be found at the end of the article.

majority of certificates, contributing to the underreporting and reducing the information of death due to AD in the country.

Keywords

Dementia, Alzheimer disease, mortality, nutritional value, survivorship

This article is included in the [Agriculture, Food and Nutrition](#) gateway.

Corresponding author: Juliana Sartori Bonini (juliana.bonini@gmail.com)

Author roles: **de Gregorio E:** Conceptualization, Writing – Original Draft Preparation; **Mendes DHC:** Conceptualization, Writing – Review & Editing; **Patrzyk LH:** Conceptualization; **Felski L:** Conceptualization; **de Freitas GBL:** Conceptualization; **Bosetto AK:** Investigation; **Fermino BL:** Project Administration; **Haskel MVL:** Conceptualization; **Ivanski F:** Conceptualization; **Bonini JS:** Methodology, Supervision; **Diedrich C:** Conceptualization; **da Silva WCFN:** Supervision

Competing interests: No competing interests were disclosed.

Grant information: This study was funded by the Association of studies, research and assistance to people with Alzheimer's disease (AEPAPA), the Araucaria Foundation and Coordination of Improvements of Higher Education Personnel (CAPES).

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Copyright: © 2018 de Gregorio E *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: de Gregorio E, Mendes DHC, Patrzyk LH *et al.* **Nutritional status, survival and mortality in Alzheimer patients - a cross-sectional study [version 1; peer review: 1 approved with reservations, 1 not approved]** F1000Research 2018, 7:137 <https://doi.org/10.12688/f1000research.12984.1>

First published: 01 Feb 2018, 7:137 <https://doi.org/10.12688/f1000research.12984.1>

Introduction

The dementias are classified among the most frequent health problems in elderly people¹. Alzheimer disease (AD) stands out as the most prevalent², occurring in more than 50% of the cases^{3,4}.

Alzheimer disease facilitates the advent of opportunistic diseases, which combined to the fragility of the person, deglutition disturbances, and malnutrition can increase the death risks¹. People with AD live on average 8.3 years from diagnosis among 65 years old, and 3.4 with diagnosis after 90 years^{4,5}.

According to the World Health Organization (WHO), AD can be considered as a cause of death and must be registered on the death certificate of the patients^{5,6}. Nevertheless, in the majority of cases, the main death cause is not related to AD, but other issues are usually listed as immediate causes. According to Ministry of Health the immediate cause of death is the disease, injury or last complication that occurred immediately prior to the moment of death, having a direct correlation with the basic cause of death⁷.

The lack of national data still constitutes a gap in the knowledge of the mortality due to AD, although it has a known impact on the patient, family and caregiver.

It is known that at the present time there is no medical intervention capable of preventing or curing AD, but a protective effect can come from a good diet and quality of life, therefore, nutrition is shown to play an essential role. In this context, the present study aimed to investigate whether nutritional status was associated with AD survival and mortality, and if AD was recorded as the underlying cause of death in the death certificate.

Method

The present study was conducted in the city of Guarapuava, central-west region of Paraná state, Brazil. We performed a cross sectional study with elderly citizens of the community registered in the National Health System (SUS), through which they receive, at no charge, specific drugs for AD⁸.

The patients of this study had their diagnosis of AD performed by SUS doctors, according to the “Neurological and Communicative Disorders and Cerebral Vascular Accident National Institute and the Association of Alzheimer Disease and Related Disturbs (NINCDS – ADRDA)”⁹.

Recruitment

Data were accessed in CELEPAR System (Information and Communication Technology Company of Paraná) after research project approval. After the identification (name and address) of the 66 patients with AD, provided by a computerized system (CELEPAR System), visits were made to patients’ homes. Patients / caregivers were invited to take part in the study, and a written informed consent form was signed by a person responsible/patient caregiver who agreed voluntarily to participate in the study.

Data collection

Data collection was carried out in two phases: the first between August and October 2011, for the anthropometric, nutritional measures, and hematologic exams. “Exclusions from the study were as follows: 7 patient due to death, 11 patient because they had moved from the city, 2 were not found at the address registered in the system, and 16 the caregivers did not accept to participate due to the patient status of weakness”. This left 30 patients remaining in the study.

Research was done in two phases, between August 2011 and June 2013. The first stage was based on collecting nutritional and anthropometric measurements, as well as hematological tests. One and a half years later (June 2013), the researchers contacted the patients or caregivers, verifying that 30% (n=9) of the patients died since the first stage, in 2011. Death certificates (Dc) were evaluated in accordance with International Disease Classification (CID-10)¹⁰. It was defined as death due to AD in cases which had AD as the main cause of the death on the death certificate. Death with AD was recorded when it was mentioned in any part of the medical report of the death certificate. It was considered as codes CID G30.0 to G30.9¹⁰.

With the intention of evaluating the anthropometrical measures of the patients, we performed a body mass index (BMI). The weight and the height were collected according to the methods advocated in the feed and nutritional surveillance system (SISVAN)¹⁰. BMI measurements were taken using a digital precision scale with kilograms scale from Plenna®. To obtain the height values, a stadiometer was used with a centimeter scale. When it was not possible to obtain the weight and height, as some patients could not stay in the orthostatic position since the patients were bedridden, estimated values were used from the formula proposed for Chumlea (1985)¹¹. BMI was calculated using the correlation between the square of total corporal weight (kilograms) and the height (meters), using the cut points for elderly people proposed for Lipschitz (1994)¹².

The nutritional state of the participants was evaluated using the mini nutritional assessment (MAN) (13). The MAN is an instrument composed of measures and practical questions that comprise anthropometric evaluations (weight, arm and calf circumferences, height and loss of weight record), global evaluation (life style, drugs, mobility and diseases), dietary evaluation (qualitative and quantitative) and self-evaluation (nutrition perception). The sum of MAN scores allows discrimination between patients, where values below 17 characterize the patient as undernourished, between 17 and 23.5 at malnutrition risk and between 23.5 and 30 as normal¹³. The MAN was applied to the patients classified with Clinical Dementia Rating (CDR) 2 or 3. The food consumption was evaluated through the patient or caregiver report of consumed food through memory of 24 hour estimated in home measurements converted to grams¹⁴. This data was analysed on Avanutri 4.0® software. Each nutrient was compared to the Dietary Reference Intake (DRI’s)^{14,15} according to gender and age, due to the lack of specific recommendations for AD patients.

Also, for the staging of the demential process the Clinical Dementia Rating (CDR) was used. The clinical evaluation of dementia classifies the development stage of AD, where zero rating represents normal, 0.5 dementia questionable (CDR 0.5), 1 mild dementia (CDR 1), 2 moderate dementia (CDR 2) and 3 severe dementia (CDR 3)⁸.

The blood collection was performed at patients' home according to the recommendations for venous blood collection from the Brazilian Society of Clinical Pathology and Laboratory Medicine (2010)¹⁶.

The samples of serum were analysed in biochemistry semi-automated equipment CA 2006 (SHEL – B4B Group, Brazil), and commercial kits (Labtest® - Minas Gerais, Brazil). The total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, very low-density lipoprotein (VLDL) cholesterol and triglycerides were evaluated according to the parameters from the Brazilian Cardiology Society, 2013^{17,18}. The glucose levels were classified according to parameters from the Brazilian Diabetes Society, 2014¹⁸. The albumin was dosed through colorimetric methodology, using bromocresol green on the biochemistry semi-automated equipment CA 2006 (SHEL – B4B Group, Brazil), and ALBUMINA PP (Cat# 419, Gold Analisa Diagnostica SA, Brazil) and evaluated following Painter, Cope and Smith parameters¹⁹.

The complete blood count (CBC) was carried out in a hematology analyser Cell-dyn Ruby (Abbott, Illinois, USA) with 33 parameters that use flow cytometry for the white cells, erythrocytes and platelets analysis and the spectrophotometric methodology for the determination of hemoglobin. The hematological parameters were taken from the WHO²⁰.

Statistical analysis

The statistical analysis was completed using SPSS package version 20.0. Initially, it was carried out using non-parametric

analysis due to the large number of variables that do not fall in a normal distribution when evaluated for Shapiro-Wilk test. The first step of the analysis consisted of the comparison of the initial evaluation (base line) between the subjects who have died during the study, and those reevaluated in a later phase according to the test proposed by Mann-Whitney. This step also analyzed the survival according to the tests proposed by Kaplan-Maier and considering CDR, IMC, clinical variables, such as age and, diagnosis data as time variable. This step was also analyzed by Qui-Square test with corrections to verify associations between death and sociodemographic and clinical variables.

Ethics and consent

The study was approved by the Research Education Committee of the State University of the Center-West - COMEP / UNICENTRO through process 026/2011. Written informed consent was obtained from a person responsible/patient caregiver for all participants.

Results

Respiratory issues accounted for the majority of deaths (Table 1). Alzheimer disease was specified in 22% of cases (n=2) and the patients without a specific cause of death on the death certificate was 22% (n=2). No patient had ICD G30.0, early-onset Alzheimer's disease (Table 1)⁹.

As shown in Table 2, the anthropometric variables and macronutrients ingestion are compared between live and patients who died up until two years after the study evaluation. None of the subjects showed values greater than zero on basophils, atypical lymphocytes, blasts, myelocytes and metamyelocytes variables; values greater than zero indicate pathologies.

Table 3 shows the differences on micronutrients consumption between the two groups investigated. The only significant difference found between live and deceased patients, was the phosphorus consumption. Figure 1 shows that the phosphorus consumption was lower those who died compared to the live

Table 1. Death causes according to gender and CID registered on the death certificate.

Gender	N	%	CID*	Cause of Death in DO#
Female	2	22%	J 31.1	Chronic nasopharyngitis
Male	0			
Female	0	11%	J 44.9	Chronic obstructive lungs disease not specified.
Male	1			
Female	0	11%	J 15.9,	Pneumonia bacterial not specified
Male	1			
Female	1	11%	K 57.9	Diverticular intestine disease, location not specified
Male	0			
Female	2	22%	G 30.9,	Alzheimer disease not specified
Male				
Female	1	22%	R 99	Other not well defined or not specified causes of death
Male	1			

*CID, codes according to the International Disease Classification review (CID -10), DO, death certificate.

Table 2. Comparison between nutritional, hematological and biochemistry parameters among live and deceased patients with AD.

	Living		Deceased		P*
	MD	P75-P25	MD	P75-P25	
Weight	64.8	15.30	54.9	29.80	0.894
BMI†	24.8	4.20	22.6	7.30	0.594
CC‡	33	3.00	31	3.00	0.689
Total MNA§ score	21	5.00	21	8.00	0.283
R24 Kcal Hours	1487	1014	1633	857	0.790
Adequacy % Kcal R24	86.1	29.60	87.9	75.40	0.657
PTN/KG	1.1	0.70	0.7	0.40	0.077
CHO¶ %	52.1	12.50	58.9	13.80	0.137
PTN %	19.0	3.60	15.3	3.40	0.086
LIP** %	28.7	7.50	27.6	10.80	0.894
Hematological Parameters					
Erythrocytes	4.7	0.42	4.3	0.58	0.124
Hemoglobin	13.9	1.70	12.3	2.65	0.097
Volglob	42.3	2.80	38.6	5.55	0.066
Vgm	89.9	5.10	90.9	10.08	0.881
Hgm	29.5	1.42	29.9	3.44	0.754
Chgm	32.9	1.57	32.5	1.46	0.669
Rdw	13.1	0.60	13.2	0.85	0.711
Leukocytes	7310	2650	6635	3615	0.549
Eosinophils	140.6	418.5	227.7	164	0.798
Lymphocytes	2152.5	783.6	2133.6	908.7	0.977
Monocytes	703.0	288.3	551.3	123.8	0.374
Rods	79.1	36.0	66.3	63.6	0.344
Segmented	4508.7	1662.4	4106.6	2676.4	0.842
Neutrophils	4587.8	1689.4	4172.8	2800.7	0.798
Platelets	223000	65000	217000	78500	0.842
Biochemical Parameters					
HDL (mg/dL)	41.0	15.0	42.0	17.0	0.475
LDL (mg/dL)	103.0	47.0	93.0	28.0	0.798
CT†† (mg/dL)	170.0	52.0	161.0	22.0	0.887
VLDL (mg/dL)	22.0	17.0	24.0	16.0	0.842
Glucose (mg/dL)	86.0	22.0	83.0	25.0	0.344
TRIG§§ (mg/dL)	112.0	86.0	118.0	81.0	0.842
Albumin (g/dL)	3.0	1.0	3.0	1.0	0.671

*P<0.05 †BMI: Body Mass Index; ‡CC: Calf circumference; §MNA: Mini Nutritional Assessment; ||PTN: Protein; ¶CHO: Carbohydrate; **LIP: Lipids; ††CT: Total Cholesterol; §§TRIG: Triglycerides. Mann-Whitney U test.

Table 3. Nutritional ingestion values comparison between live and deceased AD patients*.

	Living		Deceased		P
	MD	P75-25	MD	P75-P25	
Vit. A (RE):	234.8 (26.1%)	787 (89.0%)	321.3 (37.9%)	235.4 (20.3%)	0.894
Vit. D (mcg):	2.8 (18.7%)	2.30 (15.40%)	1.7 (11.3%)	1.20 (15.3%)	0.104
Vit. B1 (mg):	1.4 (120.9%)	0.90 (79%)	1.4 (118.3%)	0.8 (70.2%)	0.244
Vit. B2 (mg):	1.5 (113.6%)	0.7 (65.4%)	1.3 (109.2%)	0.8 (77.4%)	0.226
Vit. B3 (mg):	20.6 (128.4%)	22.0 (136.2)	15.5 (96.6%)	8.4 (55.8%)	0.283
Vit. B5 (mg):	3.0 (59.8%)	1.9 (38.0%)	2.6 (51.4%)	1.1 (22.2%)	0.226
Vit. B6 (mg):	1.1 (70.0%)	1.1 (74.0%)	0.8 (50.6%)	0.6 (39.8%)	0.077
Vit. B12 (mcg):	3.0 (125.4%)	4.5 (188.3%)	2.2 (92.9%)	2.7 (113.7%)	0.372
Vit. C (mg)	53.8 (62.8%)	88.4 (116.90%)	42.9 (57.2%)	57.8 (75.3%)	0.929
Vit. E (mg):	9.6 (64.0%)	8.4 (56.00%)	14.8 (98.7%)	6.7 (44.7%)	0.397
Fol. (mcg):	109.9 (27.5%)	95.2 (23.80%)	119.3 (29.8%)	71.3 (17.8%)	0.594
Ca (mg):	482.1 (40.2%)	300.9 (25.10%)	403.0 (33.6%)	278.8 (23.2%)	0.625
P (mg):	962.9 (137.6%)	439.7 (62.80%)	731.5 (104.5%)	197.6 (28.2%)	0.011
Mg (mg):	176.6 (47.0%)	67.1 (19.10%)	136.6 (35.4%)	85.1 (32.3%)	0.209
Fe (mg):	12.5 (156.3%)	8.1 (101.30%)	8.9 (111.3%)	6.3 (78.8%)	0.137
Zn (mg):	8.9 (87.5%)	7.0 (67.50%)	8.5 (77.3%)	6.7 (98.1%)	0.533
Cu (mcg):	0.9 (0.1%)	0.3 (0.00%)	0.8 (0.1%)	0.5 (0.0%)	0.226
I (mcg):	46.5 (31.0%)	41.8 (27.90%)	45.7 (30.5%)	17.4 (11.6%)	0.790
Se (mcg):	50.9 (92.5%)	64.2 (116.70%)	43.0 (78.2%)	23.5 (42.7%)	0.086
Mn (mg):	1.3 (72.2%)	1.7 (94.40%)	1.6 (69.6%)	0.5 (21.8%)	0.894
K (mg):	1848.3 (39.3%)	846.4 (18.00%)	1451.4 (30.9%)	667.8 (14.2%)	0.137
Na (mg):	2002.0 (166.8%)	1822.9 (141.34%)	2018.0 (168.2%)	1376.1 (122.6%)	0.859

*Gross value (% adequacy). Mann-Whitney U test

Figure 1. Phosphorus ingestion (P) and adequacy (%) in AD patients distributed by health condition. *Mann-Whitney U test.

group, although the phosphorus consumption was sufficient for both groups.

In addition, Table 4 shows that there were no deaths in patients classified as eutrophic (MAN specification), while all the undernourished patients and at risk of it had died.

According to the CDR classification of the patients who died, 55% were in mild cognitive failure. Of these, 44% were male, which represents half of the male group of the sample. The health conditions showed that 23% (n=7) of the patients had some type of cancer, and from them, 42% (n=3) have died.

Figure 2 shows the AD patient survival curve as a function of age. The survival rate is modified for the disease stage and the results demonstrate a lower survival rate for the patients in the early stages of the disease.

Discussion

This study has observed that the respiratory issues may appear as one of the main death cause in AD patients, which may be related to age, due to the advanced age of the majority of the

patients. The limitation of the respiratory functional system on AD, due to the depletion of the cough reflex and the accumulation of discharge, reduce the pulmonary ventilation and the elderly immunological system is more affected, facilitating the occurrence of infection, especially respiratory ones^{21,22}.

The elderly with dementia can exhibit dysphagia, making necessary the use of enteral probes for feeding and the elimination of the discharge from upper airways, increasing the respiratory infections. Pneumonia is one of the most common causes of hospitalization of AD patients and its pathology is directly related to its mortality²¹⁻²⁴.

Furthermore, seniors are more likely to present with secondary drug effects, increasing the death risks. The elevated chance of pneumonia in AD patients has to be remembered when treating these people²⁵. A study in Finland compared the risk of pneumonia associated with acetylcholinesterase inhibitors (AChEIs) (donepezil, Transdermal rivastigmine, galantamine and memantine) in people with AD diagnosis and concluded that people who used rivastigmine and memantine in comparison with donepezil had an increased risk of pneumonia²⁶. This risk occurred, not only from

Table 4. AD patients according to health conditions and gender.

		Living			Deceased		
		n	% Total	% Living	n	% Total	% Deceased
Gender	Female	13	43.3%	61.9%	05	16.7%	55.6%
	Male	08	26.7%	38.1%	04	13.3%	44.4%
High Cholesterol	No	14	46.7%	66.7%	06	20.0%	66.7%
	Yes	07	23.3%	33.3%	03	10.0%	33.3%
Diabetes	No	15	50.0%	71.4%	05	16.7%	55.6%
	Yes	06	20.0%	28.6%	04	13.3%	44.4%
High Blood Pressure	No	07	23.3%	33.3%	03	10.0%	33.3%
	Yes	14	46.7%	66.7%	06	20.0%	66.7%
Cancer	No	17	56.7%	81.0%	06	20.0%	66.7%
	Yes	04	13.3%	19.0%	03	10.0%	33.3%
BMI#	Low weight	07	23.3%	33.3%	04	13.3%	44.4%
	Euthrophic	11	36.7%	52.4%	02	6.7%	22.2%
	Over weight	03	10.0%	14.3%	03	10.0%	33.3%
MNA§ Classification	Normal	05	16.7%	23.8%	00	0.0%	0.0%
	Risk of malnutrition	11	36.7%	52.4%	05	16.7%	55.6%
	Malnourished	05	16.7%	23.8%	04	13.3%	44.4%
CDR* Value	Mild Dementia	05	16.7%	23.8%	05	16.7%	55.6%
	Moderate Dementia	07	23.3%	33.3%	01	3.3%	11.1%
	Serious Dementia	09	30.0%	42.9%	03	10.0%	33.3%

*CDR: Clinical Dementia Rating; †MMSE: Mini Mental State; § MNA Examination Mini nutritional Assessment, # Body Mass Index (BMI).

Figure 2. Survival curve of AD patients distributed by health condition (A) and (B) disease stage. *Kaplan-Meier test.

the drug characteristics, but also for the severity of the AD. The same study considered the use of pneumococcal vaccination for elevated risk of pneumonia with great efficiency²⁶. In Brazil, memantine is used only in moderate and severe stages of the disease.

Other medicines that deserve special attention are the neuroleptics, or tranquilizers, used in AD patients to control the agitation, hostility, delusions and hallucinations²⁶. These medicines are antagonists of dopamine, decreasing its transmission and compromising the deglutination function, facilitating aspiration pneumonia²⁶. The effects of the neuroleptics on the dopaminergic system usually occurs in severe AD, so it is used in lower doses.

On the other hand, the benzodiazepines that can also be used as tranquilizers in AD have slight effects on the dysphagia, decreasing aspiration pneumonia²⁶.

For cause of death analysis, the death certificates must be filled in a correct form. The death certificate is the only source of mortality data and depends directly on the quality of the information provided by the doctor^{27–29}.

The underlying death cause was defined by the World Health Organization as a disease or lesion that had initiated the pathological events chain and brought the patient directly to death⁶. In line with the methodology proposed for this study, it was recorded as AD with the codes CID G30.0 to G30.9. Underlying cause of death being AD, the code G30.0 did not appear in any certificate, reinforcing the idea that the death certificates

frequently register the immediate death causes instead of to register AD as a cause^{28,29}.

AD generally causes undernourishment to the elderly and it can be associated with physiological alterations, dental issues, physical limitations, and diseases that decrease the appetite, food absorption and, drug interactions^{7,30}.

Although there is no difference between the groups in this study, it could be observed that values are below those recommended by the Dietary Reference Intakes - DRIS (15) for almost all micronutrients. Figure 1 shows that phosphorus was the only micronutrient with significant differences found between the live and dead group³¹. However, this difference cannot explain the observed mortality rates, since the percentage of this micronutrient adequacy was inside the normal values in those who died and above the recommended level in the live group^{7,31}. In addition, the most significant symptoms of phosphorus deficiency include bone weaknesses, discomfort in many joints, weakness, dental decay and rickets^{31,32}. In this study, there was no biochemical analysis of phosphorus dosage in the study groups due to the methodology limitations.

Therefore, the early diagnosis of malnutrition is important due the association with the greater mortality in AD. The data from this study supports this, since all the patients who have died were undernourished according to MAN classification^{7,32}.

The consequences of the weight loss and malnutrition in people with dementia occurs due to the dependency of care, difficulties in mobility, food preparation, chewing and deglutition. Moreover,

the nutritional status of the elderly AD patients has a significant impact on the disease course, affecting cognitive parameters and functional symptoms^{7,30,31}.

Additionally, the malnutrition causes a decrease in white blood cells, leading to alterations in antibodies production and immune resistance, decreasing the survival rate in undernourished patients³³. Thus, to reduce or at least delay the AD prevalence, maintaining a proper diet from childhood is crucial and reinforced due the fact that the cardiovascular risks are directly related with the development of dementia.

In relation to the AD associated factor, our study reveals that 33% of those who died had higher levels of cholesterol and 44% had diabetes. An epidemiological study has demonstrated the directly relation between high cholesterol levels and the increased risk of cognitive issues, vascular alterations and AD³⁴. In terms of diabetes, in this study its presence was not associated with the mortality rates; the survival curve did not show differences between subjects with and without diabetes ($p=0.572$), although diabetes mellitus is a disease which has risk factors common to AD³⁴.

A prospective study from 2010 has evaluated the associated factors of evolutionary differences and mortality due to AD between males and females. The males had more comorbidities due the differences in exposure, work, alcohol consumption, tobacco consumption and differences on the attitudes related to the disease, increasing the chance of death³⁵, reinforcing our study, where 44% of the those who died during the study were males. In some cases, the male mortality occurs due to external causes, given that females have higher chances of developing AD in advanced ages, correlating with our sample composition^{27,35}. On the other hand, a study conducted by Teixeira *et al.* (2015) shows a higher mortality in AD females, which may be explained by the prevalence of cases in this gender in Brazil and other countries.

Among the possible comorbidities occurring in this population, cancer stands out, decreasing survival in the elderly. This effect was not completely observed in this study, where 76.7% of the patients were not cancer patients. From the 23.3% that were cancer patients, 57% have died since the beginning of the study. Still according to Teixeira *et al.* (2015), the neoplasms were more frequent in patients without AD²⁹.

In the study performed by Mussico *et al.* (2013), elderly patients with cancer have a reduced risk of dementia due to AD and vice-versa³⁶. Although demonstrating common pathophysiological mechanisms such as mitochondrial dysfunction, oxidative stress and DNA damage that are propitious to the genetic and metabolic connections between cancer and neurodegeneration, there is an inverse association between the pathologies^{36,37}. Romero (2014), in a prospective study, analyzed the cancer notification proportion on death certificates of dementia patients and

concluded that AD patients have a lower risk of mortality due to malignant neoplasia³⁸. In our study, the survival curve has not shown significant differences when the subjects with and without cancer were compared ($p=0.998$).

A decrease in the survival rate was observed in [Figure 2](#) showed a difference between the distinct disease stages. However, the lower survival values were observed in patients who were classified in the mild dementia stage, an unexpected result that is not in line with the literature^{6,23,28}. Nevertheless, the death of patients of the study is strongly related to respiratory issues and to the progression of the disease. The risk factors for pneumonia on initial AD stage are not sufficiently understood, but one possibility is that a silent aspiration of saliva or bolus without causing cough, respiratory difficulty or other external sign can cause pneumonia due to aspiration^{24,39}. Also, because the symptoms and effects caused by the AD are less evident in mild disease stage patients, the preoccupation with immunological care may be reduced³³.

Furthermore, while several studies use the diagnostic time as the survival time, this study has not used it; first due to the difficulties, such as lack of specialized doctor in SUS to assist the great demand and the lack of information about AD, confusing its symptoms with simple senility or not searching for an appropriate diagnostic. Second, the correlation with age is associated with the disease and the survival.

The obtained results were discussed and interpreted considering the limitation of a cross sectional study with a limited number of patients. In addition, the information was not collected before the patient's death due to the improbability of each case. Nonetheless, the longest past period since the evaluation and the death was 18 months. Thus, the number and quality of the information fortify the results with social relevance, since they were obtained from a non-institutionalized dementia, where caregivers are relatives, a common situation among people with dementia in Brazil.

The nutritional status, biochemical and basic comorbidities were not confirmed in this study to explain this relation. Therefore, the AD patients profile characterization in the study and the observed reduction on the survival probability may indicate the absence of proper attention, suggesting new searches for its confirmation. At the same time, the quality of the information in the death certificates that frequently do not register dementia as an implicit cause generates underreporting of the long-term chronic degenerative diseases.

Other limitation is the quality of information given in the death certificate, which does not record AD as an implied reason, giving no notice of chronic degenerative diseases and hiding results. This suggests there is a need for more research in this area, because there is still a shortage of studies on this subject.

Data availability

All raw data was freely available on the [Open Science Framework](https://openframeworks.org/) site: [Doi: 10.17605/OSF.IO/PE38C](https://doi.org/10.17605/OSF.IO/PE38C).

Competing interests

No competing interests were disclosed

Grant information

This study was funded by the Association of studies, research and assistance to people with Alzheimer's disease (AEPAPA), the

Araucaria Foundation and Coordination of Improvements of Higher Education Personnel (CAPES).

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgments

The authors would like to extend their gratitude to Association of studies, research and assistance to people with Alzheimer's disease (AEPAPA), to Araucária Foundation and Higher Education Personnel Improvement Coordination (CAPES).

References

- Alzheimer's Association: **2011 Alzheimer's disease facts and figures**. *Alzheimer Dement*. 2011; **7**(2): 208–44.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Aprahamian I, Martinelli JE, Yassuda MS: **Doença de Alzheimer: revisão da epidemiologia e diagnóstico**. *Rev Bras Clin Med*. 2009; **7**: 27–35.
[Reference Source](#)
- Prince M, Guerchet M, Prina M: **The Global Impact of Dementia 2013–2050**. London: Alzheimer's Disease International. 2013; **8**.
[Reference Source](#)
- Wimo A, Winblad B, Jönsson L: **The worldwide societal costs of dementia: estimates for 2009**. *Alzheimer's Dement*. 2010; **6**(2): 98–103.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Mendonça FM, Drumond E, Cardoso AM: **Problemas no preenchimento da Declaração de Óbito: estudo exploratório**. *Rev Bras Estud Popul*. 2010; **27**(2): 285–95.
[Publisher Full Text](#)
- Ferreira AB, Ribeiro FF, Fontenele RP, et al.: **Mortalidade pela Doença de Alzheimer no Brasil entre os anos de 2000 a 2013**. *Acta Ciênc & Saúde*. 2015; **1**(1): 100–115.
[Reference Source](#)
- Teixeira JB, Souza Junior PR, Higa J, et al.: **Mortality from Alzheimer's disease in Brazil, 2000–2009**. *Cad Saude Publica*. 2015; **31**(4): 850–860.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Brasil: **Portaria nº 1.298, de 21 de novembro de 2013. Aprova o Protocolo Clínico e Diretrizes Terapêuticas da Doença de Alzheimer**. Diário Oficial da República Federativa do Brasil, Brasília, DF.
[Reference Source](#)
- Dubois B, Feldman HH, Jacova C, et al.: **Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria**. *Lancet Neurol*. 2007; **6**(8): 734–46.
[PubMed Abstract](#) | [Publisher Full Text](#)
- World Health Organization: **ICD10. International Statistical Classification of Diseases and Related Health Problems - ICD-10**. 10th. São Paulo, EDUSP, 2016.
[Reference Source](#)
- Ministério da Saúde: **Protocolos do Sistema de Vigilância Alimentar e Nutricional – SISVAN na assistência à saúde**. Brasília: Ministério da Saúde; 2008.
[Reference Source](#)
- Chumlea WC, Roche AF, Steinbaugh ML: **Estimating stature from knee height for persons 60 to 90 years of age**. *Am J Geriatr Soc*. 1985; **33**(2): 116–20.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Lipschitz DA: **Screening for nutritional status in the elderly**. *J Prim Care*. 1994; **21**(1): 55–67.
[PubMed Abstract](#)
- Vellas B, Villars H, Abellan G, et al.: **Overview of the MNA—its history and challenges**. *J Nutr Health Aging*. 2006; **10**(6): 456–465.
[PubMed Abstract](#)
- Padovani RM, Amaya-Farfan J, Colugnati FA, et al.: **Dietary reference intakes: aplicabilidade das tabelas em estudos nutricionais**. *Rev Nutr PUC-Campinas*. 2006; **19**(6): 741–760.
[Publisher Full Text](#)
- Institute of Medicine (US) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes: **Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride**. Washington (DC): National Academies Press (US); 1997.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Sociedade Brasileira de Patologia Clínica/Medicina Laboratorial BPC/ML: **Recomendações da Sociedade Brasileira de Patologia Clínica para Coleta de Sangue Venoso**. 2th ed. Barueri, SP, Minha Editora. 2010.
- Malachias MV, Souza WK, Plavnik FL, et al.: **7ª diretriz brasileira de hipertensão arterial**. *Arq Bras Cardiol*. 2016; **107**(3): 370.
[Reference Source](#)
- Sociedade Brasileira de Diabetes: **Diretrizes da Sociedade Brasileira de Diabetes 2013–2014**. São Paulo: AC Farmacêutica, 2014.
[Reference Source](#)
- Painter PC, Cope JY, Smith JL: **Reference information for the clinical laboratory**. In: Burtis CA, Ashwood ER eds. *Tietz textbook of clinical chemistry*. Philadelphia: WB Saunders Company, 1999; 477–540.
- World Health Organization, DeMaeyer EM, Dallman P, et al.: **Preventing and controlling iron deficiency anaemia through primary health care: a guide for health administrators and programme managers**. Geneva. 1989.
[Reference Source](#)
- Hendriks SA, Smalbrugge M, van Gageldonk-Lafeber AB, et al.: **Pneumonia, Intake Problems, and Survival Among Nursing Home Residents With Variable Stages of Dementia in the Netherlands: Results From a Prospective Observational Study**. *Alzheimer Dis Assoc Disord*. 2017; **31**(3): 200–208.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Larson EB, Shadlen MF, Wang L, et al.: **Survival after initial diagnosis of Alzheimer disease**. *Ann Intern Med*. 2004; **140**(7): 501–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Bonsignore M, Heun R: **Mortality in Alzheimer's disease**. *Dement Geriatr Cogn Disord*. 2003; **15**(4): 231–36.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Wada H, Nakajoh K, Satoh-Nakagawa T, et al.: **Risk factors of aspiration pneumonia in Alzheimer's disease patients**. *Gerontology*. 2001; **47**(5): 271–276.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Lampela P, Tolppanen AM, Tanskanen A, et al.: **Use of antidementia drugs and risk of pneumonia in older persons with Alzheimer's disease**. *Ann Med*. 2016; **49**(3): 230–39.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Zagozdzon P, Goyke B, Wrotkowska M: **Mortality Rates in Users of Typical and Atypical Antipsychotics: A Database Study in Poland**. *Drugs Real World Outcomes*. 2016; **3**(3): 345–51.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Otero UB, Rosenfeld S, Gadelha AJ: **Óbitos por desnutrição em idosos em São Paulo e Rio de Janeiro: análise de séries temporais, 1980–1986**. *Rev Bras Epidemiol*. 2001; **4**(3): 191–205.
- James BD, Leurgans SE, Hebert LE, et al.: **Contribution of Alzheimer disease to mortality in the United States**. *Neurology*. 2014; **82**(12): 1045–50.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Bonini JS, Goes VF, Oliveira CF, et al.: **Psychophysiological, cognitive and behavioral aspects of malnutrition in Alzheimer's disease: a review**. *Rev Bras Ciênc Envelhecimento Humano*. 2014; **11**(3): 245–56.
[Publisher Full Text](#)
- Hernando-Requejo V: **Nutrition and cognitive impairment**. *Nutr Hosp*. 2016; **33**(Suppl 4): 346.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Andrási E, Páli N, Molnár ZS, et al.: **Brain aluminum, magnesium and phosphorus contents of control and Alzheimer-diseased patients**. *Am J Alzheimer's Dis*. 2005; **7**(4): 273–84.
[PubMed Abstract](#) | [Publisher Full Text](#)

33. Schäufele M, Bickel H, Weyerer S: **Predictors of mortality among demented elderly in primary care.** *Int J Geriatr Psychiatry.* 1999; **14**(11): 946–56.
[PubMed Abstract](#) | [Publisher Full Text](#)
34. Lopes da Silva S, Vellas B, Elemans S, *et al.*: **Plasma nutrient status of patients with Alzheimer's disease: systematic review and meta-analysis.** *Alzheimers Dement.* 2014; **10**(4): 485–502.
[PubMed Abstract](#) | [Publisher Full Text](#)
35. Kivipelto M, Helkala EL, Hänninen T, *et al.*: **Midlife vascular risk factors and late-life mild cognitive impairment: A population-based study.** *Neurology.* 2001; **56**(12): 1683–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
36. Driver JA: **Inverse association between cancer and neurodegenerative disease: review of the epidemiologic and biological evidence.** *Biogerontology.* 2014; **15**(6): 547–57.
[PubMed Abstract](#) | [Publisher Full Text](#)
37. Sinforiani E, Citterio A, Zucchella C, *et al.*: **Impact of gender differences on the outcome of Alzheimer's disease.** *Dement Geriatr Cogn Disord.* 2010; **30**(2): 147–54.
[PubMed Abstract](#) | [Publisher Full Text](#)
38. Musicco M, Adorni F, Di Santo S, *et al.*: **Inverse occurrence of cancer and Alzheimer disease: a population-based incidence study.** *Neurology.* 2013; **81**(4): 322–328.
[PubMed Abstract](#) | [Publisher Full Text](#)
39. Romero JP, Benito-León J, Louis ED, *et al.*: **Alzheimer's disease is associated with decreased risk of cancer-specific mortality: a prospective study (NEDICES).** *J Alzheimers Dis.* 2014; **40**(2): 465–73.
[PubMed Abstract](#) | [Publisher Full Text](#)

Open Peer Review

Current Peer Review Status: ? ✖

Version 1

Reviewer Report 04 September 2018

<https://doi.org/10.5256/f1000research.14080.r30464>

© 2018 Vega I. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Irving E Vega

Department of Translational Science & Molecular Medicine, Michigan State University, Grand Rapids, MI, USA

The authors addressed two important aspects related to Alzheimer's disease: 1) accuracy of mortality rates, and 2) nutrition as a risk factor. However, the experimental design presented in the current version of the manuscript fall short in addressing both issues. Several important shortcomings in the experimental design and interpretation of the results render this manuscript unacceptable. For example:

1. The authors compare or use different variables in the study but does not present a power analysis to support that the number of participant is sufficient to draw any conclusion.
2. It is unclear how nutritional status relate to the death certificate. The introduction is confusing as to what is the gap in knowledge and the relationship of the proposed questions.
3. The main limitation of death certificate is that, in the case of AD, the diagnosis is not confirmed (i.e. neuropathology). The authors did not address this major limitation.
4. Who completed the MAN? A caregiver? How this data was collected?
5. Cancer patients need to be segregated from the data since may have contributed to the only difference observed; phosphorus level.
6. The participants are not segregated based on stage of AD (i.e. mild, moderate, severe). It is expected that the stage of the disease will affect their nutritional level.
7. The discussion section addressed issues not supported by the data or even related to it. For example: There is no data on the use of any of the drugs mentioned by the research participants. How is this information relevant to the study?

In summary, in the present form, the authors do not have any supporting data for the

interpretations and conclusion presented in the manuscript.

Is the work clearly and accurately presented and does it cite the current literature?

No

Is the study design appropriate and is the work technically sound?

No

Are sufficient details of methods and analysis provided to allow replication by others?

No

If applicable, is the statistical analysis and its interpretation appropriate?

No

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

No

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 12 March 2018

<https://doi.org/10.5256/f1000research.14080.r31762>

© 2018 Stewart R. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Robert Stewart

Institute of Psychiatry, Psychology and Neuroscience (IoPPN), King's College London, London, UK

The report is of a small study of 30 people with Alzheimer's disease, 9 of whom died within 1.5 years of baseline assessment. Information is provided on recorded cause of death and participants who died are compared to the remainder on a range of anthropometric, haematological, biochemical and nutritional indices recorded at baseline.

I'm all in favour of data being in the public domain; however, the discussion section needs to be fundamentally revised before the paper can be viewed as accepted. The conclusions which can be drawn are very limited by the sample size and do not adequately support the extensive material presented in the discussion, so this should be substantially abbreviated as described below. There

are also aspects of the methodology which need to be clearer.

1. While it is reasonable to display a breakdown of causes of death, and reasonable to comment on the relatively low proportion of death certificates mentioning AD (which has been described in other samples), it is not appropriate to draw conclusions about dementia-related factors contributing to causes of death. Conditions such as respiratory disease are common causes of death in any older population and the study does not evaluate whether they are any higher in people with dementia than the general population, so it is misleading to be discussing, for example, elevated risks of pneumonia or cancer or whatever.
2. Although I don't object to the authors displaying descriptive data on their baseline covariates stratified according to subsequent death, a study of this size would only be able to identify very large differences at statistical significance; therefore I don't feel that it is appropriate to be discussing the findings in any more detail than a simple presentation of descriptive data. The difference in phosphorus levels is highly likely to represent type 1 statistical error because of the very large number of comparisons made, so it is reasonable not to draw any inferences from this. The rest of the discussion about risk factors for mortality is not justified because the study does not have statistical power to detect these associations and, indeed, no significant associations are identified.
3. It is reasonable to comment on levels of survival in the sample, but I don't think that anything can be concluded about stage of dementia and survival because the numbers are simply not large enough.
4. The repeated description of the study as cross-sectional is misleading. The study took a group of 30 people and followed them up for mortality. It is therefore surely a cohort study? Similarly, I don't understand the sentence in the third-to-last paragraph: "In addition, the information was not collected before the patient's death due to the improbability of each case." Surely all the information was collected before death (apart from the death certification)?
5. As far as I can tell, the participants were people who were recorded as receiving medications for AD and who were then approached and visited at home. There does not appear to have been any formal evaluation of the diagnosis, apart from the completion of a CDR. Is this correct? It would be helpful if the sample identification and recruitment process was a little more clear.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Dementia epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research