Short Communication

Principal Component Analysis Applied to Alzheimer's Disease: USA by State

Bodo Parady, Children's Hospital Oakland Research Institute, Oakland, CA, USA

Correspondence:

Bodo Parady Ph.D.

Sphinx Pharma. Inc

Suite 299, 696 Danville Blvd

Danville, CA 94526

boparady@yahoo.com

Abstract

Principal Component Analysis (PCA) of Alzheimer's disease (AD) and twelve epidemiological and socio-economic components of the USA states inform etiology by extracting large scale patterns. The twelve components demonstrate simple pairwise Pearson correlations to AD, and then are analyzed by PCA for loadings associated with AD. Repetitive factor analysis and the culling of questionable data reduced the factors (all per capita) associated with AD to two, one factor with the components dentists and wine consumption and another factor with the components beer consumption and dentists. Dentists and wine are likely associated with reduced AD incidence because of the known inverse association with elevated education. Dental care is known to be inversely associated with AD incidence. The contribution of beer consumption to AD incidence is likely because of the negative effect on the innate immune system from either phytoestrogens in hops, or detritus from fermentation permitting the fungal colonization seen in AD brains.

Keywords: Alzheimer's disease, principal component analysis, socio-economics, wine, dental care, beer, fungi

1 Introduction

In 1906 Alois Alzheimer described AD in the eponymous woman Auguste D. [1], [2], and found abnormal deposits of amyloid protein plaques (A β) and fibrous protein tangles (neurofibrillary tau). A 1939 review speculated on various causes of AD [3], noting the development of plaques near the site of previous trauma mentioning “intercurrent infection”, suggesting chronic infection is a component of AD. More recently there are a number of reports noting the presence of various fungi in affected portions of all examined AD patient brains [4], [5], [6], [7], [8]. The most common widespread commensal fungus is *Candida albicans* which is in the same family as *Saccharomyces cerevisiae* yeast used in fermentation. This report describes the analysis of the frequency of AD in the states of the USA versus various social and epidemiological factors.

2 Methods

To illuminate the etiology of AD, examination of epidemiological data requires a suitable dataset. The WHO dataset was not used because medical identification of AD cases and autopsy procedures lack standardization, and because poverty limits data collection [9]. The USA statewide data is used because of the availability of social and health data, and relatively standard autopsy data is used instead of relying on sometimes subjective AD diagnoses that can conflate vascular dementia and AD. All of the data used in analysis by state, disease, and lifestyle choice is drawn from government and industry public websites and is in Supplemental Table 1 [10], [11], [12], [13], [14], [15], [16], [17], [18], [19], [20].

PCA is an established method of multivariate data analysis [21] dating back to Pearson [22] who conceived the notion of a correlation ellipsoid. The idea is to least squares fit low-dimensional subspaces to a cloud of data and relate them to a multidimensional correlation ellipsoid [23]. The analysis goal is to reduce the linear combinations of covariates that are uncorrelated and have maximal variance, i.e. have axes at perpendicular maxima on the correlation ellipsoids.

Epidemiological, social and health data from all states are analyzed by creating a correlation matrix, and from this correlation matrix, PCA and Varimax rotation are applied for exploratory component analysis [24] [25]. Factor loading levels are evaluated according to standard practice [26]. The state data for the items in the cross-correlation matrix are examined for unweighted correlation coefficients [27] measured against AD65 (AD cases per 100,000 of the over 65 population) assuming that all of the socio-economic factors apply evenly over a lifetime. Factors were removed when the communal loadings were too low to warrant including them in a 4 factor analysis. Data from CA, FL, NV, and NH were excluded for various reasons. Nevada was removed because it has a many celebratory visitors that alter alcohol consumption, and similarly New Hampshire has no sales tax, driving significant cross border alcohol sales [28]. Florida and California were excluded because of the large differences between the elderly social profiles and the youth social profiles. The medium and small states tend to have lowest mobility, and highest proportion of older residents living most of their lives in one state. In the remaining 46 state data there are correlations between AD65 and beer consumption, wine consumption, dentists per capita, doctors per capita, cigarette smoking, smokeless tobacco, overweight percentage, and income level.

3 Results

AD65 and epidemiological and socio-economic data from the 46 states are calculated into a correlation matrix (Supplemental Table 1). Varimax factor analysis is then applied and is shown in Table 1. Four factors account for 76% of the variance in the data.

Factor Matrix (rotated Varimax)	Unweighted, 46 states					
	Wealth	Death Rate	Alcohol	AD & Beer	Corr Coef AD	P-value
Factor number	1	2	3	4		
AD deaths per 100k over 65 (AD65) 2014 [11]	0.256	-.0085	0.197	0.824	1.000	
Beer Gal of ethanol per capita 2013 [12]	0.253	0.069	-0.496	0.631	0.306	0.038
Wine Gal of ethanol per capita 2013 [12]	-0.467	0.329	-0.430	-0.271	0.360	0.014
Spirits Gal of ethanol per capita 2013[12]	-0.074	0.132	-0.892	-0.047	-0.119	0.432
Dentists per 10,000 people 2011 [18]	-0.697	0.393	-0.069	-0.377	-0.485	0.001
Live births Percent < 2.5 Kg: 2013 [10]	0.065	-0.853	0.191	0.013	0.031	0.838
Physicians in patient care /10k 2012 [18]	-0.931	-.0037	-0.142	-0.008	-0.328	0.026
Age-adjusted death rate /100k: 2013 [13]	0.136	-0.920	0.103	-0.039	0.031	0.840
Cigarette smoking percent 2014 [14]	0.518	-0.643	-0.054	0.200	0.323	0.028
Smokeless tobacco percent 2010-11 [14]	0.814	-0.138	-0.097	0.188	0.331	0.024
Percent Obese or Overweight 2014 [16]	0.671	-0.521	-0.055	0.197	0.364	0.013
Substance abuse (2010-11) [18]	-0.284	0.577	-0.424	0.319	-0.373	0.897
Median per capita income 2014 [19]	-0.718	0.224	-0.373	-0.235	-0.373	0.011
Sum of squares	3.7056	2.946	1.6712	1.5669		
Factor loading guidelines (Comrey & Lee, 1992)						
1. > .70 - excellent						
2. > .63 - very good						
3. > .55 - good						
4. > .45 - fair						
5. > .32 - poor						

Note:
Excludes CA, FL,
NV, NH

Table 1: Rotated Varimax exploratory component analysis with AD and 12 social and health factors for 46 USA states.

Factor analysis shows that AD65 and per capita beer consumption are the most significant components of Factor 4 in Table 1, and they are positively correlated ($r=0.306$, $p=0.038$). None of the other loadings in Factor 4 were significant although there were minor loadings for dentists per capita and substance abuse. Thus 6.35% of the variance in the state data is attributed to AD65 or beer consumption, and neither appear as significant loadings in the other factors.

43% of the variance in the socio-economic data is attributed to Factor 1, which is composed of various economic components that refer to the wealth of the various states. Factor 2 loadings are labeled “Death Rate”, and may be summarized as “risky and poor life choice behavior leading to early death and thus increasing age adjusted death rate.” Cigarette smoking, overweight and substance abuse are major components of Factor 2. Altogether Factor 2 contributes 16% of the total variance and AD65 has no loading it. The use of AD65 instead of age adjusted death rate (AADR) due to AD is validated by AD65 showing no loading for Factor 2: Since AD can only occur at maturity, and because early death reduces the occurrence rate of AD, use of AADR due to AD induces a confounding anti-correlation with overall AADR. Factor 3, labeled “Alcohol”, includes significant loadings from all forms of alcohol consumption and addictive behavior (9.4% of the variance), and again, no loadings are associated with AD65.

Starting with this initial exploratory PCA, successive reductions were performed on the cofactors of AD65 to remove components with high common loadings: e.g. physicians per capita and retaining dentists per capita both have high loadings in the primary wealth factor, and additionally dentists have some loading in the AD/Beer factor which makes Physicians per capita a redundant wealth factor, lacking any other loadings. Also, beer consumption in gallons of beer per capita replaced gallons of ethanol in beer in final analysis because a non-alcohol component appears associated with the incidence of AD; this change increases Pearson correlation and decreases p.

Washington state data was removed from analysis because of a change in reporting procedure before 2000 that exaggerates the diagnosis of AD at death. For every year since 2000 Washington is the state with the highest annual AD65 (e.g. Supplemental Figure 1), and has a raw AD death rate and AD AADR of approximately 44 per 100,000 population up from 11 per 100,000 before 1998. Removing the Washington state data from analysis elevated all correlation coefficients and reduced all p values for wine, beer and dentists per capita, suggesting anomaly.

Factor Matrix (rotated Varimax)	Unweighted, 45 states			
	Wealth/ Education	AD/Beer	Correlation Coef to AD	P-Value
Factor number	1	2		
AD death rate per 100k over 65 (AD65) 2014 [11]	0.65057	0.52151	1.000	
Beer Gal per capita 2016 [29]	0.05513	0.93893	0.401	0.0063
Wine Gal of ethanol per capita 2013 [12]	-0.90429	0.10590	-0.423	0.0038
Dentists per 10,000 people 2011 [18]	-0.74009	-0.43418	-0.584	2.57E-05
Sum of squares	1.79175	1.35328		

Table 2: Reduced rotated Varimax confirmatory component analysis with AD, beer, wine and dentists as factors for 45 USA states (excludes Washington).

The results of component reduction are shown in Table 2. Wealth/Education is labeled that way, because wine consumption is seen here as a proxy for education [30] and wealth. Beer has no

loading in the Wealth/Education factor and dominates factor 2. AD65 loading is evenly split between the two factors which means that AD incidence likely has two cofactors in this analysis: One is wealth and the other is associated with beer and dentistry, but neither wine nor spirits. Dentist loadings have two aspects: Dentists are associated with a wealthy population, and they also manage the oral hygiene of the population. Better dental hygiene has been associated with reduction and management of fungal infections and biofilms [31] [32] [33] which could enter the brain through oropharyngeal tracts. The components of factor 2 point to a biological, not socio-economic contribution.

4 Discussion

High Pearson correlations are found for per capita wine and beer consumption and per capita dentists compared to AD65. Of the initial 12 component study, only state-wise per capita beer ethanol consumption has strong loading with AD65 in PCA Varimax rotation. Because of the highly correlated factors within wealth/poverty, age adjusted death rates, and risky behavior, PCA is used to isolate collinearity and identify confounding multivariate relationships. PCA deals with the problem of multi-collinearity which otherwise leads to instabilities in multivariate regression analysis [34]. Factor analysis reduced the number of linear covariates to AD65 and verified that AD65 had no extraneous loading with age adjusted death rates (Table 1).

Lower education level is a well-known risk factor of AD incidence [35] [36] and wine [37] [38] is well correlated to elevated wealth and education [39]. The frequent comment when beer is shown correlated with AD is: “Beer drinking is probably associated with class or poverty.” The loadings in factor analysis show that beer consumption factor loadings with AD65 are independent of the wealth/poverty factor.

Published work indicates that beer might be a factor in the development of AD and dementia [40]. Iceland has lowest rate of AD in Europe with 1.19% of the population which is much lower than the EU average AD rate of 1.55% [41]. A fact that supports a role for beer in the development of AD is that Iceland banned beer until 1989 [42]. Another factor in the development of AD could be the extremely low incidence of mild hyperthyroidism in Iceland (4x lower) compared to the incidence of mild hyperthyroidism in Europe’s elderly [43]. Thyroid disease was identified as a risk factor for AD in a Canadian study [44]. Beer consumption (>1000ml/week) was associated with goiter incidence in a German study [45] which suggests that beer interferes with iodine mobilization. Note the first case of AD was in Auguste D. from the famous beer consuming region of Bavaria [11].

The Copenhagen City Heart study found that the relative risk (RR) of all dementia was around 2x for occasional to daily beer drinkers [46]. RR was 2.47 for light and moderate beer drinkers in a multi-city study in China [47]. And RR was 1.96 for daily beer drinkers in a New England study [48]. The Helsinki study of beer drinkers at autopsy found reduced A β aggregation [49], but they cautioned that the study was too small to observe relative risk of AD onset; reduction of A β aggregation may be evidence of innate immune suppression.

Of the reasons to associate beer consumption with the development of AD, consider either yeast (live or dead and its detritus), or hops. Yeast might overload the innate immune system and limit control of systemic fungal/yeast infections [50]. Hops contain high levels of phytoestrogens

which may induce many estrogenic disorders [51], including “brewer’s droop [52].” Women with nM levels of estrogen/estradiol have the highest risk of AD (those with 0 or μ M levels have lowest risk of AD) [53]. These nM levels may correspond to the significant increases in phytoestrogens from hops [54], and estradiol from drinking beer or wine [55]; after consuming beer (alcoholic or non-alcoholic) the estradiol levels in men appear to be almost 3x those found in postmenopausal women.

Results here are in line with smaller studies that find reduced risk for AD associated with both wine (an education correlate) and the availability of dental care (related to wealth and the risk factors associated with beer), and elevated risk of AD for beer consumption irrespective of wealth. There is a need to establish uniform reporting rules for AD at death to make USA data more consistent for epidemiological studies.

5 Acknowledgements

The author wishes to thank Prof Bruce Ames for encouragement, and Luis Carrasco Llamas for offering updated research findings.

6 Supplement

State	AD death rate per 100k over 65 2014	Beer Gal per capita 2013	Wine Gal per capita 2013	Spirits Gal per capita 2013	Dentists per 10,000 people 2011	Live births Percent less than 2.5 Kg: 2013	Physicians in patient care /10,000 2012	Age-adjusted death rate per 100k: 2013	Cigarette smoking percent 2014	Smoke less tobacco percent 2010-11	Percent Obese or Over weight 2014	Substance abuse 2010-11	Median per capita income 2014
Alabama	259.024	1.14	0.25	0.6	4.4	9.98	20.5	1037.9	21.1	6.1	67	0.067	\$23,606
Alaska	101.936	1.06	0.52	1.16	7.4	5.81	22.6	944.6	19.9	6.8	64.8	0.093	\$33,062
Arizona	229.646	1.13	0.42	0.81	5.1	6.95	21	873.5	16.5	3.2	64	0.103	\$25,715
Arkansas	258.144	1	0.2	0.6	3.9	8.84	19.4	996.3	24.7	6.9	70.6	0.068	\$22,883
Colorado	195.977	1.2	0.5	1.11	6.5	8.77	25	856.1	15.7	4.2	57.4	0.099	\$32,357
Connecticut	169.471	0.85	0.61	0.91	7.5	7.8	33.9	857.5	15.4	1.8	60.4	0.09	\$39,373
Delaware	122.418	1.25	0.72	1.63	4.6	8.32	24.5	1001.9	19.9	2.2	67.4	0.079	\$30,488
Georgia	212.912	1.03	0.25	0.69	4.4	9.36	19.9	1037.4	29.2	5	65.7	0.069	\$25,615
Hawaii	143.695	1.26	0.54	0.78	8.1	8.19	29.7	752.2	14.1	1.7	58.1	0.086	\$29,736
Idaho	160.729	0.96	1.08	0.77	5.8	6.47	17.4	856.6	15.9	5.7	65.7	0.092	\$23,938
Illinois	188.774	1.13	0.42	0.78	6.3	8.19	26.1	973.8	16.5	2.6	63.8	0.084	\$30,417
Indiana	237.963	1	0.28	0.81	4.7	7.97	21	962	22.9	4.9	66.5	0.083	\$25,140
Iowa	266.964	1.33	0.22	0.8	5.3	6.58	19.7	848.2	18.5	4.9	66.9	0.087	\$28,361
Kansas	192.595	0.99	0.14	0.76	5	7.12	22.4	867.2	18.1	5.5	66	0.084	\$27,870
Kentucky	237.669	0.95	0.2	0.7	5.6	8.82	22	1024.5	26.2	7	66.7	0.064	\$23,684
Louisiana	266.353	1.34	0.32	0.93	4.7	10.88	24.3	1074.6	24	5.7	68.9	0.075	\$24,800
Maine	184.710	1.36	0.42	0.91	5	6.82	28.7	918.7	19.3	2	64.5	0.068	\$27,978
Maryland	114.858	0.89	0.39	0.9	7.3	8.71	35.4	985.2	14.6	2.5	64.9	0.068	\$36,338
Massachusetts	165.945	1.01	0.66	0.9	8.4	7.63	39.6	884.8	14.7	1.5	58.9	0.102	\$36,593
Michigan	224.725	1.02	0.37	0.85	6.1	8.34	26	966	21.2	3.9	65.6	0.086	\$26,613
Minnesota	210.859	1.13	0.43	1.16	6.1	6.47	27.2	825.2	16.3	5	64.1	0.091	\$32,638
Mississippi	264.180	1.35	0.16	0.73	3.9	11.67	17.3	1071.4	23	8.5	70.7	0.071	\$21,036
Missouri	223.516	1.19	0.36	0.89	4.7	7.89	24.1	952.4	20.6	5.1	65.6	0.073	\$26,126
Montana	148.405	1.63	0.49	0.95	5.7	7.31	21.9	890.2	19.9	8	63	0.103	\$25,989
Nebraska	189.975	1.39	0.21	0.72	6.2	6.58	23.5	867.9	17.3	5.3	66.7	0.08	\$27,446
New Jersey	151.450	0.9	0.62	1.03	8	8.32	30.1	956	15.1	1.7	63.1	0.082	\$37,288
New Mexico	144.267	1.17	0.34	0.85	4.6	8.82	22.2	891.9	19.1	4.3	64.9	0.092	\$23,683
New York	92.140	0.93	0.51	0.77	7.7	8	35	973.7	14.4	2.2	61.1	0.084	\$33,095
North Carolina	221.508	1.04	0.39	0.6	4.5	8.87	23.4	986	19.1	4.3	65.6	0.07	\$25,774
North Dakota	324.191	1.68	0.32	1.37	5.1	6.42	24.1	818.4	19.9	7.6	68.8	0.094	\$33,071
Ohio	232.175	1.22	0.3	0.53	5.2	8.57	26.2	967.4	21	4.2	66.7	0.089	\$26,937
Oklahoma	215.871	1.11	0.19	0.63	5	8.17	19.3	961.4	21.1	6.3	68.2	0.089	\$25,229
Oregon	219.645	1.2	0.57	0.89	6.8	6.19	26.4	893	17	4.6	61.7	0.098	\$27,646
Pennsylvania	165.805	1.34	0.31	0.68	6.2	8.09	29.6	963.4	11.3	4.4	64.1	0.089	\$29,220
Rhode Island	245.496	1	0.58	0.98	5.5	7.46	34.6	889.6	16.3	1.9	62.4	0.107	\$30,830
South Carolina	253.473	1.25	0.25	0.81	4.6	9.7	21.6	1030	21.5	4.4	67	0.081	\$24,596
South Dakota	335.262	1.52	0.28	1.01	5	6.24	22.2	846.4	18.6	6.6	65.2	0.1	\$26,959
Tennessee	271.081	1.05	0.25	0.69	4.9	9.11	24.8	1011.8	24.2	4.8	67.1	0.082	\$24,922
Texas	212.534	1.3	0.32	0.63	4.5	8.35	20.3	947.6	14.5	4.3	67.8	0.08	\$27,125
Utah	192.309	0.67	0.19	0.51	6.4	6.92	19.6	823.2	9.7	2.9	59.5	0.063	\$24,877
Vermont	259.682	1.54	0.74	0.72	5.8	6.51	33.3	908.6	16.4	2.8	60.2	0.1	\$29,178
Virginia	155.971	1.02	0.46	0.62	6	8.04	25.8	963.1	19.5	4	64.7	0.082	\$34,052
Washington	332.961	0.95	0.53	0.76	7	6.23	25.1	869.4	15.3	3.7	63.4	0.087	\$31,841
West Virginia	195.316	1.24	0.1	0.46	4.7	9.4	23.8	1031.5	26.7	9.4	69.6	0.071	\$22,714
Wisconsin	218.729	1.45	0.38	1.18	5.7	7.12	24.9	879.1	17.4	4.3	67.4	0.086	\$28,213
Wyoming	203.489	1.24	0.29	1.13	5	8.43	18.8	897.4	19.5	8.8	64.6	0.083	\$29,698

Supplemental Table 1: 46 state epidemiological and socio-economic data

Supplemental Figure 1: 46 State Per capita beer consumption and age adjusted AD mortality rate for 2014

-
- [1] Alzheimer, A. (1907) "Über eine eigenartige Erkrankung der Hirnrinde". *Allgemeine Zeitschrift für Psychiatrie und Psychiatrisch-gerichtliche Medizin* 64, 146–148.
- [2] Dahm, Ralf. "Alzheimer's discovery." *Current Biology* 16.21 (2006): R906-R910.
- [3] McMenemey, WH. "Alzheimer's disease: a report of six cases." *Journal of neurology and psychiatry* 3.3 (1940): 211.
- [4] Pisa, Diana, Ruth Alonso, Alberto Rábano, Izaskun Rodal, and Luis Carrasco. "Different brain regions are infected with fungi in Alzheimer's disease." *Scientific reports* 5 (2015).

-
- [5] Pisa, Diana et al. "Direct visualization of fungal infection in brains from patients with Alzheimer's disease." *Journal of Alzheimer's Disease* 43.2 (2015): 613-624.
- [6] Alonso, R., D. Pisa, A. Rábano, and L. Carrasco. "Alzheimer's disease and disseminated mycoses." *European journal of clinical microbiology & infectious diseases* 33, no. 7 (2014): 1125-1132.
- [7] Pisa, Diana, Ruth Alonso, Alberto Rábano, Michael N. Horst, and Luis Carrasco. "Fungal Enolase, β -Tubulin, and Chitin Are Detected in Brain Tissue from Alzheimer's Disease Patients." *Frontiers in Microbiology* 7 (2016).
- [8] Pisa, Diana, Ruth Alonso, Alberto Rábano, and Luis Carrasco. "Corpora Amylacea of Brain Tissue from Neurodegenerative Diseases Are Stained with Specific Antifungal Antibodies." *Frontiers in neuroscience* 10 (2016).
- [9] Emard, Jean-François, Jean-Pierre Thouez, and Denis Gauvreau. "Neurodegenerative diseases and risk factors: a literature review." *Social Science & Medicine* 40.6 (1995): 847-858.
- [10] https://www.cdc.gov/nchs/pressroom/stats_of_the_states.htm , 2014.
- [11] http://www.alz.org/downloads/facts_figures_2012.pdf.
- [12] <http://pubs.niaaa.nih.gov/publications/surveillance102/CONS13.pdf>
- [13] <http://www.cdc.gov/nchs/hus/contents2014.htm>
- [14] <https://chronicdata.cdc.gov/health-area/tobacco-use>
- [15] <http://www.cdc.gov/asthma/brfss/2013/tableL21.htm>
- [16] <http://stateofobesity.org/adult-obesity/>
- [17] http://www.cdc.gov/tb/statistics/reports/2014/pdfs/tb-surveillance-2014-report_updated.pdf
- [18] <https://www.cdc.gov/nchs/hus/contents2014.htm>
- [19] US Census. "DP03 SELECTED ECONOMIC CHARACTERISTICS 2014 American Community Survey 1-Year Estimates." https://factfinder.census.gov/faces/tableservices/jsf/pages/productview.xhtml?pid=ACS_14_1YR_DP03&prodType=table
- [20] Henry J. Kaiser Foundation. "Percent of Adults Who are Overweight or Obese" <https://www.kff.org/other/state-indicator/adult-overweightobesity-rate/?currentTimeframe=2&sortModel=%7B%22colId%22:%22Location%22,%22sort%22:%22asc%22%7D>. Downloaded January, 2018.
- [21] Bollen, Johan, Herbert Van de Sompel, Aric Hagberg, and Ryan Chute. "A principal component analysis of 39 scientific impact measures." *PloS one* 4, no. 6 (2009): e6022.
- [22] K. Pearson. "On Lines and Planes of Closest Fit to Systems of Points is Space." *Philosophical Magazine* (6) , 23:559–572, 1901.
- [23] De Leeuw, Jan. "History of nonlinear principal component analysis." *Visualization and Verbalization of Data* (2011).

-
- [24] Kaiser, Henry F. "The varimax criterion for analytic rotation in factor analysis." *Psychometrika* 23, no. 3 (1958): 187-200.
- [25] Zaiontz, Charles, "Real Statistics Using Excel: Varimax Algorithm", <http://www.real-statistics.com/linear-algebra-matrix-topics/varimax/>
- [26] Comrey, A. L., and H. B. Lee. "Interpretation and application of factor analytic results." *Comrey AL, Lee HB. A first course in factor analysis* 2 (1992).
- [27] Peers, Ian. *Statistical analysis for education and psychology researchers: Tools for researchers in education and psychology*. Routledge, 2006.
- [28] "States that drink the most beer - USA Today." 2014. 14 Sep. 2016
<<http://www.usatoday.com/story/money/business/2014/07/06/states-drinking-most-beer/12025609/>>
- [29] Beer Institute, "Beer Consumption by State per Capita: Source Beer Institute", <http://beerinfo.com/beer-consumption-by-state-per-capita/> (downloaded 4/5/2018).
- [30] Jones, Jeffrey M. "Drinking Highest Among Educated, Upper-Income Americans." *Well Being*. <<http://news.gallup.com/poll/184358/drinking-highest-among-educated-upper-income-americans.aspx>>.
- [31] Ship, Jonathan A., and Scott A. Puckett. "Longitudinal study on oral health in subjects with Alzheimer's disease." *Journal of the American Geriatrics Society* 42, no. 1 (1994): 57-63.
- [32] Kim, Jae-Min, Robert Stewart, Martin Prince, Sung-Wan Kim, Su-Jin Yang, Il-Seon Shin, and Jin-Sang Yoon. "Dental health, nutritional status and recent-onset dementia in a Korean community population." *International journal of geriatric psychiatry* 22, no. 9 (2007): 850-855.
- [33] Pizzo, Giuseppe, Rosario Guiglia, Lucio Lo Russo, and Giuseppina Campisi. "Dentistry and internal medicine: from the focal infection theory to the periodontal medicine concept." *European journal of internal medicine* 21, no. 6 (2010): 496-502.
- [34] Kleinbaum, David G., Lawrence L. Kupper, Azhar Nizam, and Eli S. Rosenberg. *Applied regression analysis and other multivariable methods*. Cengage Learning, 2013.
- [35] Ott, Alewijn, Monique MB Breteler, Frans Van Harskamp, Jules J. Claus, Tischa JM Van Der Cammen, Diederick E. Grobbee, and Albert Hofman. "Prevalence of Alzheimer's disease and vascular dementia: association with education. The Rotterdam study." *Bmj* 310, no. 6985 (1995): 970-973.
- [36] Hebert, Liesi E., Paul A. Scherr, Julia L. Bienias, David A. Bennett, and Denis A. Evans. "Alzheimer disease in the US population: prevalence estimates using the 2000 census." *Archives of neurology* 60, no. 8 (2003): 1119-1122.
- [37] Lindsay, Joan, Danielle Laurin, René Verreault, Réjean Hébert, Barbara Helliwell, Gerry B. Hill, and Ian McDowell. "Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging." *American journal of epidemiology* 156, no. 5 (2002): 445-453.
- [38] Letenneur, Luc, Veronique Gilleron, Daniel Commenges, Catherine Helmer, Jean-Marc Orgogozo, and Jean-Francois Dartigues. "Are sex and educational level independent predictors

-
- of dementia and Alzheimer's disease? Incidence data from the PAQUID project." *Journal of Neurology, Neurosurgery & Psychiatry* 66, no. 2 (1999): 177-183.
- [39] Nielsen, N. R., P. Schnohr, G. Jensen, and M. Grønbaek. "Is the relationship between type of alcohol and mortality influenced by socio-economic status?." *Journal of internal medicine* 255, no. 2 (2004): 280-288.
- [40] Letenneur, Luc. "Risk of dementia and alcohol and wine consumption: a review of recent results." *Biological research* 37, no. 2 (2004): 189-193.
- [41] "Iceland - 2013: The prevalence of dementia in Europe - Country ...". 21 Sep. 2016 <<http://www.alzheimer-europe.org/Policy-in-Practice2/Country-comparisons/2013-The-prevalence-of-dementia-in-Europe/Iceland>>
- [42] "Why Iceland banned beer - BBC News - BBC.com." 2015. 21 Sep. 2016 <<http://www.bbc.com/news/magazine-31622038>>
- [43] Laurberg, Peter, et al. "Iodine intake and the pattern of thyroid disorders: a comparative epidemiological study of thyroid abnormalities in the elderly in Iceland in Jutland, Denmark." *The Journal of Clinical Endocrinology & Metabolism* 83.3 (1998): 765-769.
- [44] Lindsay, Joan, Danielle Laurin, René Verreault, Réjean Hébert, Barbara Helliwell, Gerry B. Hill, and Ian McDowell. "Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging." *American journal of epidemiology* 156, no. 5 (2002): 445-453.
- [45] Wrede, B., E. Klar, and M. Klett. "Do environmental factors influence goiter size in strumectomized patients?." *Experimental and Clinical Endocrinology & Diabetes* 114, no. S 1 (2006): P13_166.
- [46] Truelsen, Thomas, Dorte Thudium, and Morten Grønbaek. "Amount and type of alcohol and risk of dementia The Copenhagen City Heart Study." *Neurology* 59, no. 9 (2002): 1313-1319.
- [47] Deng, Juan, David HD Zhou, Jingcheng Li, Y. John Wang, Changyue Gao, and Man'E. Chen. "A 2-year follow-up study of alcohol consumption and risk of dementia." *Clinical neurology and neurosurgery* 108, no. 4 (2006): 378-383.
- [48] Mukamal, Kenneth J., Lewis H. Kuller, Annette L. Fitzpatrick, William T. Longstreth Jr, Murray A. Mittleman, and David S. Siscovick. "Prospective study of alcohol consumption and risk of dementia in older adults." *Jama* 289, no. 11 (2003): 1405-1413.
- [49] Kok, Eloise H., Toni T. Karppinen, Teemu Luoto, Irina Alafuzoff, and Pekka J. Karhunen. "Beer drinking associates with lower burden of amyloid beta aggregation in the brain: Helsinki sudden death series." *Alcoholism: Clinical and Experimental Research* 40, no. 7 (2016): 1473-1478.
- [50] Krause, W, H Matheis, and K Wulf. "Fungaemia and funguria after oral administration of *Candida albicans*." *The Lancet* 293.7595 (1969): 598-599.
- [51] Cos, Paul et al. "Phytoestrogens: recent developments." *Planta medica* 69.07 (2003): 589-599.

-
- [52] Buhner, Stephen Harrod. *Sacred and herbal healing beers: the secrets of ancient fermentation*. Brewers Publications, 1998.
- [53] Paganini-Hill, Annlia, and Victor W Henderson. "Estrogen deficiency and risk of Alzheimer's disease in women." *American journal of epidemiology* 140.3 (1994): 256-261.
- [54] Promberger, Andrea, Eva Dornstauder, Claus Frühwirth, Erich R. Schmid, and Alois Jungbauer. "Determination of estrogenic activity in beer by biological and chemical means." *Journal of agricultural and food chemistry* 49, no. 2 (2001): 633-640.
- [55] Catharina, J Th. "Acute effects of drinking beer or wine on the steroid hormones of healthy men." *Journal of steroid biochemistry* 31.4 (1988): 467-473.