Alzheimer's Disease Mortality Trends in Turkey, 2009-2018

Türkiye'de Alzheimer Hastalığına Bağlı Mortalite Eğilimleri, 2009-2018

Nurhan Doğan[1]*, İsmet Doğan[1]

1.*Department of Biostatistics and Medical Informatics, Faculty of Medicine, Afyonkarahisar Health Sciences University, Afyonkarahisar/Turkey*

ABSTRACT

Aim: World population has aged as a result of developments and improvements in the living conditions, care and health services. The most important risk factor of Alzheimer's disease is age, and with the aging of the population, both prevalence and mortality rates increase. The study aimed to determine the trend of mortality rates due to Alzheimer's disease over the years according to gender and age groups, between 2009-2018.

Methods: Alzheimer's disease-related data was obtained from the Turkish Statistical Institute death database. Age-standardized mortality rates were calculated through the direct method to the World Standard Population. Joinpoint Regression Analysis was used to estimate annual percentage change, average annual percentage change, and 95% confidence intervals.

Results: Over the period observed, more than 95 000 persons died due to Alzheimer's disease (37 961 males and 57 936 females). Joinpoint Regression Analysis indicated that the trend in Alzheimer's mortality rates a significant increase of 13.3% (95% CI: 10.6;16.2; p<0.001) every year from 2009 to 2015, and a non-significant decrease of 0.5% % (95% CI: -5.3;4.7; p=0.82), from 2015 to the end of the period. When evaluated according to gender, both in females and males, mortality rates showed a significant increase from 2009 to 2015. And then until the end of the period a non-significant decrease in males and a non-significant increase in females.

Conclusion: The findings from this study can provide information about current and future health planning and policy development in medicine, social work, public policy and public health.

Keywords: Alzheimer disease; mortality; trend; Joinpoint Regression

ÖZ

Amaç: Dünyada, yaşam koşullarındaki iyileşmeler, bakım ve sağlık hizmetlerindeki gelişmelerin bir sonucu olarak nüfus yaşlanmaktadır. Alzheimer hastalığına ait en önemli risk faktörü yaştır ve nüfusun yaşlanmasıyla birlikte hem prevalans hem de mortalite oranları artmaktadır. Çalışmanın amacı, 2009-2018 yılları arasında Alzheimer hastalığına bağlı mortalite oranlarının cinsiyet ve yaş gruplarına göre yıllar itibari ile nasıl bir eğilim gösterdiğini belirlemektir.

Metot: Alzheimer hastalığı ile ilgili veriler Türkiye İstatistik Kurumu ölüm veri tabanından elde edildi. Yaşa göre standartlaştırılmış ölüm oranları, Dünya Standart Popülasyonuna göre doğrudan yöntem kullanılarak hesaplandı. Yıllık yüzde değişim, ortalama yıllık yüzde değişimini ve %95 güven aralıklarının (GA) tahmini için Joinpoint Regresyon Analizi'nden yararlanıldı.

Bulgular: Gözlemlenen dönemde Alzheimer hastalığından dolayı 95,000'den fazla kişi hayatını kaybetmiştir (37,961 erkek ve 57,936 kadın).

Joinpoint regresyon analizi, yaşa göre standartlaştırılmış Alzheimer ölüm oranı, 2009'dan 2015'e kadar her yıl %13.3'lük anlamlı bir artış (%95 GA: 10.6;16.2; p<0.001) ve 2015'den dönem sonuna kadar ise %0,5'lik anlamlı olmayan bir azalış (%95 GA: 5,3;4,7; p=0,82) göstermiştir. Cinsiyete göre değerlendirildiğinde ise hem kadınlarda hem de erkeklerde ölüm oranları 2009'dan 2015'e kadar önemli bir artış göstermiştir. Daha sonra dönem sonuna kadar erkeklerde önemsiz bir düşüş, kadınlarda ise önemsiz bir artış olmuştur.

Sonuç: Bu çalışmadan elde edilen bulgular tıpta, sosyal hizmetlerde, kamu politikasında ve halk sağlığında şimdiki ve gelecekteki sağlık planlaması ve politikalar geliştirme hakkında bilgi verebilir.

Anahtar Kelimeler: Alzheimer hastalığı; mortalite; eğilim; Joinpoint Regresyon

*Corresponding Author: Nurhan Doğan. Department of Biostatistics and Medical Informatics, Faculty of Medicine, Afyonkarahisar Health Sciences University, Afyonkarahisar, Turkey, +905326480776, nurhandogan@hotmail.com

ORCİD: 0000-0001-7224-6091

INTRODUCTION

Alzheimer's disease, a neurological disorder, is defined as the loss of memory and cognitive functions of the brain cells over time. Alzheimer's disease is considered the most common among dementia-caused disorders discomfort and constitutes 60-80% of cases [1]. The percentage of people with Alzheimer's dementia increases significantly with age [2,3]. In light of its characteristics as a non-physical and non-visible disease, Alzheimer's is often overlooked as a disease, resulting in insufficient research being performed on this subject, though in the past decade, a significant increase in public awareness in high-income countries has occurred, with the disease being increasingly discussed in the media [2]. Alzheimer's prevalence and mortality appear to increase with the aging of the population and the disease is now considered a growing Global public health problem [4]. All over the world, scientific and technological developments in the field of medicine, prevention of diseases, provision of early diagnosis and treatment, as well as the development of preventive health services, are among the principal reasons for the increase in the elderly population [5]. In European Union countries [6], France [7], Mexico [8], Brazil [9], as well as in Alzheimer's related mortality studies conducted in America [10], it is stated that the age-standardized mortality rates have increased over the years; in the 75 years age group, these increases are even higher. According to a study conducted in China, it was stated that there is a slight decrease in mortality rates in recent years [3]. The Turkish Neurological Society has reported some 300 000 Alzheimer's patients in Turkey. It is projected that as Turkey's current younger population will grow old, the disease will become one of the most prominent health problems over the next 30 to 40 years [11]. The purpose of our study of Alzheimer's disease in Turkey between the years 2009 and 2018, according to gender and age groups, was to determine the trend of the mortality rate (stable/increase/decrease) in this country.

MATERIALS AND METHODS

Data Source

This population-based observational study covers ten years and was performed using data on gender and age of death associated with Alzheimer's disease, which was obtained from the Turkish Statistics Institute [12]. Annual data on the number of deaths due to Alzheimer's disease was analyses using code G30 in the 10th revision of the International Classification of Diseases (ICD). Age-standardized mortality rates (ASR) were determined using the direct standardization method to the WHO reference population [13]. Age-specific mortality rates were calculated for the age intervals from 0 to 80 and over a 10-year period. The results are not shown for the subgroups aged <45 years because fewer than five cases of Alzheimer's deaths occurred in any given year. In the analysis, subjects were age-grouped as 45 to 64, 65 to 74, 75 to 84 and ≥ 85 years.

Statistical analysis

Joinpoint Regression Analysis is a statistical method used to identify significant time points in the data set and model changing trends over time. This method has been widely used in epidemiological studies such as incidence, mortality or the survival of a population, to reveal any disease-related tendency. In such studies, the main goal is to give reliable estimates of incidence, mortality or survival rates, that provide information about current trends. The Joinpoint regression model is a piecewise regression model that characterizes the trend behavior in data, by defining the significant time points at which changes occur. The model with minimum error squares among the determined models, is the most suitable joinpoint regression model [14].

$$(x_1, y_1), \ldots, (x_n, y_n), x_1 \leq \cdots \leq x_n$$

including,

$$E[y|x] = \beta_0 + \beta_1 x + \delta_1 (x - \tau_1)^+ + \cdots + \delta_k (x - \tau_k)^+$$

x: independent variable (time),

y: dependent variable,

$\beta_0, \beta_1, \delta_1, \delta_k$: regression coefficients,

τ_k: unknown joinpoint,

δ_k = differences in slope,

Annual Percent Change (APC), which is one of the significant concepts in joinpoint regression analysis, is used to describe the behavior of mortality trends. APC between τ_j ve $\tau_{(j+1)}$ is estimated as follows.

$$APC = \{Exp(b_i) - 1\}x100$$

One of the significant concepts in Joinpoint regression analysis, Average Annual Percentage Change (AAPC) is a summary measure of the trend in a predetermined fixed range. It is the weighted average of the APCs and is estimated as follows [15].

$$AAPC = \left\{Exp\left(\frac{\sum w_i b_i}{\sum w_i}\right) - 1\right\}x100$$

If there is no joinpoint in the model, APC and AAPC will be equal to each other. In the study, the death data of Alzheimer's disease, covering the period 2009-2018 and taken from the Turkstat database, were analyzed according to gender and age groups using the Joinpoint Regression Analysis Method. For each gender ASR, APC, AAPC values, and confidence intervals (CI) calculate [16]. In the analyzes, the Grid search method, which is suggested by Lerman, was used to predict change points. The Grid search method is applied to determine the number of possible breakpoints that can found in the data [17]. The Monte Carlo permutation and Bonferroni multiple comparison tests were used to test the determined breaking points [14]. Mortality trends from Alzheimer's were determined using the joinpoint regression software (4.6.0.0). The study was conducted in accordance with the ethical approval with the protocol number of 2019/11-341 from the Faculty of Medicine, Afyonkarahisar Health Science University.

RESULTS

The number of deaths and female/male rates by gender by years are given in Table 1. The data from a total of 95 897 persons diagnosed with Alzheimer's disease in Turkey between the years 2009 to 2018, is also shown in Table 1. The proportion of those who lost their lives is 39.6% for males (37 961 individuals) and 60.4% for females (57 936 individuals). Considering the share of the number of people who died due to Alzheimer's in total deaths, it was 1.4 (Male: 1.0; Female: 1.8) in

2009 and 3.3 (Male: 2.3; Female: 4.5) in 2018. In view of the ratio of females to males in Table 1, it is seen that deaths are higher in females.

Table 1. Number of deaths by gender and female / male ratio by years

Year	Deaths	Gender		Female/Male
		Male	Female	Rate
2009	3870	1596	2274	1.42
2010	5333	2125	3208	1.51
2011	6301	2618	3683	1.41
2012	7696	3046	4650	1.53
2013	8984	3683	5301	1.44
2014	10382	4131	6251	1.51
2015	12279	4906	7373	1.50
2016	13269	5179	8090	1.56
2017	13831	5354	8477	1.58
2018	13952	5323	8629	1.62
Total	95897	37961	57936	1.53

Changes in the ASR rate and their comparison with the previous year are provided in Table 2. Looking at the percentage change in ASR, the maximum change occurred in 2010 with 21% for males and 32% for females. Both genders decreased in 2017 and 2018, compared to the previous year.

Table 2. Distribution of Standardized Mortality Rates by Gender and percentage change in ASRs (Compared to the Previous Year). 2009-2018 (100 000).

Year	General ASR*	Gender		ASR (% Change)	
		Male	Female	Male	Female
2009	4.77	5.05	4.57	-	-
2010	6.09	6.11	6.02	21	32
2011	6.83	7.34	6.45	20	7
2012	7.85	8.06	7.65	10	19
2013	8.69	9.36	8.22	16	7
2014	9.56	9.91	9.24	6	12
2015	10.74	11.29	10.34	14	12
2016	11.24	11.55	10.99	2	6
2017	11.21	11.38	11.01	-1	0
2018	10.67	10.59	10.63	-7	-3

*ASR: Age-standardized mortality rates

Table 3 shows the results of the Joinpoint Regression Analysis (AAPC, APC and Cis, for each joinpoint point and gender). As can be seen from Table 3, when evaluated in general, the model with a single joinpoint is the best. Age-standardized Alzheimer's mortality rates showed a significant increase of 13.3% every year, from 2009 to 2015. Although there is an annual decrease of 0.5% from 2015 to the end of the period, this decrease is not statistically significant.

Table 3. Annual percentage change and average annual percentage change by gender and age groups (2009-2018); Joinpoint Regression Analysis results.

	AAPC(95% CI) (2009-2018)	Trend 1		Trend 2	
		Period	APC (95% CI)	Period	APC (95% CI)
Male 45-64	2.4 (5.7;10.3) (p=0.12)	-	-	-	-
65-74	2.9 (0.6;5.1) (p=0.01)	2009-2014	8.1 (4.4;11.8) (p<0.05)	2014-2018	-3.3(-7.8;1.6) (p=0.14)
75-84	7.9 (3.2;12.7) (p<0.05)	2009-2015	14.5 (9.1;20.2) (p<0.05)	2015-2018	-4.3(-17.1;10.4) (p=0.46)
85+	11.7 (8.6;14.9) (p<0.05)	2009-2015	19.3 (15.7;23.1) (p<0.05)	2015-2018	-2.2 (-10.8;7.3) (p=0.57)
Total (Male)	8.0 (5.7;10.3) (p<0.05)	2009-2015	13.6 (10.2;17.1) (p<0.05)	2015-2018	-2.4 (-7.8;3.3) (p=0.32)
Female 45-64	4.7 (0.4;9.2) (p=0.04)	-	-	-	-
65-74	3.3 (1.1;5.6) (p=0.01)	-	-	-	-
75-84	7.3 (3.5;11.4) (p<0.05)	2009-2015	12.4 (7.9;17.1) (p<0.05)	2015-2018	-2.1 (-13.2;10.3) (p=0.66)
85+	12.6 (9.7;15.5) (p<0.05)	2009-2015	18.4 (15.2;21.8) (p<0.05)	2015-2018	1.8 (-6.3;10.7) (p=0.60)
Total (Female)	8.9 (7.1;10.8) (p<0.05)	2009-2015	13.1 (10.61;15.7) (p<0.05)	2015-2018	1.0 (-4.0;6.2) (p=0.65)
Total	8.5 (6.6; 10.5) (p<0.05)	**2009-2015**	13.3 (10.6;16.2) (p<0.05)	2015-2018	-0.5 (-5.3;4.7) (p=0.82)

CI: Confidence Interval; AAPC: Average Annual Percent Change; APC: Annual Percent Change

When evaluated according to genders, it is seen that the model with a single joinpoint was the best significant model for both males and females. Age-standardized Alzheimer's mortality rates showed a significant increase of 13.6% in males and 13.1% in females, every year from 2009 to 2015. Although an annual decrease of 2.4% in males and an increase of 1.0% in females, this was not statistically significant (2015 to the end of the period). Joinpoint Regression Analysis results regarding age-specific mortality rates for each gender given in Table 3.

In males, a similar structure was observed in all age groups except for the 45-64 age group. There was a non-significant increasing trend during the period specifically in the 45-64 age group. In the 65-74 age group, there was a continuous significant increase (2.9%; p = 0.01) until 2014, and after 2014 there were decreases, although insignificant. There was a similar trend in the 75-84 and 85+ age groups. In both age groups, there was a significant increase until 2015, and after 2015, there were non-significant decreases. The model with zero joinpoints provided the best model for females in the 45-64 and 65-74 age groups. In both age groups, a significant increase was observed during the period. The single-join

point model was the best model for the 75-84 and 85+ age groups. In both age groups, 2015 was determined as the joinpoint. In the 75-84 age group, a continuous significant increase (12.4%, p <0.05) occurred until 2015, while decreases observed in the annual percentage change from 2015 to the end of the period. In the 85+ age group, the increase continued somewhat after 2015, but this increase was not significant (p = 0.60).

DISCUSSION

According to the results obtained from the study, significant increases were observed in all female age groups throughout the period, while considering the age groups. In males, a significant increase was observed only in the age group 65 and over. The study by Niu et al. covering 28 European Union countries, stated that the death rates from Alzheimer's disease increased eight times in males and 12 times in females, between 1985-2004 [6]. A mortality study conducted in the United States emphasized that the mortality rates standardized by age have increased over the years, from 16.5 in 1999, to 25.4 in 2014 (per 100 000 people), and that chronic diseases and diabetes may cause this increase in Alzheimer's mortality [7,9]. In another study, it was stated that there is a strong relationship between the decrease in the incidence of dementia and preventive measures for better control and treatment of vascular risk factors [18]. A study conducted in China covering the years of 2009-2015, stated that the mortality rates of Alzheimer's disease increased in 2009-2010, and then there was a decrease until the end of the period [3]. A study by Teixeira et al. in Brazil found an annual increase of 8.4% for females aged 60 to 79, and 7.7% for males, 15.5% for females, and 14% for males aged 80 and over [9]. Likewise, a study in France stated that mortality increased in the group above 80 years old [7]. Taylor et al., for their part, reported that the mortality rate in females is higher than in male, and the mortality rate increases with age, especially in the group above 75 years old [10]. A study in Mexico stated that there is an increase in Alzheimer's mortality trends in males and females over the age of 40 [8]. A study by Moschetti et al. reported that the age-standardized mortality rates increased from 45.3 in 1999 to 50.0 in 2008 [19].

In females as well as males, the influence of longevity, biological differences, differences in cognitive performance and gendered social roles and opportunities, can differentially affect the risk and progression of Alzheimer's disease [20]. One reason why females living with Alzheimer's are found in higher numbers than males is likely that females live longer on average than males, and that older age is the biggest risk factor for Alzheimer's. Life expectancy at birth for females in Turkey (80.7 in 2018) males (75.3 in 2018) is estimated to be longer by TurkStat [12]. This may partially explain the observed differences between the genders.

Population aging can be suspected as the primary reason for the increase in the number of people living with Alzheimer's disease. Therefore, it is reasonable to believe that the disease burden caused by Alzheimer's disease will increase rapidly in the coming years. Escalating research on risk factors for Alzheimer's disease and its preclinical stage supports the development of Alzheimer's disease prevention programs, that will have a significant impact on public health by delaying the onset of Alzheimer's disease, even if only by a few years. Also, it is stressed that identifying individuals at risk of developing Alzheimer's disease may be the key to the success of further intervention studies [21].

Limitations of the Study

We had to use a short time period in our study: mortality data prior to 2009 was not included in the study, since it only covered provincial and district centers. In addition, death certificate data may be subject to potential miscoding and misclassification. Despite these limitations, this data provided the most comprehensive assessment of cause-specific Alzheimer's disease mortality rates at the national level.

Conclusion and recommendations

This study has the distinction of being the first comprehensive study examining trends in mortality in Alzheimer's disease in Turkey. In providing a portrayal of the extent of the disease in this country, it emphasizes the offers important new evidence for the planning of future public health policy for the benefit of the elderly in our society. According to the results obtained from this study, Alzheimer's total mortality shows a negative trend in Turkey during the ten years that were observed. Furthermore, there are some insignificant decreases, in both females and males, after 2015. However, according to World Health Organization Data, by the year 2050 Turkey will be one of four countries in the world with the highest incidence of Alzheimer's disease. At present, an estimated 400 000 Alzheimer's patients exist in Turkey, with a disease that is known to be more widespread than reported and which is evolving in an aging of the population. In this context, it is necessary to increase the awareness of the disease in our society and to find solutions to the problem of prevention and care. Alzheimer's disease primarily affects the elderly and there is presently no effective treatment to stop or slow the progression of the disease. An intensification of the illness among the elderly population in the coming years, combined with increasing life expectancy and citizens concerned with care for the elderly, will become an important concern for the Turkish economy. The decline in mortality rates in recent years in the world and a desire to actively strive for better prevention and treatment of diseases associated with Alzheimer's, can be connected to create greater awareness in society. Various health and social services should provide support for Alzheimer's and dementia patients, and projects should be produced by non-profit associations, non-governmental organizations, private organizations, municipalities and governments, to raise public awareness on dementia and Alzheimer's disease. The principal goal is to make such institutions widespread throughout the world.

Peer-review: Externally and internally peer reviewed.

REFERENCES

1. Alzheimer's association report. 2020 Alzheimer's disease facts and figures. Alzheimer's Dement. 2020;16:391–460. DOI: 10.1002/alz.12068.

2. Alzheimer's association report. 2019 Alzheimer's disease facts and figures. Alzheimer's Dement. 2019;15:321-387. DOI: 10.1016/j.jalz.2019.01.010.

3. Bo Z, Wan Y, Meng SS, Lin T, Kuang W, Jiang L, Qiu P. The temporal trend and distribution characteristics in mortality of Alzheimer's disease and other forms of dementia in China: Based on the National Mortality Surveillance System (NMS) from 2009 to 2015. PloS one. 2019;14(1):1-14. DOI: 10.1371/journal.pone.0210621.

4. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990-2016: a systematic analysis for the Global Burden of Disease Study 1990-2016. Lancet Neurol. 2019;18(1):88-106. DOI: 10.1016/S1474-4422(18)30403-4.

5. Demans Bakım Modeli Raporu. Aile ve Sosyal Politikalar Bakanlığı Sosyal İçerme Politikaları Alanında Kurumsal Kapasitenin Artırılması Projesi. Ankara: Kasım 2017. Available at: https://www.ailevecalisma.gov.tr/media/9332/demans-bak%C4%B1m-modeli-proje-kitab%C4%B1.pdf. Accessed June 10, 2020.

6. Niu H, Alvarez-Alvarez I, Guillen-Grima F, Al-Rahamneh MJ, Aguinaga-Ontoso I. Trends of mortality from Alzheimer's disease in the European Union, 1994–2013. Eur. J. Neurol. 2017;24(6):858-66. DOI: 10.1111/ene.13302.

7. Brosselin P, Duport N, Bloch J. Mortality with Alzheimer's disease and dementia in France, 2006. Rev Epidemiol Sante Publique. 2010;58(4):269-76. DOI: 10.1016/j.respe.2010.04.007.

8. Cabrera-Pivaral CE, Báez-Báez MG, Celis-Orozco A, Gabriel-Ortiz G, Zavala-González MA. Mortalidad por enfermedad de Alzheimer en México de 1980 a 2014. Gac Med Mex. 2018;154(5):550-4. DOI: 10.24875/GMM.18003361.

9. Teixeira JB, Souza Junior PR, Higa J, Filha T, Miranda M. Mortality from Alzheimer's disease in Brazil, 2000-2009. Cad Saude Publica. 2015;31:850-60. DOI: 10.1590/0102-311X00144713.

10. Taylor CA, Greenlund SF, McGuire LC, Lu H, Croft JB. Deaths from Alzheimer's Disease—the United States, 1999–2014. MMWR. 2017;66(20):521-6. DOI: 10.15585/mmwr.mm6620a1

11. Türkiye Alzheimer Derne.i. Available at: https://www.alzheimer-europe.org/Alzhei10, 2020.

12. Turkish Statistical Institute (TurkStat).

13. Ahmad OB, Boschi-Pinto C, Lopez AD, Murray CJL, Lozano R, Inoue M. Age standardization of rates: a new WHO standard. Geneva: World Health Organization. 2001;9(10). Available at: https://www.who.int/healthinfo/paper31.pdf. Accessed May 20, 2020

14. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. Stat Med. 2000;19(3):335−51. DOI: 10.1002/(SICI)1097-0258(20000215)19:3<335::AID-SIM336>3.0.CO;2-Z

15. Clegg LX, Hankey BF, Tiwari R, Feuer EJ, Edwards BK. Estimating the average annual percent change in trend analysis. Stat Med. 2009;28(29):3670−82. DOI: 10.1002/sim.3733.

16. Kim, HJ, Luo J, Chen HS, Green D, Buckman D, Byrne J, et al. Improved confidence interval for average annual percent change in trend analysis. Stat Med. 2017;36(19):3059−74. DOI: 10.1002/sim.7344.

17. Lerman PM. Fitting segmented regression models by grid search. Appl Stat. 1980;29(1):77-84. DOI: 10.2307/2346413.

18. Schrijvers EM, Verhaaren BF, Koudstaal PJ, Hofman A, Ikram MA, Breteler MM. Is dementia incidence declining? Trends in dementia incidence since 1990 in the Rotterdam Study. Neurology. 2012;78(19):1456–63. DOI: 10.1212/WNL.0b013e3182553be6.

19. Moschetti K, Cummings PL, Sorvillo F, Kuo T. Burden of Alzheimer's disease–related mortality in the United States, 1999–2008. J Am Geriatr Soc. 2012;60(8):1509-14. DOI: 10.1111/j.1532-5415.2012.04056.x.

20. Andrew MK, Tierney MC. The puzzle of sex, gender and Alzheimer's disease: Why are women more often affected than men?. Women's Health. 2018;14:1-8 DOI: 10.1177/1745506518817995

21. Crous-Bou M, Minguillón C, Gramunt N, Molinuevo JL. Alzheimer's disease prevention: from risk factors to early intervention. Alzheimers Res Ther. 2017;9(1):71. DOI: 10.1186/s13195-017-0297-z

Author/ORCID	Authorship Contribution
Nurhan Doğan 0000-0001-7224-6091	Concept, design, materials, data collection; Interpiretion, literature search, manuscript writing, final approval, critical review
İsmet Doğan 0000-0001-9251-3564	Concept, design, materials; Interpiretion, literature search, manuscript writing, final approval, critical review