Original article / *Araştırma*

Treatment of ADHD for at least three years may prevent long-term complications: a preliminary study on long-term prognosis of children diagnosed with ADHD at a single center in Turkey

Emel SARI GÖKTEN,[1] Nagihan SADAY DUMAN,[2] Burcu UÇKUN,[3] Ali Evren TUFAN[4]

ABSTRACT

Objective: *ADHD is known to be associated with psychiatric comorbidities and psychosocial adversities in the long term. The existing literature is focused on predominantly Western samples. There are no studies evaluating long-term functionality of youth diagnosed with ADHD in Turkey.* ***Methods:*** *Patients diagnosed with ADHD at a study center in between 2011 and 2012 were contacted and current functionality was assessed via phone interviews. Univariate and bivariate analyses were conducted to determine correlates of functioning. Sequential logistic regression analyses were conducted to evaluate predictors of still receiving treatment for ADHD, improvement in attention/ academics, improvement in behavior and in peer relationships. p was set at 0.05.* ***Results:*** *Information on functioning of 433 patients (78.3% male) could be collected. Male patients with ADHD tended to be more frequently under treatment at follow-up and they displayed behavior problems at follow-up significantly more frequently. Legal problems were reported in 3.7% and substance use in 2.3%.* ***Discussion:*** *Treatment for ADHD lasting at least 3 years predicted improved functioning and less psychosocial adversity. Earlier diagnosis of ADHD and longer treatment appears to protect against psychosocial adversity also in Turkish samples. Multi-center studies from Turkey with larger samples are needed.* ***(Anatolian Journal of Psychiatry 2018; 19(5):509-517)***

Key words: *ADHD, long-term, follow-up, methylphenidate, atomoxetine, functioning*

Üç yıl ve üzerindeki DEHB tedavisi uzun dönem komplikasyonları engelleyebilir: Türkiye'de tek bir merkezde DEHB'li çocukların uzun dönem prognozu ile ilgili bir ön çalışma

ABSTRACT

Amaç: *DEHB uzun dönemde psikiyatrik komorbiditeler ve ruhsal-toplumsal zorluklarla ilişkili olan bir bozukluktur. Günümüzde literatür daha çok batılı kaynaklardan edinilmektedir. Türkiye'de DEHB tanılı gençlerin uzun dönem işlevsellikleri ile ilgili bir çalışma bulunmamaktadır.* ***Yöntem:*** *2011 ve 2012 yıllarında bir çocuk ve ergen psikiyatrisi merkezinde DEHB tanısı almış olan çocuklara ulaşıldı ve telefon görüşmeleriyle şimdiki işlevselliklerine dair bilgiler alındı. İşlevsellikteki korelasyonları değerlendirmek için tek değişkenli ve iki değişkenli analizler uygulandı. Sıralı lojistik regresyon analizleri halen DEHB tedavisi alıyor olma, dikkat/akademik işlevsellik, davranış ve akran ilişkilerindeki düzelmeyi tahmin etmek için kullanıldı. p<0.05 değeri anlamlı olarak kabul edildi.* ***Sonuçlar:*** *Dört yüz otuz üç olguya (%78.3 erkek) ulaşıldı ve bilgi alındı. İzlemde erkek olgular daha fazla sıklıkta tedavi altındaydı ve daha*

[1] Dr. Öğr. Üyesi, Üsküdar Üniversitesi NPİstanbul Beyin Hastanesi, Çocuk ve Ergen Psikiyatrisi, İstanbul, Türkiye
[2] Uzm. Dr., Afyonkarahisar Devlet Hastanesi, Türkiye, Çocuk ve Ergen Psikiyatrisi Kliniği, Afyonkarahisar, Türkiye
[3] Psk., Yüksek İhtisas Eğitim ve Araştırma Hastanesi, Çocuk ve Ergen Psikoloğu, Bursa, Türkiye
[4] Doç. Dr., Acıbadem Üniversitesi Tıp Fakültesi, Çocuk ve Ergen Psikiyatrisi ABD, İstanbul, Türkiye
Correspondence address / *Yazışma adresi:*
Dr. Öğr. Üyesi Emel SARI GÖKTEN, Üsküdar Üniversitesi NPİstanbul Beyin Hastanesi, Çocuk ve Ergen Psikiyatrisi, Ümraniye/İstanbul, Türkiye
E-mail: esgokten@hotmail.com
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fazla oranda davranış problemleri göstermekteydi. Yasal problemler %3.7 ve madde kullanımı %2.3 oranında saptandı. ***Tartışma:*** *Üç yıl ve üzeri sürede DEHB tedavisi işlevsellikte düzelme ve daha az oranda psikososyal zorlukla ilişkiliydi. Erken tanı ve uzun süreli tedavi Türk örnekleminde de ruhsal-toplumsal zorluklara karşı koruyucu olarak saptandı. Çok merkezli ve geniş örneklemli yeni çalışmalara ihtiyaç vardır.* ***(Anadolu Psikiyatri Derg 2018; 19(5):509-517)***

Anahtar sözcükler: *DEHB, uzun dönem, izlem, metilfenidat, atomoksetin, işlevsellik*

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is the most common neuro-developmental disorder of youth with a global prevalence of 3.4-5.3%.[1,2] The disorder is characterized by age-inappropriate and impairing symptoms of inattention, hyperactivity and impulsivity and classified according to predominant symptoms as hyperactive/impulsive (HI), inattentive (IA) and combined subtypes.[3]

Follow-up studies reported that ADHD was not limited to childhood and that homotypic continuity may be seen in adolescence and adulthood. According to those studies the symptoms may continue either unchanged or with partial remission in approximately two-thirds of patients. Accordingly, among a sample of young adults (i.e. 25 years old) 15.0% were found to meet all while 66.0% met some of the criteria for ADHD.[4] Adolescent and adult continuity of ADHD was found to be associated with lower academic achievement,[7] reduced vocational functioning,[8] elevated rates of criminal offenses and felonies,[9] substance use,[10] interpersonal problems[11] and psychiatric comorbidities.[12]

Pharmacotherapy is the most supported method of treatment of ADHD, although there are still controversies on persistence of its effects.[5,13-15] Despite arguments on persistence of long-term effects, beneficial effects of pharmacotherapy are widely acknowledged in ADHD.[16]

Studies from Turkey are generally in accordance with those from other countries in terms of the prevalence, comorbidities, prognosis and treatments of ADHD.[17-20] However, almost all of those studies are cross-sectional in nature, and they have not ascertained the functional status of children diagnosed with ADHD in the past. Children who were once diagnosed with ADHD and currently transitioning to young adulthood or late adolescence may have important, unmet needs.[21] Addressing the needs of such patients in developing countries such as Turkey may be more important due to persistence of misconceptions on diagnosis and treatment, even among mental health professionals.[22,23] There is only one study from Turkey in the literature which reported elevated internalizing symptoms in adolescents who were diagnosed with ADHD in their childhood and this study also depended on cross-sectional evaluations.[24] Although parent/teacher reports were used in this study, the upper age limit was 18 precluding the evaluation of effects of ADHD in young adulthood. Other limitations of this study was a limited sample size. Therefore, this study was undertaken to evaluate the effects of ADHD on long-term functionality (i.e. six years after diagnosis) via parental reports gathered with phone interviews within single-center design.

METHODS

Study center and time frame

The study was conducted at Bursa Yüksek İhtisas Training and Research Hospital in between January 2017 and September 2017. Institutional Review Board approval was procured from Bursa Yüksek İhtisas Training and Research Hospital. Informed consent was procured from the parents prior to study entry. All of the study procedures were in accordance with the Declaration of Helsinki and local laws and regulations.

Sampling

Records of children who received a primary diagnosis of ADHD at the Child and Adolescent Psychiatry outpatient department of Bursa Yüksek İhtisas Training and Research Hospital between March 2011 and March 2012 were reviewed. The study center like all hospitals providing child and adolescent psychiatry services in Turkey uses the ICD-10 system of codes for diagnoses. For eligibility the child had to have a primary diagnosis of F90 (hyperkinetic disorders), F90.0 (disorder of activity and attention), F90.1 (hyperkinetic conduct disorder), F90.8 (other hyperkinetic disorders) and F90.9 (unspecified hyperkinetic disorders) at the initial evaluation. Those diagnostic codes were previously found to be valid and reliable in a previous study when compared with pharmacy records.[18]

Children with any other medical/psychiatric comorbidities were eligible for enrollment. The study flowchart in accordance with CONSORT

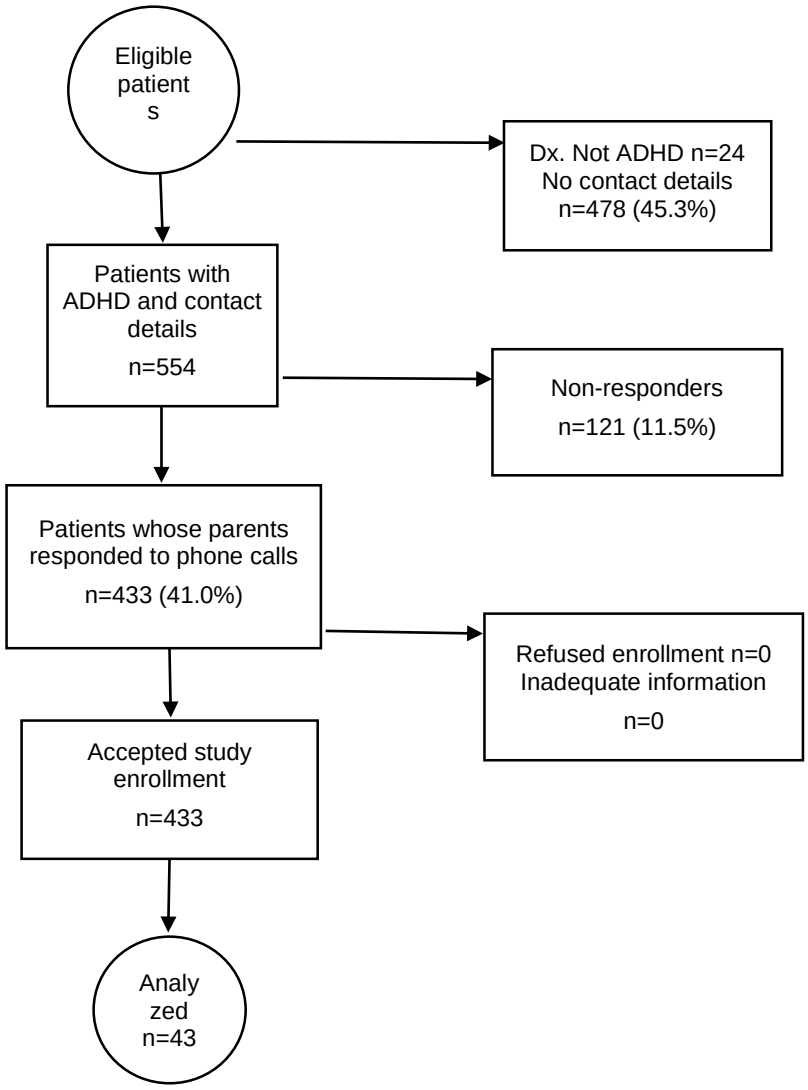

Figure 1. Study flow-chart for long term prognosis of children diagnosed with ADHD

statement is provided in Figure 1.[25]

Evaluations

The parents were interviewed by telephone conversations. The interview covered current age, gender, educational status of the index patient as well as the ages, vocational and academic details of parents. Patient charts were screened for age of patients at diagnosis, ADHD subtypes, DBD comorbidity, comorbidity of other psychopathologies, chronic medical disorders and family histories of psychopathology. Those details were also corroborated at the phone interviews.

Parental interview on current functioning of their children included questions on academical (i.e. academic achievement, retention at any grade, school attendance), social (i.e. peer relationships, oppositonality, behavior problems) and legal (i.e. delinquent behavior, criminal offenses, substance use) domains. Behavior problems were operationalized as displaying any of the symptoms listed for ODD and/or CD diagnosis in DSM-5 within the past six months at a severity sufficient to impair functioning.[3]

Parents were also interviewed for length of treatment of ADHD in their children (ordinal, 1-3 months, 4-6 months, 7-12 months, 13-24 months, 25-36 months, ≥3 years), use of medications (stimulants and/or atomoxetine, coded as dummy variables).

Statistical analyses

The data were entered into a database prepared with Statistical Program for Social Sciences,

Version 23.0 (IBM Inc.). Nominal variables were summarized as frequencies while quantitative variables were summarized either as means and standard deviations or medians and inter-quartile ranges depending on assumptions of normality. Assumptions of normality were tested with Kolmogorov-Smirnov test. Bivariate comparesons for nominal variables were conducted with chi-square tests with Yates' and Fisher's corrections as required. Bivariate comparisons of quantitative variables were conducted with either Student's t or Mann-Whitney U tests depending on assumptions of normality. Binomial logistic regression analyses were conducted to evaluate predictors of still receiving treatment for ADHD, improvement in attention/academics, improvement in behavior and in peer relationships. Effect sizes for significant findings were also presented. P was set at 0.05.

RESULTS

Rates for missing data varied between 0.2% (gender) to 2.8% (paternal age). The analyses were conducted as planned with pair-wise deletion.[26]

Information on functioning of 433 patients (78.3% male) could be collected. Median ages for children, mothers and fathers were 15.0 (IQR=5.0), 40.0 (IQR=6.0) and 43.0 (IQR=7.0) years; respectively.

The sociodemographic features of the sample are illustrated in Table 1. The clinical features of patients according to gender are illustrated in Table 2. The sample as a whole received treatment for more than 3 years (51.6%, n=193) with no difference between genders. Current functioning of the sample is illustrated in Table 3.

Male patients with ADHD tended to be more frequently under treatment at follow-up and they displayed behavior problems at follow-up significantly more frequently.

Bivariate associations for still receiving treatment for ADHD were found for ADHD-inattentive

Table 1. Current sociodemographic features of patients with ADHD between March 2011 and March 2012

	Male (n=339)		Female (n=94)		
	n	%	n	%	p*
Grade					
Primary school	10	2.9	4	4.3	0.52
Secondary school	148	43.7	32	34.0	0.09
High school (inc. graduations)	143	42.2	52	55.3	0.02
University (inc. graduations)	20	5.9	4	4.3	0.79
Left education	18	5.3	2	2.1	0.27
Maternal education					
Primary school	180	53.1	47	50.0	0.28
Secondary school	52	15.3	14	14.9	0.92
High school	66	19.5	21	22.3	0.57
University	41	12.1	12	12.8	0.86
Maternal vocation					
None	233	69.1	74	79.6	0.08
Unskilled/menial	71	20.9	11	11.7	0.06
Semi-skilled	-		-		-
Skilled/managerial	33	9.8	8	8.6	0.87
Paternal education					
Primary school	145	42.8	32	34.0	0.13
Secondary school	53	15.7	24	25.5	0.04
High school	83	24.5	21	22.3	0.77
University	58	17.1	17	18.1	0.95
Paternal vocation					
None	21	6.4	5	5.4	1.00
Unskilled/menial	254	76.9	73	88.5	0.68
Semi-skilled	-		-		-
Skilled/managerial	55	16.7	15	16.1	0.95

** Chi-square test with Yates' and Fisher's corrections as needed.*

Table 2. Clinical features of patients with ADHD at study center within March 2011 and March 2012

	Male (n=339)		Female (n=94)		
	n	%	n	%	p*
ADHD type					
ADHD-combined	260	76.7	57	60.6	0.003
ADHD-IA	65	19.2	30	31.9	0.012
ADHD-HI	13	3.8	7	7.4	0.163
ODD	77	22.8	20	21.3	0.865
CD	56	16.6	9	9.6	0.130
Comorbidities other than DBD	159	47.0	45	47.9	0.886
Chronic medical conditions requiring treatment	37	10.9	12	12.8	0.758
Baseline treatment status	292	86.4	82	87.2	0.967
Baseline treatment agent					
MPH	203	59.9	40	42.6	0.003
ATX	43	12.7	24	25.5	0.004
MPH and ATX	46	13.6	18	19.1	0.236
Family history of psychopathology	92	27.2	34	36.2	0.091
Psychopathology in family member					
Maternal	50	14.7	24	25.5	0.021
Paternal	17	5.0	2	2.1	0.391
Sibling	25	7.4	8	8.5	0.883

** Chi-square test with Yates' and Fisher's corrections as needed*

Table 3. Current functioning of patients with ADHD at study center between March 2011 and March 2012

	Male (n=339)		Female (n=94)		
	n	%	n	%	p*
Still under treatment	112	33.1	22	23.4	0.07
Attention and academics (improved)	239	81.6	71	86.6	0.37
Behavior problems (improved)	232	79.2	66	70.2	0.92
Peer relations (improved)	214	63.1	57	60.6	0.66
Retention in any grade	33	9.8	7	7.4	0.68
Continuing education	303	89.6	87	92.6	0.65
Current oppositionality	126	37.3	34	36.2	0.84
Current behavior problems	33	9.8	1	1.1	0.01
Criminality	16	4.7	-	-	-
Alcohol/substance use	8	2.4	2	2.1	1.00

** Chi-square test with Yates' and Fisher's corrections as needed*

type at baseline (p=0.00, Phi=0.14), ADHD-combined type at baseline (p=0.01, Phi=0.13), methylphenidate treatment at baseline (p=0.001, Phi=0.16), receiving treatment for at least three years (p<0.001, Phi=0.66), improvement in attention/academics (p<0.001, Phi=0.24), improvement in behavior (p<0.01, Phi=0.20) and continuing education (p=0.001, Phi=0.19).

Children still under treatment for ADHD received significantly earlier diagnoses (z=-5.0, p<0.001), were younger (z=-4.0, p<0.001) and had younger parents (z=-1.9, p=0.06 for mothers and z=-2.4, p=0.02 for fathers) compared to those not under treatment (all Mann-Whitney U test).

Binomial logistic regression with enter method was used to evaluate predictors of still receiving treatment for ADHD at the time of study and variables showing significant associations at bivariate analyses were used as predictors. The model without any predictors correctly classified all of those not under treatment but none of those still under treatment achieving overall 64.5% correct classification. Adding predictors to the null model correctly classified 82.8% of those still under treatment and 84.1% of those not under treatment (i.e. overall correct classification of

83.7%). The model as a whole was statistically significant (χ^2=215.4, df=15, p<0.001) and could explain 62.0% of the variation for continuing to receive treatment for ADHD.

Bivariate associations for improvement in attention and academic achievement were found for receiving at least 3 years of treatment (p<0.01, Phi=0.29) and improvement in behavior (p<0.01, Phi=0.57). Children who were reported to improve in attention and academic achievement did not differ significantly from those who were not reported to improve in terms of age, age at diagnosis, and parental ages (all Mann-Whitney U test).

Bivariate associations for improved behavior were found for IA subtype (p<0.01, Phi=0.21), Combined subtype (p=0.001, Phi=0.17), receiving at least three years of treatment (p<0.01, Phi=0.26) and continuing education (p=0.01, Phi=0.17). Those with improved behavior at follow-up tended to be older (z=-1.7, p=0.09) although no other differences were significant in terms of age at diagnosis and parental ages (all Mann-Whitey U test).

Bivariate associations for improved peer relationships at follow-up were found with baseline oppositional behaviors (p<0.01, Phi=0.19), baseline conduct problems (p<0.01, Yates' correction, Phi=0.16), presence of comorbid psychopathology other than DBD (p<0.01, Phi=0.18), presence of organic disorders at baseline (p=0.05, Yates' correction, Phi=0.10) and current oppositional behaviors (p<0.01, Phi=0.19).

Children with improved peer relationships at follow up were significantly more likely to be diagnosed at later ages (z=-2.7, p=0.01).

Binomial logistic regression with enter method was used to evaluate predictors of improvement in attention and academic achievement, in behavior, and in peer relations at the time of study and variables showing significant associations at bivariate analyses were used as predictors. The model as a whole was statistically significant (χ^2=113.5, df=3, p<0.001) and could explain 43.3% of the variation for improvement in attention and academic achievement. The model as a whole was statistically significant (χ^2=45.7, df=8, p<0.001) but could explain only 18.0% of the variation for improvement in behavior. The sole statistically significant predictor in this model was receiving at least 3 years of treatment for ADHD (O.R.=3.4, 95% CI=1.9-6.1, p<0.001). Also, the model as a whole was statistically significant (χ^2=52.6, df=6, p<0.001) but could explain only 15.6% of the variation for improve-ment in peer relations.

DISCUSSION

In this single-center, retrospective cohort study we evaluated current functioning and outcomes of Turkish youth six years after they were diagnosed with ADHD.

Previous studies conducted in various countries and which followed patients with ADHD until late adolescence/early adulthood reported that symptoms may continue and disrupt functioning even at subthreshold levels.[5,13,15] As far as we are aware, this is the first study from Turkey focusing on long-term functioning of youth diagnosed with ADHD in the past. We found that 30.9% of the sample was still receiving treatment at follow-up and that in those without treatment symptoms persist despite improvements in academic and social functioning. Those results are in accordance with the literature and support the view that ADHD may display homotypic and heterotypic continuity through development.

Previous studies on long-term functioning of youth with ADHD report that rates of leaving school are high.[5,15] In a recent study with a similar duration of follow-up (i.e. 8 years); grade retention was reported in 51.0% and leaving school was reported in 13.0% of the sample.[15] We found grade retention in 9.2% of the sample while 4.6% of the sample had already left formal schooling at the time of the phone interviews. Those results may have been affected by the nature of the interviews (i.e. phone rather than in person), high rate of attrition in the original sample or by recall and reporting bias. Alternatively, the limited age range may have affected our results and those still receiving university education may repeat courses or leave colleges/ universities in longer term.[27] Recent changes in Turkish educational system providing more stringent criteria for grade retention and school expulsion may also partially explain our findings.[28,29]

Previous studies with long-term follow-up of youth with ADHD report elevated rates of delinquency, legal problems and alcohol-substance use.[15,30,31] There are only retrospective case-control studies on rates of legal problems, delinquency and alcohol-substance use in Turkish youth with ADHD and the results of those are in accordance with studies from other countries.[32-34] The rate of legal problems was 3.7% in our

sample while that of alcohol/substance use was 2.3% which are much lower. Those results may have been affected by the nature of the interviews (i.e. phone rather than in person), high rate of attrition in the original sample or by recall and reporting bias. The limited age range of our sample (i.e. adolescence) may also have affected our results and longer term follow-up preferably with personal interviews may provide more accurate rates.

Social problems in youth with ADHD have been receiving increasing attention in research. Patients with ADHD were found to have delays in emotion recognition, theory of mind, poor self-esteem and social relationships.[35-37] Studies from Turkey also report impaired emotion recognition and social cognition in youth with ADHD.[38,39] According to those studies youth with DBD comorbidity may be especially impaired in social and emotional skills and pharmacotherapy may have transient and limited effects on social/emotional functioning.[40] We found that improvement in attention/academic skills was more common than improvement in behavior (71.6% vs. 68.8%) in our sample and that peer relationships showed the least improvement (62.6%). Receiving long-term treatment predicted improvement in all domains while baseline oppositionality and psychopathology other than DBDs predicted less improvement in peer relationships. Our results support the view that social and emotional problems in youth with ADHD may be less amenable to treatment and that comorbid psychopathology especially DBDs may be important in this regard. ATX vs MPH vs combination therapy may have differential effects on social-emotional functioning in youth with ADHD.[41,42] Augmenting pharmacotherapy with various methods of psychotherapy may be more effective for lingering social-emotional problems especially in late adolescence and young adulthood.[43] These possibilities should be evaluated with further studies.

Our results should be evaluated within existing limitations. Firstly, the results are valid for the clinical sample at the study center evaluated within the time frame and their ecological validity for other samples may be limited. Secondly, the diagnoses were reached with DSM-IV-TR based clinical interviews and coded with ICD-10 codes but structured interviews and measurements for symptom severity were not used. Thirdly, we did not evaluate parental psychopathology and family stressors with structured interviews. Fourth, the follow-up interviews were conducted via phone interviews with both parents and youth and information collected with this method may be affected by shared method variance, recall and reporting bias. We also did not use a structured evaluation of current functioning. Fifth, the rate of attrition of the original sample may have affected our results. Despite those limitations our study is the first of its kind from Turkey which evaluates current functioning of youth diagnosed with ADHD in the past by a large clinical sample from a single study center.

Conclusions

We found that the majority of youth diagnosed with ADHD in childhood continue to receive treatment in mid to late adolescence and early adulthood and that long term treatment was associated with improved academic/attentional, peer and behavioral functioning.

Yazarların katkıları: *E.S.G: Sorumlu araştırmacı, konuyu bulma, literatür tarama, araştırmayı yürütme, makaleyi yazma; A.E.T: Planlama, literatür tarama, istatistik; N.S.D: İstatistiksel analiz, planlama; B.U: Planlama, araştırmayı yürütme, makaleyi yazma.*

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