The Association between Attention-Deficit/Hyperactivity Disorder and Retinal Nerve Fiber/Ganglion Cell Layer Thickness Measured by Optical Coherence Tomography – A Systematic Review and Meta-analysis.

Running title: Review on ADHD and Retinal Nerve Fiber Layer Thickness

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Availability of data and materials

The datasets supporting the conclusions of this article are included within the article.

Authors' contributions

SLL, KWK, ASHC, XJZ, LJC, WWKY, CCT, ALY, ICKW, PI and JCY designed the study. SLL and ASHC conducted the literature search and extracted data into a customized database. KWK involved as a third reviewer for the selection of eligible articles. SLL, KWK, ASHC, LJC and JCY performed the analysis and interpretation of data. SLL drafted the manuscript. All authors were involved in the revision of the manuscript and approved the final version of the submitted manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Not applicable.

ABSTRACT

Purpose

Retinal Nerve Fiber/Ganglion Cell Layer (RNFL/GCL) thickness measured using Optical Coherence Tomography has been proposed as an ocular biomarker for children with Attention-Deficit/Hyperactivity Disorder (ADHD), but findings varied in different studies. This study aims to determine the association between RNFL/GCL thickness and ADHD in children by systematic review and meta-analysis.

Methods

We performed a literature search in Embase, PubMed, Medline, Web of Science, and PsycINFO for relevant articles published up to 29th February 2020. All studies with original data comparing RNFL/GCL thickness in ADHD and healthy children were included. The Newcastle Ottawa Scale (NOS) was used to assess bias risk and quality of evidence. Pooled estimates of the differences in thickness of RNFL or GCL between ADHD and healthy subjects were generated using meta-analysis with a random-effect model due to significant inter-study heterogeneity. Sensitivity analysis was also performed.

Results

We identified four eligible studies involving a total of 164 ADHD and 150 control subjects. Meta-analysis revealed that ADHD in children was associated with a reduction in global RNFL thickness (SMD, -0.23; 95% CI, -0.46, -0.01; p=0.04). The global GCL thickness was examined in two studies with 89 ADHD and 75 control subjects, but the pooled difference in global GCL thickness between ADHD children and controls was not statistically significant (SMD, -0.34; 95% CI, -1.25, 0.58; p=0.47).

Conclusion

Existing evidence suggests a possible association between ADHD and RNFL thinning in children. In view of the limited number of reports, further studies in large cohorts should be warranted.

Keywords: attention-deficit/hyperactivity disorder, retinal nerve fibre thickness, meta-analysis, neurodevelopmental disorder, optical coherence tomography

INTRODUCTION

Attention-Deficit/Hyperactivity Disorder (ADHD) is the most common neurodevelopmental disorders in children. A recent meta-analysis reported an estimated prevalence of 6.3% in Chinese children, and a prevalence of 6.4% in Hong Kong children [1]. The prevalence in Hong Kong children with ADHD on medication increased by 14-fold between 2001 and 2013 [2]. Children with ADHD fared significantly worse in psychosocial aspects of their daily life compared to children without ADHD [3,4].

Optical Coherence Tomography (OCT) is a non-invasive method for capturing high-resolution in-vivo images and for performing volumetric analyses of the neuroretina and optic nerve head. Compared to time domain OCT, spectral domain OCT (SD-OCT) is faster and has better image quality, and can be used to acquire 3D data [5]. It has been extensively used in ophthalmology to diagnose and monitor various ocular pathologies, such as glaucoma that affects ganglion cells [6]. Studies have shown that SD-OCT has good repeatability in both children and adults [7,8].

As part of the central nervous system (CNS), the eye can reflect abnormalities and pathologies of the CNS [9-11]. Thinning of the retinal nerve fiber layer, retinal layers and ganglion cell layers, and overall retinal volume changes have been reported in neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, and cognitive impairment [11,12]. In recent years, an increasing number of studies have examined the retinal features in ADHD children, but these studies have been relatively small with varied methodologies. Some of these studies have suggested an association between ADHD and retinal nerve fiber layer (RNFL) or ganglion cell layer (GCL) thickness in children, but findings have been inconsistent. Such retinal features in children with ADHD are important as they can potentially serve as ocular biomarkers for childhood neurodevelopment and long-term visual problems. Therefore, we conducted a systematic review and meta-analysis to evaluate the available evidence on RNFL/GCL thickness in children with ADHD.

METHODS

Search strategy

We performed a comprehensive literature search in Embase, PubMed, Medline, Web of Science, and PsycINFO for relevant articles published up to 29 February 2020. Both controlled vocabularies and free words including "attention-deficit hyperactivity disorder" combined with "retinal nerve fiber layer" or "ganglion cell layer" were used as the search terms. The search strategies are summarized in the online supplementary file. The searches

included journal articles, review papers, and conference proceedings. Citation lists in these articles were screened for additional eligible studies that might have been missed in the electronic search.

Eligibility criteria and study selection

The primary objective of the present review was to examine the relationship between ADHD and associated neuroretinal features (i.e., retinal layer thickness and ganglion cell layer thickness). The eligibility criteria were chosen to be broad and to include as many relevant studies as possible. The eligibility criteria included:

1. Any original human study with a case-control, cross-sectional, or prospective design;
2. Any study that recruited participants with a diagnosis of ADHD or symptoms of ADHD objectively measured or based on diagnostic interviews;
3. Any study that included RNFL or GCL thickness as the outcome measures; and/or
4. Any study that investigated the association between ADHD and RNFL/GCL with reported effect sizes.

These criteria were applied to all titles, abstracts, and full manuscripts. Case reports, editorials, commentaries, animal studies, conference abstracts, and studies not meeting the above-mentioned criteria were excluded from the review.

Study selection and bias risk assessment

We examined the quality of studies using the Newcastle Ottawa Scale (NOS), which is an evidence-based quality assessment tool for systematic reviews of non-randomized studies [13]. Studies were assessed on three dimensions: (1) selection of the study groups, (2) comparability of the groups, and (3) ascertainment of either exposure or outcomes of interest, respectively. The NOS provides an overall score of the methodological quality on a scale of up to nine stars, with higher scores indicating better quality.

Data collection

Two reviewers (S. L. and A. C.) independently extracted data into a customized database. Discrepancies were resolved through discussions with a third reviewer (K.W.K.). The extracted information included authors and titles of the study, publication year, methods of eye selection (i.e., single or both eyes), OCT model, details of each study population (sample size, age, and sex), and outcome variables of RNFL and GCL in terms of mean and standard deviation. The outcome variables included global values, and if any, the measured area of each sector. We extracted all the information from the published reports and calculated the average values in multiple subsectors as appropriate. For studies that reported OCT measurements of the left and right eye separately, we used the left eye measurements in the meta-analysis.

Data synthesis and analysis

We used RevMan software (version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) for the statistical analyses. We analyzed RNFL and GCL thickness as continuous variables. In studies that reported eight sectors of the RNFL instead of four sectors, the mean and standard deviations of the thickness of relevant subsectors were transformed into a combined value with corresponding standard deviations. As different models of OCT might have been adopted for measuring RNFL/GCL thickness, we standardized the mean difference to give a more uniform summary estimate. We used means and standard deviations to estimate the standardized mean difference (SMD) with 95% confidence intervals (CIs). The amount of heterogeneity was estimated using Higgins I^2. Random effects model was used for pooled estimates in view of different OCT models that were used in different studies. Sensitivity analysis was performed by using data obtained from right eyes, and subgroups of different imaging protocols. Potential publication bias was explored with funnel plots.

RESULTS

Study selection and characteristics

A total of 16 publications were retrieved from EMBASE and MEDLINE databases, of which six studies were eligible for detailed screening and evaluation. Overall, only four articles met our criteria for inclusion in the meta-analysis (Figure 1 and Appendix 1). Data of a total of 314 participants (including 164 subjects with ADHD and 150 control subjects) were included in the analysis. Table 1 summarizes the characteristics of the included studies. The quality assessments suggested all the included studies had good methodological quality (Table 2). All four studies were from Turkey and were published between 2018 and 2020. All four cross-sectional studies had a case-control study design. All studies measured peripapillary RNFL thickness, but only two studies measured macular GCL thickness [14,15]. The age and sex significantly differed in one study, which was subsequently controlled for statistically [15].

With the exception of the study by Bodur et al., all studies excluded patients with ocular pathologies (e.g., glaucoma). All studies included both eyes in the analysis and two studies analyzed the left and right eyes separately [15,14]. All studies used spectral domain OCT: two used Heidelberg Spectralis (Heidelberg Engineering, Heidelberg, Germany) [16,17], one used Cirrus HD-OCT (Carl Zeiss Meditec, Inc., Dublin, Ireland) [15], and one used Optovue RTVue-100 (Optovue, CA, USA) [14]. All measurements were processed using the instruments' built-in programs.

RNFL thickness in ADHD subjects and controls

The studies measured the peripapillary RNFL thickness in a total of 164 ADHD patients (239 eyes) and 150 healthy controls (225 eyes). Overall, there was a slight decrease in the global RNFL thickness in patients with ADHD compared with healthy controls (SMD, -0.23; 95% CI, -0.46, -0.01; p=0.04; I^2=0%). The subsequent analysis of each quadrant showed no statistically significant differences (Figure 2). The overall global RNFL thinning among patients with ADHD remained statistically positive even after excluding studies that did not have age- and gender-matched controls (data not shown) [15].

GCL thickness in ADHD subjects and controls

The global GCL thickness was examined in two studies on 89 participants (89 eyes) and 75 healthy controls (75 eyes). There were no statistically significant differences in the global GCL thickness between ADHD patients and healthy controls (Figure 3). Only the study conducted by Bodur et al. included detailed information on the sectoral GCL thickness. Compared to age- and gender-matched healthy controls, there was significant thinning in the superior (-4.36 μm for right eyes; -3.80 μm for left eyes) and inferior (-4.67 μm for right eyes; -3.25 μm for left eyes) sectors, and total GCL thickness (-4.53 μm for right eyes; -3.59 μm for left eyes) in the ADHD group [10].

We conducted several sensitivity analyses (Appendix 2). With only right eyes included in the analysis, peripapillary RNFL thickness was found to be reduced in ADHD patients, but this result did not reach statistical significance. Out of the included studies, two studies used a circular method to measure RNFL, whereas the other studies did not clearly state the RNFL measuring protocols. Nevertheless, the findings were similar and consistent across studies after stratifying the analysis according to the different RNFL measuring protocols.

DISCUSSION

This is the first meta-analysis study of an association between RNFL/GCL thickness and ADHD in children. This study reviewed the currently published evidence on RNFL/GCL thickness and ADHD in children. We found that ADHD in children was associated with a reduction in the global peripapillary RNFL thickness but was not associated with the thickness of any individual quadrant of the RNFL. Although global GCL thickness appeared to be reduced in children with ADHD compared with normal controls, the differences were not statistically significant.

Both RNFL and GCL thickness are highly relevant in the management of glaucoma, which is a neurodegenerative condition characterized by the progressive loss of ganglion cells. Besides the evaluation of these important parameters in children with ADHD, other features such as other layers of the retina, choroid, or

the characteristic of the vasculature were not explored in the existing studies. With advancements in OCT technologies, we can visualize the different layers of the posterior segment of the eye, which should allow more study parameters to be included in such analyses.

Although the exact etiology of ADHD is still unknown, it is likely to be multi-factorial in origin involving both genetic and environmental factors. The neurodevelopmental hypothesis proposes the development of ADHD involves a delay in brain maturation caused by disrupted neurological pathways [18]. Emerging evidence suggests there is an association between ADHD and neuropathology similar to seizure disorders [19]. The RNFL contains ganglion cells with unmyelinated axons, which are considered to be an extension of the cerebral gray matter. In our review, we found there was a tendency for cell loss within the GCL and possible RNFL thinning in ADHD, which correlated with previous MRI findings of reduced cerebral gray matter in ADHD [19].

Our findings are also in line with recent evidence on other mental disorders including schizophrenia [20], bipolar disorder [21], and autism spectrum disorder [22]. However, different to these studies, the quantitative analysis in our review revealed only a small change in RNFL thickness in ADHD patients. This could be due to methodological limitations or the relatively small sample sizes of the included studies, as well as the fact that RNFL thinning in children with ADHD may take years to develop. Hence, further studies with larger sample sizes and longer follow-up are needed.

We only included high quality studies with a low risk of bias according to the published guidelines. Sensitivity analyses have further confirmed our findings, and there was no significant publications bias in the included studies. The differences in all four studies were toward the same direction, and the heterogeneity was low, suggesting the effect is consistent. Nevertheless, this meta-analysis had some limitations and our findings need to be interpreted with caution. As with other meta-analyses, our study may be affected by reporting or publication bias; however, the funnel plots suggested there was a low risk of bias. All the included studies had relatively small sample sizes, and the low number of studies found in our literature search showed there is limited research in this area. All four included studies were published from Turkey which may reduce the generalizability of this meta-analysis to the global population. Hence further larger-scale studies containing multiple ethnicities/racial groups should be warranted in view of the borderline pooled P value. Despite the ability of SD-OCT to capture images at high speed, children with ADHD may be less compliant compared to the healthy controls, resulting in the possibility that children with moderate to severe ADHD were excluded from these studies [17]. The pooled estimate of global RNFL thinning in ADHD might therefore have been underestimated, as the

studies might have only included children with milder ADHD who would be more cooperative during OCT. Lastly, none of the included studies incorporated the OCT magnification effect into the analysis of RNFL/GCL thickness, this may bias the validity of measurement in children with ADHD who tend to have higher prevalence of refractive error [23]. However, we believe that such bias would be non-differential as the four studies recruited children within a similar age range from the same country.

The included studies used different instruments to measure RNFL/GCL parameters: two used Spectralis OCT, one used Cirrus OCT, and one used Optovue RTVue-100, but they all used the SD-OCT method allowing us to compare the measurements. Matlach et al. demonstrated a high correlation between peripapillary RNFL thickness measured with Cirrus and RTVue 100 in adults (ICC 0.718 – 0.958) [7], and a good agreement between the average RNFL thickness measured with Spectralis and Cirrus in healthy adults (ICC 0.663 – 0.908) [24]. In children, the correlation between Cirrus and Spectralis was lower (ICC 0.61-0.67), with the average peripapillary RNFL thickness higher in Spectralis compared to Cirrus [25]. The average global RNFL thickness was higher in the studies by Ayyildiz et al. and Herguner et al. compared to the study by Isik et al. for both ADHD and control groups. Furthermore, two of the studies did not specify the area of measurement (Ayyildiz et al. used Heidelberg Spectralis and Isik et al. used Cirrus HD-OCT) [15,17], but their reported values were consistent with a peripapillray RNFL thickness, and were similar to the values reported in the other two studies that used a Circular protocol.

All case ascertainment adopted clinically validated diagnostic interviews (K-SADS-PL in three studies, and DSM-V in one study) and all assessments were performed by child psychiatrists. Although K-SADS-PL and DSM-V instruments are similar, a standardized diagnostic tool for defining ADHD would further improve consistency and reduce bias. The inclusion of both eyes in the analysis could lead to an erroneously high correlation. However, subgroup analysis could not be performed in this meta-analysis because of the small number of included studies. All included studies were cross-sectional in nature, which cannot rule out the possibility of reverse causation.

In summary, our study summarized the existing evidence and revealed a possible association between ADHD and retinal fiber layer thinning in children. Further larger-scale, multiethnic and longitudinal studies are warranted to confirm this association.

Figure Legend

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flowchart for study inclusion

Fig. 2 Forest plots showing differences in global and sectoral Retinal Nerve Fibre Layer (RNFL) thickness between ADHD and control groups

Fig. 3 A Forest plot showing differences in global Ganglion Cell Layer (GCL) thickness between ADHD and control groups

References:

1. Liu A, Xu Y, Yan Q, Tong L (2018) The Prevalence of Attention Deficit/Hyperactivity Disorder among Chinese Children and Adolescents. Sci Rep 8 (1):11169. doi:10.1038/s41598-018-29488-2

2. Man KKC, Ip P, Hsia YF, Chan EW, Chui CSL, Lam MPS, Wong WHS, Chow CB, Yung A, Wong ICK (2017) ADHD Drug Prescribing Trend Is Increasing Among Children and Adolescents in Hong Kong. Journal of Attention Disorders 21 (14):1161-1168. doi:10.1177/1087054714536047

3. Raman SR, Man KKC, Bahmanyar S, Berard A, Bilder S, Boukhris T, Bushnell G, Crystal S, Furu K, KaoYang YH, Karlstad O, Kieler H, Kubota K, Lai ECC, Martikainen JE, Maura G, Moore N, Montero D, Nakamura H, Neumann A, Pate V, Pottegard A, Pratt NL, Roughead EE, Saint-Gerons DM, Sturmer T, Su CC, Zoega H, Sturkenbroom MCJM, Chan EW, Coghill D, Ip P, Wong ICK (2018) Trends in attention-deficit hyperactivity disorder medication use: a retrospective observational study using population-based databases. Lancet Psychiat 5 (10):824-835. doi:10.1016/S2215-0366(18)30293-1

4. Klassen AF, Miller A, Fine S (2004) Health-related quality of life in children and adolescents who have a diagnosis of attention-deficit/hyperactivity disorder. Pediatrics 114 (5):E541-E547. doi:10.1542/peds.2004-0844

5. Schuman JS (2008) Spectral domain optical coherence tomography for glaucoma (an AOS thesis). Trans Am Ophthalmol Soc 106:426-458

6. Leung CK, Choi N, Weinreb RN, Liu S, Ye C, Liu L, Lai GW, Lau J, Lam DS (2010) Retinal nerve fiber layer imaging with spectral-domain optical coherence tomography: pattern of RNFL defects in glaucoma. Ophthalmology 117 (12) (12):2337-2344

7. Matlach J, Wagner M, Malzahn U, Göbel W (2014) Repeatability of peripapillary retinal nerve fiber layer and inner retinal thickness among two spectral domain optical coherence tomography devices. Invest Ophthalmol Vis Sci 55 (10):6536-6546

8. Yabas Kiziloglu O, Toygar O, Toygar B, Hacimustafaoglu AM (2018) Optic Nerve Head Parameters Measured with Spectral-Domain Optical Coherence Tomography in Healthy Turkish Children: Normal Values, Repeatability, and Interocular Symmetry. Neuroophthalmology 42 (2):83-89. doi:10.1080/01658107.2017.1349806

9. Petzold A, Balcer LJ, Calabresi PA, Costello F, Frohman TC, Frohman EM, Martinez-Lapiscina EH, Green AJ, Kardon R, Outteryck O, Paul F, Schippling S, Vermersch P, Villoslada P, Balk LJ, Imsvisual E-E (2017) Retinal

layer segmentation in multiple sclerosis: a systematic review and meta-analysis. Lancet Neurol 16 (10):797-812. doi:Doi 10.1016/S1474-4422(17)30278-8

10. Mutlu U, Colijn JM, Ikram MA, Bonnemaijer PWM, Licher S, Wolters FJ, Tiemeier H, Koudstaal PJ, Klaver CCW, Ikram MK (2018) Association of Retinal Neurodegeneration on Optical Coherence Tomography With Dementia A Population-Based Study. Jama Neurol 75 (10):1256-1263. doi:10.1001/jamaneurol.2018.1563

11. Chan VTT, Sun ZH, Tang SM, Chen LJ, Wong A, Tham CC, Wong TY, Chen C, Ikram MK, Whitson HE, Lad EM, Mok VCT, Cheung CY (2019) Spectral-Domain OCT Measurements in Alzheimer's Disease A Systematic Review and Meta-analysis. Ophthalmology 126 (4):497-510. doi:10.1016/j.ophtha.2018.08.009

12. Doustar J, Torbati T, Black KL, Koronyo Y, Koronyo-Hamaoui M (2017) Optical Coherence Tomography in Alzheimer's Disease and Other Neurodegenerative Diseases. Front Neurol 8. doi:ARTN 70110.3389/ fneur.2017. 00701

13. Stang A (2010) Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 25 (9):603-605. doi:10.1007/s10654-010-9491-z

14. Bodur Þ, Kara H, Açýkel B, Yaþar E (2018) Evaluation of the ganglion cell layer thickness in children with attention deficit hyperactivity disorder and comorbid oppositional defiant disorder. Turkish Journal of Clinical Psychiatry 21:222-230

15. Isik U, Kaygisiz M (2020) Assessment of intraocular pressure, macular thickness, retinal nerve fiber layer, and ganglion cell layer thicknesses: ocular parameters and optical coherence tomography findings in attention-deficit/hyperactivity disorder. Braz J Psychiatry. doi:10.1590/1516-4446-2019-0606

16. Herguner A, Alpfidan I, Yar A, Erdogan E, Metin O, Sakarya Y, Herguner S (2018) Retinal Nerve Fiber Layer Thickness in Children With ADHD. J Atten Disord 22 (7):619-626. doi:10.1177/1087054716664412

17. Ayyildiz T, Ayyildiz D (2019) Retinal nerve fiber layer, macular thickness and anterior segment measurements in attention deficit and hyperactivity disorder. Psychiatry and Clinical Psychopharmacology 29 (4):760-764

18. Sripada CS, Kessler D, Angstadt M (2014) Lag in maturation of the brain's intrinsic functional architecture in attention-deficit/hyperactivity disorder. Proc Natl Acad Sci U S A 111 (39):14259-14264. doi:10.1073/pnas.1407787111

19. Dennis EL, Thompson PM (2013) Typical and atypical brain development: a review of neuroimaging studies. Dialogues Clin Neurosci 15 (3):359-384

20. Lee WW, Tajunisah I, Sharmilla K, Peyman M, Subrayan V (2013) Retinal nerve fiber layer structure abnormalities in schizophrenia and its relationship to disease state: evidence from optical coherence tomography. Invest Ophthalmol Vis Sci 54 (12):7785-7792. doi:10.1167/iovs.13-12534

21. Khalil MA, Saleh AA, Gohar SM, Khalil DH, Said M (2017) Optical coherence tomography findings in patients with bipolar disorder. J Affect Disord 218:115-122. doi:10.1016/j.jad.2017.04.055

22. Emberti Gialloreti L, Pardini M, Benassi F, Marciano S, Amore M, Mutolo MG, Porfirio MC, Curatolo P (2014) Reduction in retinal nerve fiber layer thickness in young adults with autism spectrum disorders. J Autism Dev Disord 44 (4):873-882. doi:10.1007/s10803-013-1939-z

23. Reimelt C, Wolff N, Holling H, Mogwitz S, Ehrlich S, Roessner V (2018) The Underestimated Role of Refractive Error (Hyperopia, Myopia, and Astigmatism) and Strabismus in Children With ADHD. J Atten Disord:1087054718808599. doi:10.1177/1087054718808599

24. Tan BB, Natividad M, Chua KC, Yip LW (2012) Comparison of retinal nerve fiber layer measurement between 2 spectral domain OCT instruments. J Glaucoma 21(4):266-273

25. Ruiz Caro Larrea JM, Cabrejas Martínez L, Mahíllo Fernández I, Alonso Peralta MA, Jiménez-Alfaro Morote I (2020) Agreement in retinal nerve fiber layer values and comparison in children using two optical coherence tomography devices. Arch Soc Esp Oftalmol 2020 95(4):171-177

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flowchart for study inclusion

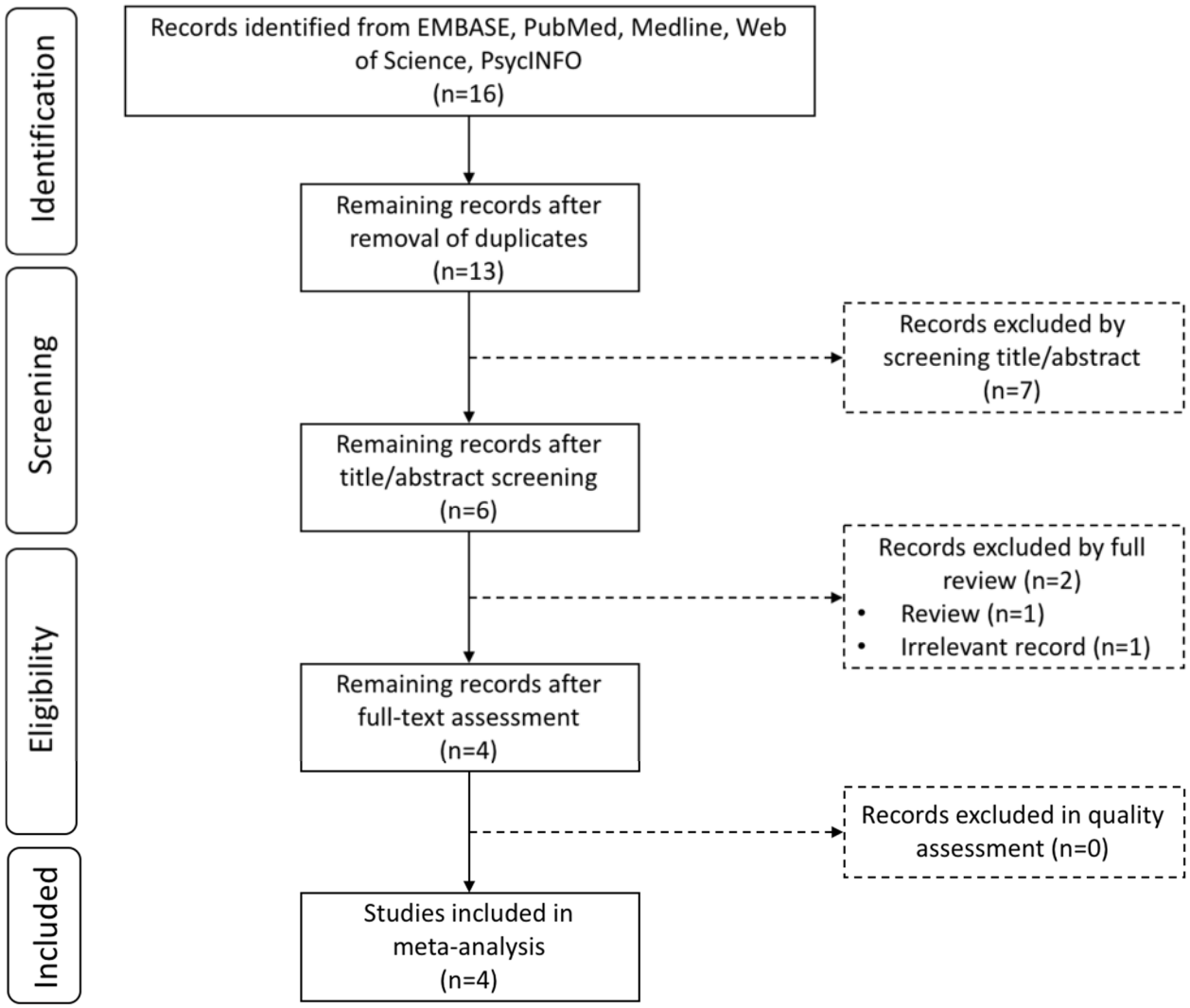
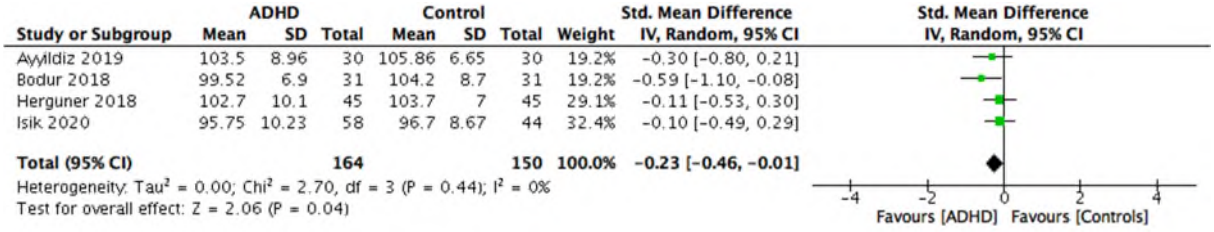
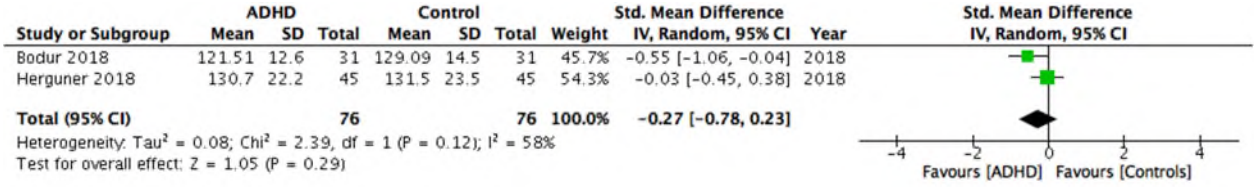


Fig. 2 Differences in global and sectoral RNFL thickness between ADHD and control groups

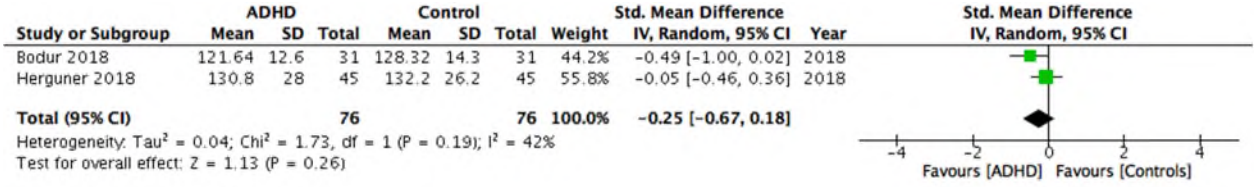
A. Global RNFL



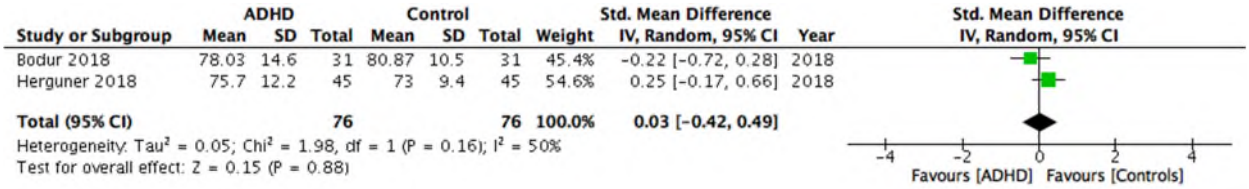
B. Superior Sector



C. Inferior Sector



D. Temporal Sector



E. Nasal Sector

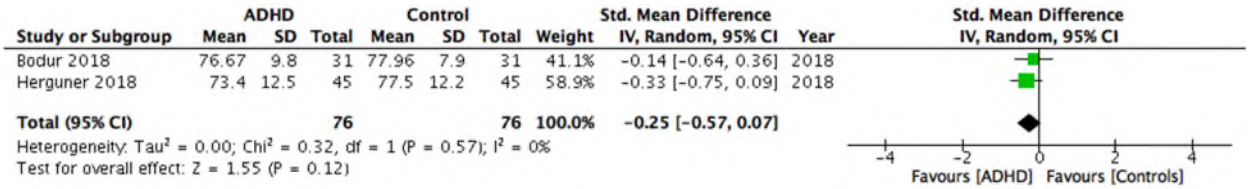


Fig. 3 Differences in global GCL thickness between ADHD and control groups

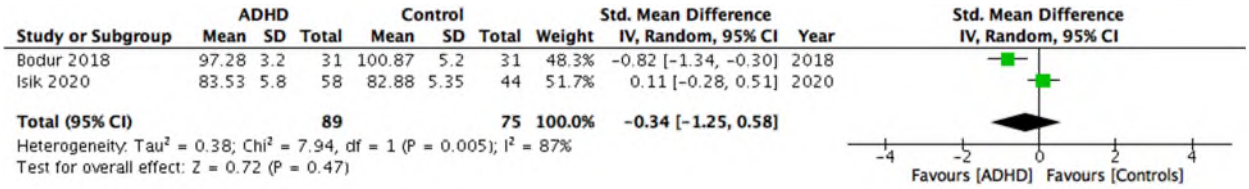


Table 1. Summary of included studies and patient characteristics

	Year	**Study location**	**Age (Yrs)**	**No. of ADHD**	**Type of ADHD**	**Treatment**	**No of control**	**OCT model & Type**
Ayyildiz	2019	Turkey	8-16	30	ADHD	No	30	Heidelberg Spectralis (SD-OCT)
Bodur	2018	Turkey	6-12	31	ADHD ADHD+ODD	No	31	OptoVue (SD-OCT)
Herguner	2018	Turkey	7-12	45	ADHD ADHD+ ODD	No	45	Heidelberg Spectralis (SD-OCT)
Isik	2020	Turkey	9±2.41	58	ADHD	No	44	Cirrus (SD-OCT)

ADHD: Attention-Deficit/Hyperactive Disorder; ODD: Oppositional Defiant Disorder; SD-OCT: Spectral Domain Optical Coherence Tomography.

Table 2. Methodological Quality Rating with NOS scale

	Selection				**Comparability**	**Exposure**			**Total**
	Case definition	Representativeness of the case	Selection of controls	Definition of controls	On basis of design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	
Ayyildiz 2019	*			*	*	*	*		*****
Bodur 2018	*			*	*	*	*		*****
Herguner 2018	*	*		*	*	*	*		******
Isik 2020	*			*		*	*		****

Note: columns represent the quality items. Stars indicate positive endorsement. The NOS ranges from 0 to 9 stars, with higher scores indicating higher quality.

Appendix 1: Search strategy

Key terms for Embase, PubMed, Medline, Web of Science, and PsycINFO search (.docx)

(Attention deficit disorder with hyperactivity OR attention deficit/hyperactivity disorder OR adhd OR addh OR hyperkinesis OR impulsive behaviour OR impulsivity) And ((retinal nerve fiber layer OR RNFL) OR (ganglion cell layer or GCL))

Key terms for Embase, PubMed, Medline, Web of Science, and PsycINFO search.

Search	Query
#1	("attention deficit disorder with hyperactivity"[MeSH Terms] OR "attention deficit disorder with hyperactivity"[All Fields] OR "attention deficit disorder hyperactivity"[All Fields] OR "attention deficit/hyperactivity disorder"[All Fields] OR "adhd"[All Fields] OR "addh"[All Fields] OR "hyperkinetic*[All Fields] OR "hyperkinesis"[MeSH Terms] OR "hyperkinesis"[All Fields] OR "impulsive behavior"[MeSH Terms] OR "impulsivity"[All Fields])
#2	("retinal nerve fiber layer" [MeSH Terms] OR "Retinal nerve fiber layer"[All Fields]) OR "ganglion cell layer"[MeSH Terms] OR "ganglion cell layer "[All Fields] OR "RNFL"[All Fields] or "GCL"[All Fields])
#3	#1 AND #2 No limits

Appendix 2

Fig. 4 Sensitivity analysis including right eyes

Global RNFL

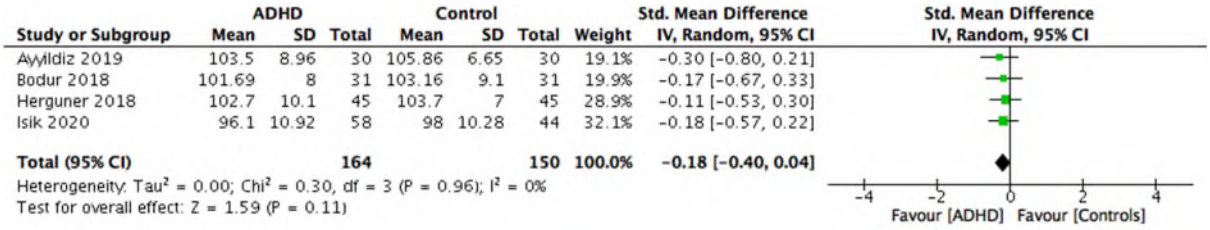
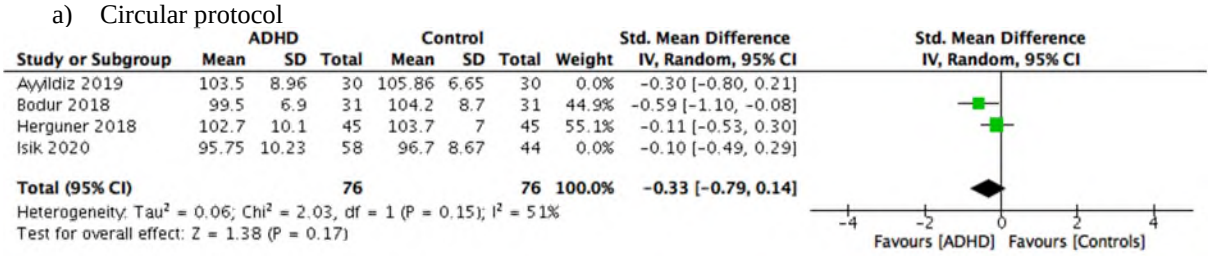


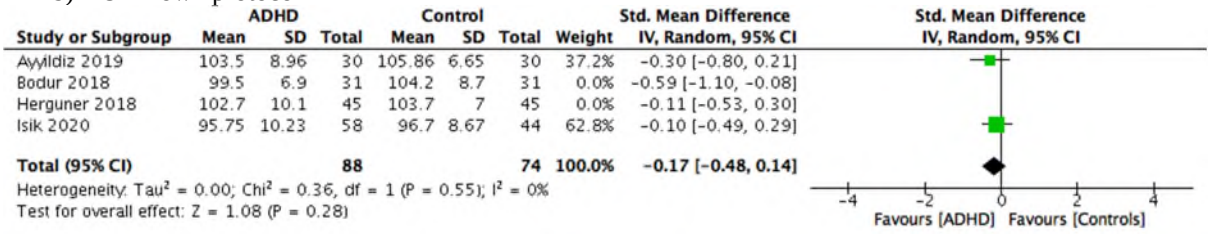
Fig. 5 Sensitivity analysis with different protocols for measuring RNFL thickness

1) Global RNFL (with left eyes included in the analysis)

a) Circular protocol

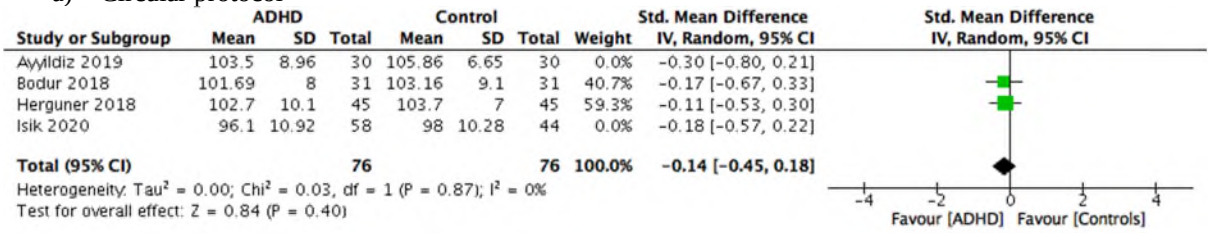


b) Unknown protocol

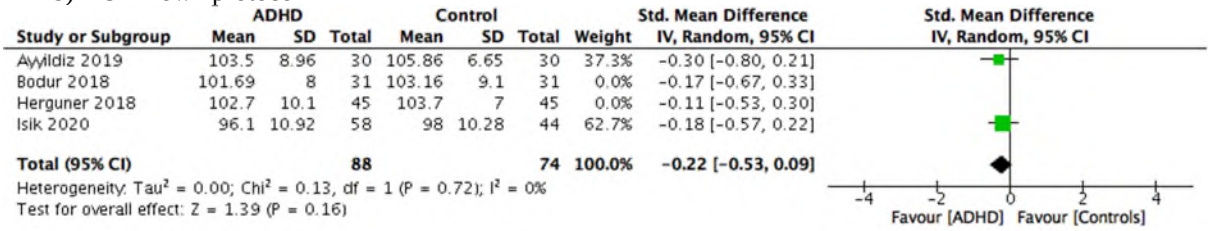


2) Global RNFL (with left eyes included in the analysis)

a) Circular protocol



b) Unknown protocol



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3-4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3-4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4, appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 2 & 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figure 2 & 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	5-6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Appendix 2
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	6-7
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	7-8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Nil

PRISMA 2009 Checklist

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