A Meta-analytic Study of ADHD Symptoms in Individuals with Neurofibromatosis Type 1

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Background

Neurofibromatosis type 1 (NF1) is a genetic disorder affecting approximately 1:3500 individuals. Prior studies found that individuals with (versus without) NF1 have higher risk for attention-deficit/hyperactivity disorder (ADHD). However, prior studies showed inconsistent findings on group differences between children with versus without NF1 in the extent of ADHD symptoms. The inconsistencies are likely due to different study and sample characteristics and the heterogeneity of ADHD symptoms in the NF1 population.

Gaps in extant literature:
. No consensus on group differences in ADHD symptoms.
. Unclear what factors are related to ADHD symptoms in children with NF1.
. No systematic review on the extent and predictors of ADHD symptoms.

Research Questions

1) To what extent do ADHD symptoms differ between individuals with and without NF1?

2) How do group differences in ADHD symptoms vary across study and sample characteristics?

Methods

Literature Search
. Database: Scopus, PsycINFO, Web of Science, PubMed, ProQuest
. Search terms: a combination of NF1 terms (e.g., neurofibromatosis type 1, NF1) and neurobehavioral function terms (e.g., attention, hyperact*, impuls*, ADHD)

Inclusion criteria
. It is a quantitative study with empirical data;
. Participants included individuals with NF1;
. Reported ADHD percent or Measured ADHD symptoms in individuals with NF1;
. Included sufficient data for calculating the study effect size;
. Written in English.

Coding procedure
. For all steps of coding (title/abstract screening, full text screening, data extraction), each paper were independently coded by two reviewers, and a third reviewer resolved discrepancies by discussing with the two reviewers.
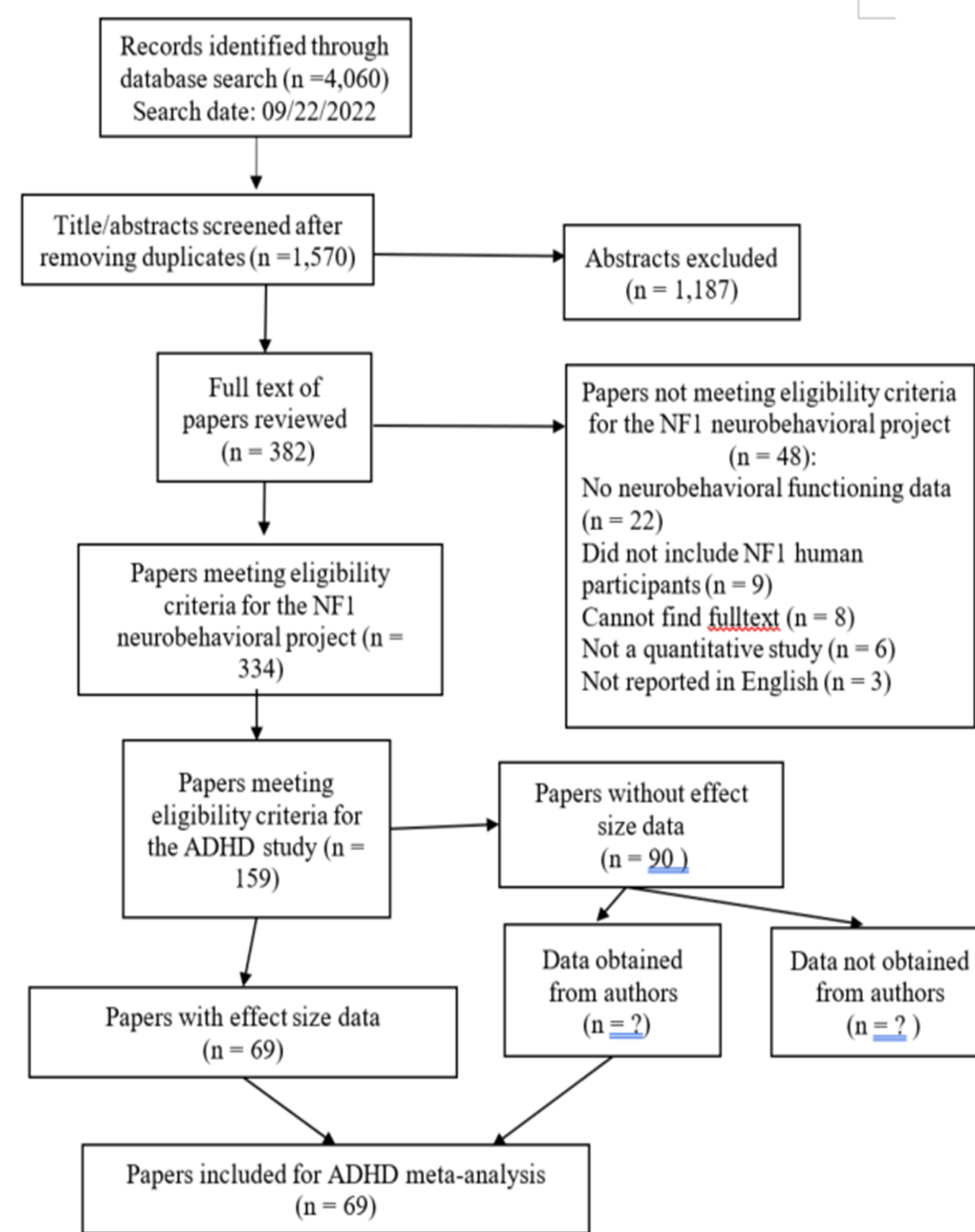

Figure 1. Flow diagram for inclusion and exclusion in meta-analysis.

Analysis and Results

Pooled effects
. **Analysis:**
. Hedges' g was calculated for group differences in ADHD symptoms between the NF1 group and the control or normative group for each study.
. ADHD total symptoms, attention problems, and hyperactivity problems are analyzed in separate models in all analyses.
. Dependence between study effect sizes was accounted using a robust standard error estimation technique (Hedges et al., 2010)

. **Results:**
. Individuals with NF1 had significantly more ADHD symptoms than the control or normative group.
. Significant between-study heterogeneity in effect sizes was observed.

Moderator results
. **Analysis:**
. Meta-regression was used to analyze potential moderators in separate models:
. NF1 sample characteristics: 1) participants' mean age, 2) female percent, 3) percent of Whites, 4) percent of participants with familial NF1, 5) mean IQ, 6) percent of participants received diagnosis of ADHD.

. Study characteristics: 1) whether the study excluded individuals with brain tumors, 2) whether the study compared NF1 group to community control group, sibling control group, or normative data, 3) whether measures of ADHD symptoms are performance-based test or informant-reported questionnaires.

. **Results:**
. Two significant moderators were identified:
. 1) Higher percent of participants with familial NF1 is associated with greater group differences in ADHD total symptoms and attention problems, but not hyperactivity problems.
. 2) Group differences in attention problems were higher in informant-reported (vs. performance-based) measures.

Table 1. Summary of Mean Effect Size across Studies

	Hedge's g	LL	UL	SE	df	p-value	n	k	Tao²	I²(%)
ADHD total	0.620	0.272	0.969	0.166	18.989	.001	20	55	1.586	97.588
Attention	0.666	0.473	0.859	0.096	59.928	<.001	61	219	1.086	96.393
Hyperactivity	0.627	0.144	1.110	0.236	29.989	<.013	31	110	2.236	98.158

Notes: LL = lower limit of 95% confidence interval; *UL* = upper limit of 95% confidence interval; *SE* = standard error; *df* = degrees of freedom; *n* = number of studies; *k* = number of effect sizes.

Table 2. Tests of Moderators

Moderator	n	k	estimate	SE	LL	UL	df	p-value
ADHD total								
Mean age	19	52	0.017	0.039	-0.087	0.121	4.350	0.683
% Girl	19	53	-0.004	0.013	-0.035	0.026	7.573	0.740
% White	5	11	0.014	0.007	-0.013	0.042	2.052	0.159
% familial NF1	**8**	**21**	**0.030**	**0.006**	**0.004**	**0.057**	**1.900**	**0.040**
Mean IQ	13	38	-0.004	0.019	-0.049	0.041	7.043	0.846
% ADHD diagnosis	12	32	0.004	0.014	-0.030	0.038	5.890	0.758
Excluded brain tumors (yes vs. no)	20	55	0.171	0.333	-0.530	0.873	17.151	0.614
Siblings (vs. community)	11	32	-0.540	0.288	-2.262	1.181	1.506	0.241
Normative data (vs. community)	18	48	-0.506	0.356	-1.262	0.250	15.987	0.175
Reported vs. performance-based	17	50	0.627	0.926	-6.398	7.653	1.291	0.599
Attention								
Mean age	57	171	-0.010	0.009	-0.035	0.015	3.977	0.343
% Girl	56	208	-0.006	0.007	-0.024	0.011	7.366	0.411
% White	9	30	0.010	0.015	-0.040	0.060	2.740	0.544
% familial NF1	**27**	**90**	**0.035**	**0.007**	**0.010**	**0.059**	**2.728**	**0.022**
Mean IQ	45	128	-0.017	0.004	-0.039	0.005	1.597	0.074
% ADHD diagnosis	33	112	-0.011	0.009	-0.035	0.013	5.187	0.285
Excluded brain tumors (yes vs. no)	61	219	0.171	0.199	-0.227	0.569	56.796	0.393
Siblings (vs. community)	31	115	-0.331	0.256	-0.964	0.302	5.716	0.245
Normative data (vs. community)	54	175	-0.148	0.214	-0.578	0.282	51.587	0.493
Reported vs. performance-based	**61**	**213**	**0.424**	**0.179**	**0.065**	**0.782**	**50.325**	**0.022**

Conclusion

. Individuals with NF1 have significantly higher levels of ADHD symptoms compared to non-NF1 peers, with medium effect sizes.

. There are substantial heterogeneity in effect sizes across studies.

. The variabilities of effect sizes across studies can be partly explained by sample characteristics (i.e., percent of familial NF1) and study design (i.e., attention problem measure)

Implications

. The higher levels of ADHD symptoms indicate the need for more support and interventions for individuals with NF1 to help improve their behavioral health.

. The heterogeneity in effect sizes suggests the need to identify predictors of ADHD within the NF1 group.

. The nonsignificant effects of some moderators explored in the current study may be due to small number of studies.

. Future studies should report more detailed descriptive information of their sample and study variables.

Next Steps

Next steps of the current study:
. Request more data from authors
. Do complementary search by looking at papers that cite the papers meeting inclusion criteria for the NF1 neurobehavioral project.
. Test group differences in ADHD diagnosis
. Test publication bias and do sensitivity analysis
. Qualitative review of findings on predictors of ADHD symptoms.

Future study: analyzing developmental patterns and predictors of ADHD symptoms among children with NF1 using large NF1 neuropsychological dataset combined from 15 studies.

Development, Equity, and Resilience (DEaR) Lab

Research topics:

Patterns and predictors of cognitive, academic, socioemotional and behavioral development in unrepresented groups, particularly, **families with NF1** or ethnic minorities.

Looking for postdocs, collaborators, and volunteers!

Specific NF grants for postdocs:
Young Investigator Award of Children's Tumor Foundation
https://www.ctf.org/

Early Investigator Research Award from DoD NFRP
https://cdmrp.health.mil/nfrp/default

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