Collaborative meta-analysis finds no evidence of a strong interaction between stress and 5-HTTLPR genotype contributing to the development of depression

R C Culverhouse, N L Saccone, A C Horton, Y Ma, K J Anstey, T Banaschewski, M Burmeister, S Cohen-Woods, B Etain, H L Fisher, N Goldman, S Guillaume, J Horwood, G Juhasz, Kathryn Lester, others

Publication date
09-06-2023

Document Version
Accepted version

Published in
Molecular Psychiatry

Link to external publisher version
https://doi.org/10.1038/mp.2017.44

Supplemental Information for

“Collaborative meta-analysis finds no evidence of a strong interaction between stress and 5-HTTLPR genotype contributing to the development of depression”

Table of contents:

Supplemental Table S1 illustrates how the datasets contributing to this meta-analysis relate to the Risch meta-analysis based on primary data (N = 14 250) and the previously published literature-based meta-analyses of Munafo (N = 6 556), Karg (N= 40 749), and Sharpley (N = 45 996).

By the terms of our protocol[1], studies from publications listing fewer than 300 subjects total were not invited to participate. In part this was due to (i) the expectation that the effective sample size would drop when stratified by genetic ancestry and full phenotyping for our analyses and (ii) the potential bias from publication bias for small studies. We do note that two of our participating studies that were previously unpublished, after stratifying by genetic ancestry and only counting subjects who were fully phenotyped for our planned analyses, resulted in usable samples of between 200 and 300 subjects.

This table links the studies in the current meta-analysis to any publications from the group on this topic, provides a link to the publication, shows which meta-analysis included data related to the publication, the sample size reported, whether the study leaders were invited to participate in the current meta-analysis, and whether they contributed data to the project (i.e. participated). Of the studies that were invited but declined, reasons for not participating included lack of IRB approval, disapproval of the analysis protocol[1], and the discovery that the data did not fit any of our long list of planned analyses. Several of the studies did not provide a reason for non-participation. We note that the current study is the largest meta-analysis (N = 38 802) to meta-analyze results from analyses using identical statistical models for every study (including the same coding of the genotypes) and harmonized depression and stress phenotypes based on a consensus of the participating studies. In addition to greatly reducing the heterogeneity of analyses, it also precludes including results from essentially the same data multiple times (if more than one publication resulted from the data).

Supplemental Table S1: Studies with data on 5-HTTLPR, stress, and depression
For the published studies, N = number of subjects reported in publication
For the unpublished studies, N = number of European ancestry subjects included in analyses (genotyped and phenotyped after cleaning)

			Meta-analyses including data/results from the study							
Study name if in consortium	**If published**	**Year**	**Munafo**	**Risch**	**Karg**	**Sharpley**	**Current study**	**N**	**Invited to consortium**	**Participated**
	Mossner	2001			x	x		**72**	**No**	-
	Caspi	2003	x	x	x	x		847	Yes	No
G1219	Eley	2004	x	x	x	x	x	377	Yes	Yes
	Kaufman	2004	x					**101**	**No**	-
	Gillespie	2005	x	x				1091	Yes	No
SHIP	Grabe	2005	x	x	x	x	x	976	Yes	Yes
	Kendler	2005	x		x	x		549	Yes	No
	Lenze	2005			x	x		**23**	**No**	-
	Nakatani	2005			x	x		1803	Yes	No
	Jacobs	2006	x		x	x		384	No	No
	Kaufman	2006	x		x	x		**196**	**No**	-
	Ramasubbu	2006			x	x		**51**	**No**	-
	Sjoberg	2006	x		x	x		**180**	**No**	-

EPIC-Norfolk	Surtees	2006	x	x	x	x	x	4175	Yes	Yes
	Taylor	2006	x	x	x	x		**118**	**No**	-
	Wilhelm	2006	x	x	x	x		**128**	**No**	-
	Zalsman	2006			x	x		**316**	**No**	-
	Cervilla	2007	x	x	x	x		737	Yes	No
PATH	Chipman	2007		x	x	x	x	2094	Yes	Yes
	Chorbov	2007		x	x	x		227	Yes	No
	Cicchetti	2007			x	x		339	Yes	No
COGA	Dick	2007			x	x	x	956	Yes	Yes
	Kilpatrick	2007			x	x		589	Yes	No
	Kim	2007	x	x	x	x	x	732	Yes	No
	Kraus	2007			x	x		**139**	**No**	-
Bologna	Mandelli	2007			x	x	x	670	Yes	Yes
NTR	Middeldorp	2007		x	x	x	x	367	Yes	Yes
Heart and Soul	Otte	2007			x	x	x	557	Yes	Yes
POUCH	Scheid	2007	x		x	x	x	568	Yes	Yes
	Brummett	2008			x	x		**288**	**No**	-
	Kohen	2008			x	x		**150**	**No**	-
NEWMOOD L1 Budapest	Lazary	2008			x	x	x	567	Yes	Yes
	Phillips-Bute	2008				x		411	No	-
	Wichers	2008			x	x		394	Yes	No
	Aguilera	2009			x	x		534	Yes	No
ALSPAC	Araya	2009			x	x	x	4334	Yes	Yes
SALVe 2006	Aslund	2009			x	x	x	1482	Yes	Yes
	Bukh	2009			x	x		**290**	**No**	-
	Bull	2009			x	x		**98**	**No**	-
	Gibb	2009				x		**100**	**No**	-
	Kim	2009			x	x		521	Yes	No
MARS	Laucht	2009		x	x	x	x	309	Yes	Yes
	Lotrich	2009			x	x		**71**	**No**	-
	McCaffery	2009			x	x		977	Yes	No
ESPRIT Montpellier	Ritchie	2009			x	x	x	942	Yes	Yes
	Wichers	2009			x	x		502	Yes	No
	Zhang, K	2009			x	x		792	Yes	No
	Zhang, JL	2009			x	x		306	Yes	No
	Antypa	2010				x		**248**	**No**	-
	Benjet	2010			x	x		**78**	**No**	-

QIMRtwin	Coventry	2010			x	x	x	3243	Yes		Yes
SEBAS	Goldman	2010			x	x	x	984	Yes		Yes
	Conway	2010				x		381	Yes		No
	Grassi	2010			x	x		**145**	**No**		-
	Hammen	2010			x	x		346	No		-
	Kumsta	2010			x	x		**125**	**No**		-
ESPRIT Montpellier	Power	2010		x	x	x	x	1421	Yes		Yes
	Ressler	2010			x	x		926	Yes		No
	Sen	2010			x	x		268	Yes		No
	Sugden	2010			x	x		2017	Yes		No
	Bakermans-Kranenberg	2011				x		**124**	**No**		-
Molise	Carli	2011				x	x	763	Yes		Yes
	Cicchetti	2011				x		492	Yes		No
	Clasen	2011				x		**273**	**No**		-
	Comasco	2011				x		**219**	**No**		-
	Comasco (2)	2011				x		**275**	**No**		-
CHDS	Fergusson	2011				x	x	880	Yes		Yes
	Hankin	2011				x		**220**	**No**		-
	Jenness	2011				x		**198**	**No**		-
	Mitchell	2011				x		1076	No		-
	Nikolova	2011				x		**60**	**No**		-
POUCH	Scheid	2011				x		698	Yes		Yes
ASPIS	Stefanis	2011				x	x	1580	Yes		Yes
	Tsuboi	2011				x		**177**	**No**		-
	Uher	2011				x		930	Yes		No
	Aas	2012				x		**118**	**No**		-
	Beaver	2012				x		2500	No		-
DeCC	Fisher	2012					x	1236	Yes		Yes
SHIP	Grabe	2012				x		1974	Yes		Yes
	Petersen	2012				x		436	Yes		No
	Quinn	2012				x		**240**	**No**		**-**
	Wilhelm	2012				x		**250**	**No**		**-**
	Zannas	2012				x		**212**	**No**		**-**
	Brown	2013				x		**273**	**No**		**-**
DeCC	Fisher	2013					x	455	Yes		Yes
DeCC	Power	2013					x	455		Yes	Yes

NEWMOOD L1 Manchester	Juhasz	2015					x	1218	Yes	Yes
NEWMOOD L1 Manchester	Gonda	2016					x	1218	Yes	Yes

Studies contributing to the current meta-analysis have not published on this topic

Study name	If published	Year	Munafo	Risch	Karg	Sharpley	Current study	N	Invited	Participated
ATP							x	657	Yes	Yes
CoFamS							x	215	Yes	Yes
COGEND							x	1573	Yes	Yes
GAN12_FRANCE							x	308	Yes	Yes
GENESIS							x	1647	Yes	Yes
MLS							x	449	Yes	Yes
Muenster							x	611	Yes	Yes
NEWMOOD L2 Manchester							x	237	Yes	Yes
TRAILS							x	1414	Yes	Yes
TREND							x	3499	Yes	Yes
VAHCS							x	210	Yes	Yes

Supplemental Table S2: Primary analyses of 5-HTTLPR, stress, and depression from our protocol[1]

Phenotypes:

Depression outcomes: Lifetime depression and Current depression
Dichotomous depression: Major depressive episode as defined by the individual study
Quantitative depression: DSM symptom count

Childhood stress:
Dichotomous exposure: Defined by the individual study (using consortium guidelines)
Quantitative measure: Childhood Trauma Questionnaire (CTQ) score

Other Life stress:
Dichotomous exposure: Defined by the individual study (using consortium guidelines)
Quantitative measure: Listing of Traumatic Events Questionnaire (LTE-Q) score

Model	Description
	1. Young adults (age 21-30)
	A. ***Stress = Childhood Maltreatment***
1Ai	i Dichotomous stress & depression (Table S9)
1Aii	ii Quantitative stress & depression (Table S10ab)
	B. ***Stress = Broad (Childhood maltreatment or other life stress)***
1Bi	i Dichotomous stress & depression (Table S9) Other life stress known to have occurred within 5-years prior to assessment
1Bii	ii Quantitative stress & depression (Table S10ab) Other life stress known to have occurred within 5-years prior to assessment
	2. All Ages
	A. ***Stress = Childhood Maltreatment***
2Ai	i Dichotomous stress & depression (Table 1)
2Aii	ii Quantitative stress & depression (Table S11ab)
	B. ***Stress = Broad (Childhood maltreatment or other life stress)***
	i Dichotomous stress & depression
2Bia	a Other life stress known to have occurred within 5-years prior to assessment (Table 1)
2Bib	b Other life stress could have occurred at any time (Table 1)
	ii Quantitative stress & depression
2Biia	a Other life stress known to have occurred within 5-years prior to assessment (Table S11ab)
2Biib	b other life stress could have occurred at any time (Table S11ab)
2C	C. ***Broad analysis*** (Table S12) Analyses based on count data for dichotomous stress and depression. Allows the inclusion of information from datasets that do not have observations in all strata (e.g. single sex, all subjects exposed to stress) and so could not be included in the meta-analyses above.

Supplemental Table S3: Data formatting instructions for the meta-analysis script

Formatting data for 5-HTTLPR script

Notes:

1. Data files should be stratified by ancestral group (e.g. European ancestry, Admixed European and African).
   Each distinct ancestral group should be in a separate file.
2. Each data file must be in csv (comma separated values) format.
3. The first line of the data file is a header line containing an ordered list of the variables in the file.
4. All variable names begin with an upper case letter followed by all lower case characters.
5. Id, Sex, Age, and Gen5 (the 5-HTTLPR L vs S genotype) are required.
   Please omit any other variables that are missing for all subjects.
6. **First depressive episode** during the subject's lifetime is our primary depression phenotype.
   If information about this episode is available, please include variable values based on this information.
   If ONLY current depression was assessed, please use the "current" variables in your dataset.
   If BOTH were assessed **AND Life stress variables (exposure/quantitative) differ for the 2**, please create 2 datasets
   (If both were assessed, but Life stress variables can be shared, only one dataset is needed).
7. The test data file (TEST_ALLVARS.csv) included in the download package illustrates the required format.

Below is the complete list of variables and instructions for coding.
Please email Amy Horton (achorton@wustl.edu) if you have any questions

	Variable	Coding	Description of variable
1	Id	alpha numeric variable	Unique identification value for each subject
Demographic Variables			
2	Sex	0 = female 1 = male -9 = missing	Sex of subject
3	Age	> 0 (decimal years) -9 = missing	Age of subject at interview in years
4	Birth_decade	4 digit decade of birth e.g. 1950 for birthdates from Jan 1, 1950 to Dec 31, 1959	4 digit decade of birth
Genetic Variables			
5	Gen5	LL = 2 copies of the long allele LS = heterozygote SS = 2 copies of the short allele -9 = missing	Genotype of subject for 5HTTLPR L=long allele S=short allele
6	rs25531	0 = 0 copies of the G allele 1 = 1 copy of G 2 = 2 copies of G -9 = missing	# of G alleles for rs25531 Note: The G allele for rs25531 occurs most frequently with the L allele for 5HTTLPR. If phasing for Gen5 and rs25531 is known, set this variable to the number LG alleles. Otherwise, ambiguous haplotypes (double heterozygotes) will be assumed to be SA-LG
Depression Variables			
7	Dep_dx_life	0 = no lifetime diagnosis (dx) of major depressive disorder 1 = positive lifetime dx of major depressive disorder -9 = missing	Ever in life had a depression diagnosis Subject has at some time during his or her lifetime qualified for a diagnosis of major depressive disorder ***NOTE: Preferred phenotype. Use if available.***
8	Dep_quant_life	≥ 0 if assessed -9 = missing	Maximum Lifetime quantitative depression scale If subject has a lifetime diagnosis of major depressive disorder, give symptom count when first met diagnosis. Otherwise, give maximum lifetime value. **Use DSM-IV symptom count if it is available.** *Otherwise, use your own scale, **BUT** ensure that all scored values are ≥ 0, to avoid conflict with the missing value, -9. (Add a constant to all values if needed.)* ***NOTE: Preferred phenotype. Use if available.***

9	Dep_dx_curr	0 = no current diagnosis of major depressive disorder 1 = current diagnosis of major depressive disorder -9 = missing	Current depression diagnosis Subject has a diagnosis of major depression at the time of interview (e.g. within the last 6 months or last year)
10	Dep_quant_curr	≥ 0 if assessed -9 = missing	Current quantitative depression measure **Use current DSM-IV symptom count if it is available.** *Otherwise, use your own scale, **BUT** if necessary add a constant to all values so all scored values ≥ 0* *(This avoids a conflict with using -9 for missing values.)*
11	Dep_life_ao	≥ 0 if known (decimal years) -9 = missing	Age of onset (decimal) of first major depressive episode during lifetime If never depressed = age at interview+1[1] ***NOTE: Preferred phenotype. Use if available.***
12	Dep_curr_ao	≥ 0 if known (decimal years) -9 = missing	Age of onset of current depression episode If not currently depressed = age at interview+1[1]
Childhood Maltreatment Variables			
13	CTQ_EA	≥ 5 if assessed -9 if missing	CTQ[2] sub-score for emotional abuse *For those assessed, this value ranges from 5 to 25*
	Variable	**Coding**	**Description of variable**
14	CTQ_PA	≥ 5 if assessed -9 = missing	CTQ sub-score for physical abuse *For those assessed, this value ranges from 5 to 25*
15	CTQ_SA	≥ 5 if assessed -9 if missing	CTQ sub-score for sexual abuse *For those assessed, this value ranges from 5 to 25*
16	CTQ_EN	≥ 5 if assessed -9 = missing	CTQ sub-score for emotional neglect *For those assessed, this value ranges from 5 to 25*
17	CTQ_PN	≥ 5 if assessed -9 if missing	CTQ sub-score for physical neglect *For those assessed, this value ranges from 5 to 25*
18	Child_mal_exp	0 = not exposed to childhood maltreatment 1 = exposed to childhood maltreatment -9 = unknown	**Exposure** to Childhood Maltreatment ***ONLY create this variable IF*** at least one of CTQ subscales for Physical Abuse (v14), Sexual Abuse (v15), or Physical Neglect (v17) is not available for most (or all) of the dataset[3]
19	Child_mal_q	≥ 0 if assessed -9 = missing	Quantitative Childhood Maltreatment score ***ONLY create this variable IF*** at least one of CTQ subscales for Physical Abuse (v14), Sexual Abuse (v15), or Physical Neglect (v17) is not available for most (or all) of the dataset[3]
Life Stress Variables (stress other than childhood maltreatment) NOTE: If your data contain **multiple assessments of Life stress** (e.g. from longitudinal data) **that differ** relative to first depressive episode and current depressive episode, please create 2 separate datasets: one with information about the first depressive episode during lifetime (and related life stress), the other with information about current depression (and related life stress).			
20	Life_stress_exp	0 = not exposed to LIFE stress during period assessed 1 = exposed -9 = missing	**LIFE stress** exposure (dichotomous) (NOT including childhood maltreatment) NOTE: The group's consensus was that Life stress "exposure" using the LTE-Q (Brugha criteria) should require ≥ 2 events. Studies with other LIFE stress measures must each define stress "exposure" for their data.
21	Life_stress_q	≥ 0 if assessed -9 = missing	**Use LTE-Q score, if available** *Otherwise, use your own scale, **BUT** ensure all values are ≥ 0 to avoid conflict with the missing value, -9. (Add a constant to all values if needed.)*
22	Age_last_stress_before_dep1	-1 = no LIFE stress events during period assessed ≥ 0 = age of most recent LIFE stress event before first	Age during most recent LIFE stress event *before* **FIRST** major depressive episode NOTE 1: LIFE stress is stress OTHER THAN childhood maltreatment

		depressive episode (if EVER depressed) **OR** age at most recent LIFE stress event before interview (if NEVER depressed) -9 = exposure unknown or age of exposure unknown	NOTE 2: If no major depressive episodes, list age of most recent LIFE stress before interview
22	Age_last_stress_before_dep1	-1 = no LIFE stress events during period assessed ≥ 0 = age of most recent LIFE stress event before first depressive episode (if EVER depressed) **OR** age at most recent LIFE stress event before interview (if NEVER depressed) -9 = exposure unknown or age of exposure unknown	Age during most recent LIFE stress event *before* **FIRST** major depressive episode NOTE 1: LIFE stress is stress OTHER THAN childhood maltreatment NOTE 2: If no major depressive episodes, list age of most recent LIFE stress before interview
23	Age_last_stress_before_dep_curr	-1 = no LIFE stress events during period assessed ≥ 0 = age of most recent LIFE stress event before current depressive episode (if CURRENTLY depressed) **OR** age at most recent LIFE stress event before interview (if NOT currently depressed) -9 = exposure unknown or age of exposure unknown	Age during most recent LIFE stress event ***before* CURRENT** major depressive episode NOTE 1: LIFE stress is stress OTHER THAN childhood maltreatment NOTE 2: If no current major depressive episode, list age of most recent LIFE stress before interview
24-26: Additional timing variables for lifetime depression (create ONLY if one of variables 11 or 22 is missing)			
24[4]	Stress_before_dep1	0 = First major depressive episode occurred before first LIFE stress event 1 = LIFE stress occurred before first depression, **OR** no LIFE stress during assessed period **OR** no lifetime depression diagnosis -9 = unknown timing	Assessed LIFE stress occurred before first depressive episode**.** ***ONLY create this variable if*** variable 7 or variable 8 is present *For reference* *v7 = lifetime depression diagnosis* *v8 = lifetime quant depression*
25[4]	Dep1_5yr_stress_exp	0 = Not exposed to LIFE stress in the 5 years prior to ***first depression*** (if ever depressed) OR ***interview*** (if no lifetime depression dx[5]) 1 = Exposed to LIFE stress in the 5 years prior to ***first depression*** (if ever depressed) OR ***interview*** (if no lifetime depression dx) -9 = unknown 5-year timing	LIFE stress before, but not more than 5 years prior to first depressive episode ***ONLY create this variable if*** variable 7 or variable 8 is present *For reference* *v7 = lifetime depression diagnosis* *v8 = lifetime quant depression*

26[4]	Dep1_5yr_stress_q	≥ 0 if assessed for the 5 years prior to ***first depression*** (if ever depressed) OR ***interview*** (if no lifetime depression) -9 = unknown 5-year timing	Quantitative measure of LIFE stress during the 5 years prior to first depressive episode ***ONLY create this variable if*** variable 7 or variable 8 is present *For reference* *v7 = lifetime depression diagnosis* *v8 = lifetime quant depression*
27-29: Additional timing variables for current depression (create ONLY if one of variables 12 or 23 is missing)			
27[4]	Stress_before_dep_curr	0 = Current depression occurred before first LIFE stress event 1 = LIFE stress occurred before current depression **OR** no LIFE stress during the period assessed **OR** no current depression diagnosis -9 = unknown (stress exposure unknown or timing unknown)	Assessed LIFE stress occurred before current depressive episode ***ONLY create this variable if*** variable 9 or variable 10 is present *For reference* *v9 = current depression diagnosis* *v10 = current quantitative depression*
28[4]	Dep_curr_5yr_stress_exp	0 = Not exposed to LIFE stress in the 5 years prior to ***current depression*** (if depressed) OR ***interview*** (if no current depression) 1 = Subject was exposed to LIFE stress in the 5 years prior to ***current depression*** (if depressed) OR ***interview*** (if no current depression) -9 = unknown (exposure unknown or 5 year timing unknown)	LIFE stress occurred before, but not more than 5 years prior to current depressive episode ***ONLY create this variable if*** variable 9 or variable 10 is present *For reference* *v9 = current depression diagnosis* *v10 = current quantitative depression*
29[4]	Dep_curr_5yr_stress_q	≥ 0 if assessed for the 5 years prior to ***current depression*** (if depressed) OR ***interview*** (if no current depression) -9 = unknown if quantitative LIFE stress assessed for the 5-year window	Quantitative measure of LIFE stress during the 5 years prior to current depressive episode ***ONLY create this variable if*** variable 7 or variable 8 is present *For reference* *v7 = lifetime depression diagnosis* *v8 = lifetime quant depression*

[1] This is so that R will not eliminate such subjects from appropriate analyses
[2] CTQ = Childhood Trauma Questionnaire
[3] Primary childhood maltreatment variable derived from the CTQ is based on these three variables
[4] Variables 24-29 ONLY apply to stress OTHER THAN childhood maltreatment (here called LIFE stress)
[5] dx = diagnosis

Heterogeneity assessments for the meta-analysis models: This project aimed to clarify understanding of the topic of the impact of 5-HTTLPR genotype on the relationship between stress and depression. Reducing the heterogeneity of the analysis in multiple dimensions was an important factor in our effort to achieve this goal. As a consortium we chose a hierarchy of depression and stress experiences to be examined, and strove to harmonize all included data sets to these standards. We agreed on a common set of analyses to examine the relationship, and used the same statistical code at all data sites (analysis code written in the R statistical programming language).[3] Primary analyses were stratified by genetic ancestry to minimize heterogeneity of genetic and cultural background. Other primary and secondary analyses of even more homogeneous groups (e.g. young adults, single sex) were also performed. We anticipated that considerable heterogeneity would remain among these data, which were collected using diverse ascertainments and collected from diverse locations. To assess the extent to which this might pose a challenge to interpreting our results, and to determine which analyses might contain particularly heterogeneous information, we calculated heterogeneity statistics for the interaction term for each of the meta-analyses presented (Supplemental Table S4). Each row corresponds to one of the meta-analysis tables presented below. The columns are organized by the six sets of results presented in each table. For each analysis, three heterogeneity statistics for the interaction term are listed: the I^2 statistic representing the percentage of the total variability in the set of effect sizes due to between-study variability as opposed to sampling variability[4]; the Q statistic defined by Cochran[5], and the p-value for the Q statistic.

This table contains heterogeneity information from 68 meta-analyses of the interaction term. None were statistically significant, and only one (secondary analysis: females only, current depression, broad stress occurring at any time) had a nominally significant p-value (p=0.04). Because there was so little evidence of heterogeneity overall, we do not expect that meta-analyzing even more homogeneous subsets of our data would lead to substantially different results from those found in the preceding tables.

Supplemental Table S4: Evaluation of heterogeneity in interaction terms from primary and secondary meta-analyses

		Childhood maltreatment Lifetime depression			Childhood maltreatment Current depression			Broad stress Life stress < 5 yr prior Lifetime depression			Broad stress Life stress < 5 yr prior Current depression			Broad stress Life stress any time Lifetime depression			Broad stress Life stress any time Current depression		
Table	Ages/Sexes/ Genetic Coding/Depression/Stress	I^2	Q	p	I^2	Q	p	I^2	Q	p	I^2	Q	p	I^2	Q	p	I^2	Q	p
Primary Analyses																			
1	All/Both/Add/Dx/Exposure	0.0	13.7	0.69	0.0	6.4	0.84	0.0	14.8	0.67	0.0	7.6	0.87	0.0	16.5	0.68	16.7	19.2	0.26
S9	YA/Both/Add/Dx/Exposure	0.0	0.4	0.94	-	-	-	26.9	5.5	0.24	-	-	-	0.0	7.1	0.52	-	-	-
S10a	YA/Both/Add/Dx/Quant[1]	23.4	6.5	0.26	-	-	-	1.3	1.0	0.31	-	-	-	0.0	0.5	0.93	-	-	-
S10b	YA/Both/Add/Quant/Exposure	14.6	1.2	0.28	-	-	-	0.0	0.4	0.83	-	-	-	0.0	1.2	0.76	-	-	-
S11a	All/Both/Add/Dx/Quant[1]	34.1	13.7	0.13	55.0	6.7	0.08	0.0	0.1	0.82	-	-	-	0.0	3.5	0.75	0.0	2.9	0.57
S11b	All/Both/Add/Quant/Exposure	0.0	2.2	0.54	0.0	0.9	0.84	0.0	2.3	0.67	0.0	0.1	0.99	20.3	6.3	0.28	40.3	5.0	0.17
S12	***Not a meta-analysis***																		
Secondary Analyses																			
S13	All/Both/Add/Dx(DSM-ICD)/Exposure	0.0	13.7	0.69	0.0	4.1	0.84	0.0	14.8	0.67	0.0	5.2	0.82	0.0	16.5	0.68	0.0	10.6	0.47
S14a	All/Female/Add/Dx/Exposure	0.0	14.7	0.68	0.0	4.9	0.96	0.0	16.6	0.62	0.0	9.7	0.64	9.5	24.3	0.33	41.3	27.2	0.04
S14b	All/Male/Add/Dx/Exposure	0.0	7.9	0.89	0.0	10.6	0.56	0.0	14.3	0.58	0.0	8.6	0.80	0.0	9.6	0.96	0.0	10.5	0.84
S15a	All/Both/Dominant/Dx/Exposure	0.0	6.0	0.65	0.0	6.0	0.87	0.0	11.0	0.86	0.0	8.1	0.78	0.0	16.5	0.62	38.3	24.3	0.06
S15b	All/Both/Recessive/Dx/Exposure	0.0	13.3	0.58	0.0	6.0	0.65	0.6	16.1	0.45	4.4	9.4	0.40	0.0	11.0	0.92	0.0	12.0	0.61
S15c	All/Both/Haplotype/Dx/Exposure	0.0	6.0	0.92	28.5	7.0	0.22	0.0	6.7	0.92	21.5	7.6	0.27	0.0	11.2	0.67	34.7	10.7	0.15
S16	All/Both/Add/Dx/Exposure (longitudinal studies only)	0.0	1.4	0.83	0.0	4.3	0.50	0.0	1.9	0.76	0.0	5.4	0.50	0.0	3.4	0.49	0.0	4.7	0.58

[1]For quantitative stress, results are for "life stress other than childhood maltreatment" rather than "broad stress"

Supplemental Table S5: Demographic information on studies whose data contributed to at least one primary or secondary analysis.

This table lists the number of European ancestry individuals genotyped for 5-HTTLPR and frequencies for the S allele, p-value for Hardy-Weinberg Equilibrium, female sex, lifetime and current depression diagnosis, exposure to childhood maltreatment, and exposure to other life stress.

European Ancestry	N genotyped for 5-HTTLPR	N genotyped with sex, stress, and depression phenotyped	S allele frequency	HWE p-value	Female	lifetime depression	current depression	childhood maltreatment	life stress
ALSPAC	5885	2472	42%	0.043	48%	67%	8%	9%	70%
ATP	657	426	42%	0.249	48%	-	16%	9%	-
Bologna	696	695	45%	0.009	69%	100%	-	-	69%
CHDS	714	704	42%	0.472	51%	53%	43%	23%	74%
CoFamS	215	206	43%	0.011	49%	33%	21%	23%	29%
COGA	874	776	42%	0.112	47%	30%	6%	19%	46%
COGEND	1573	1573	43%	0.830	37%	22%	-	-	81%
DeCC	2319	2319	42%	0.326	63%	53%	-	21%	30%
EPIC_Norfolk	4148	4096	42%	0.747	47%	19%	7%	4%	86%
ESPRIT	1879	1670	47%	0.437	58%	26%	3%	14%	24%
GAN12_FRANCE	308	279	48%	0.985	58%	91%	-	25%	-
GENESIS	1647	904	45%	0.290	71%	79%	58%	46%	-
Heart & Soul	549	549	43%	0.162	15%	52%	18%	-	100%
MARS	300	300	42%	0.286	55%	14%	5%	5%	60%
MLS	449	388	44%	0.684	55%	-	29%	79%	77%
Molise	781	754	48%	0.058	98%	24%	-	36%	-
Muenster (MiF & NI)	611	598	44%	0.055	57%	49%	49%	20%	41%
NESDANTR	3408	3089	43%	0.207	66%	50%	37%	21%	85%
NEWMOOD L1 Budapest	1003	999	42%	0.547	69%	21%	-	11%	29%
NEWMOOD L1 Manchester	1218	1218	44%	0.913	70%	56%	-	21%	36%
NEWMOOD L2 Manchester	237	232	42%	0.526	69%	59%	-	12%	41%
PATH	1869	1863	43%	0.007	53%	-	6%	56%	38%
POUCH_CESD	568	562	43%	0.144	100%	25%	-	-	26%
POUCH	233	233	43%	0.458	100%	26%	-	27%	21%
QIMRtwin	6607	3746	44%	0.303	58%	18%	-	-	34%
SALVe_2001	198	180	46%	0.232	60%	-	13%	14%	50%
SALVe_2006	1540	1430	45%	0.215	47%	-	12%	14%	-
SHIP	2152	1980	39%	0.327	52%	17%	-	11%	-
TRAILS	1414	1200	42%	0.643	51%	17%	10%	9%	66%
TREND	3499	3151	39%	0.829	51%	19%	-	9%	-
VAHCS	210	210	47%	0.825	64%	-	28%	-	40%
Total	47761	38802							

Supplemental Table S6: Study design and assessments. This table lists whether the study design was cross-sectional or longitudinal, the criteria used to diagnose depression, and the assessments used to determine childhood maltreatment and other stressful life events

Study	cross-sectional or longitudinal	Depression diagnostic system	Quantitative Depression system	childhood maltreatment assessment	life stress assessment
ALSPAC	longitudinal	ICD10	ICD10	Modified LEQ	Modified LEQ
ATP	cross-sectional	Clinical using DASS	Depression Anxiety Stress Scale	Custom	-
Bologna	cross-sectional	DSM-IV	Clinical	-	Clinical Interview
CHDS	longitudinal	DSM-IV	DSM-IV	Custom CSA-CPA	Custom
CoFamS	cross-sectional	DSM-IV	-	CTQ	LTE_Q
COGA	cross-sectional	DSM-IV	DSM-IV	Custom	Custom
COGEND	cross-sectional	DSM-IV	DSM-IV	-	Custom
DeCC	cross-sectional	DSM-IV	BDI	CTQ	LTE_Q
EPIC_Norfolk	cross-sectional	DSM-IV	DSM-IV	Custom	Modified LTE_Q
ESPRIT	longitudinal	DSM-IV	-	Custom	Gospel Oak Questionnaire
GAN12_FRANCE	cross-sectional	DSM-IV	-	CTQ	-
GENESIS	cross-sectional	DSM-IV	-	CTQ	-
Heart&Soul	longitudinal	DSM-IV	DSM-IV	-	Heart Attack Diagnosis
MARS	longitudinal	DSM-IV	BDI	CTQ	LTE_Q
MLS	longitudinal	DSM-IV	DSM-IV	Custom	Trauma Count
Molise	cross-sectional	DSM-IV	HAMD	CTQ	-
Muenster	cross-sectional	DSM-IV	-	CTQ	LTE_Q
NESDANTR	cross-sectional	DSM-IV	DSM-IV	CTQ	Custom
NEWMOOD L1 Budapest	cross-sectional	DSM-IV	BSI	Short CTQ	LTE_Q
NEWMOOD L1 Manchester	cross-sectional	DSM-IV	BSI	Short CTQ	LTE_Q
NEWMOOD L2 Manchester	cross-sectional	DSM-IV	MADRS	CTQ	LTE Q plus
PATH	longitudinal	Other	Other	Childhood Adversity Scale	LTE_Q
POUCH_CESD	cross-sectional	Dichotomized CES-D	CES-D	-	Modified Turner Wheaton & Lloyd
POUCH	cross-sectional	CIDI	CIDI	CTQ	Modified Turner Wheaton & Lloyd
QIMRtwin	longitudinal	DSM-IV	DSM-IV	-	LTE_Q
SALVe_2001	longitudinal	DSRS derived DSM-IV	DSM-IV	Custom	Custom
SALVe_2006	cross-sectional	DSRS derived DSM-IV	DSM-IV	Custom	-
SHIP	cross-sectional	DSM-IV	DSM-IV	CTQ	-
TRAILS_3	longitudinal	DSM-IV	DSM-IV	Custom	LSI past 3 years/EHC 5 years before
TREND	cross-sectional	DSM-IV	DSM-IV	CTQ	-
VAHCS	cross-sectional	ICD10	ICD10	-	LTE_Q

Supplemental Table S7: Demographic information on data sets for which the analysis script was run, but whose results could not be included in any of the listed analyses. Our protocol[1] called for stratified analyses of ancestral groups. The non-European samples were distributed across five strata African, African-European Admixed, Asian, Pacific Islander, and Hispanic) and were not meta-analyzed due to small sample size and lack of phenotypes in common. Two European Ancestry samples had phenotype combinations that did not allow their data to be used in our analyses. This table is grouped by the ancestry of the subjects and lists the number of individuals genotyped for 5-HTTLPR and frequencies for the S allele, female sex, lifetime and current depression diagnosis, exposure to childhood maltreatment, and exposure to other life stress.

Admixed African & European	**N genotyped**	**N genotyped with sex, stress, and depression phenotyped**	**S allele frequency**	**Female**	**lifetime depression**	**current depression**	**childhood maltreatment**	**life stress**
COGA	345	192	27%	43%	28%	5%	20%	50%
HeartSoul	168	139	23%	27%	57%	24%	-	100%
African								
POUCH	135	135	24%	100%	32%	-	38%	30%
POUCH_CESD	698	698	29%	100%	42%	-	-	42%
Asian								
HeartSoul	118	100	61%	14%	48%	14%	-	100%
PATH	62	62	62%	44%	-	5%	61%	34%
SEBAS	1036	900	70%	46%	-		-	19%
New Zealand Māori/ Pacific Islands								
CHDS	205	166	54%	47%	60%	50%	37%	77%
Hispanic								
HeartSoul	89	80	53%	28%	60%	20%	-	100%
European Ancestry								
ASPIS	1549	1548	44%	0%	-	-	-	100%
G1219	369	343	56%	59%	-	-	-	24%

Supplemental Table S8: Short descriptions of participating studies

ALSPAC (The Avon Longitudinal Study of Parents and Children)

Investigators collaborating on the 5-HTTLPR Meta-analysis:

Marcus Munafo, Bristol University, Bristol, UK
Ricardo Araya, Bristol University, Bristol, UK

The Avon Longitudinal Study of Parents and Children (ALSPAC) (1) is a large, ongoing population-based birth cohort begun in 1991-1992 when 14,501 pregnant women from the south west of the UK were recruited. Data relevant to young people's health has been collected regularly during pregnancy and the extended postnatal period, by interviews and questionnaires (i.e., at least annually) from multiple informants (enrolled women, their partners and the offspring).

References

1. Golding J, Pembrey M, Jones R. ALSPAC--the Avon Longitudinal Study of Parents and Children. I. Study methodology. Paediatr Perinat Epidemiol 2001;15(1):74-87.

ASPIS (Athens Study of Psychosis Proneness and Incidence of Schizophrenia)

Investigators collaborating on the 5-HTTLPR Meta-analysis:

Prof. Nikos Stefanis, National and Kapodistrian University of Athens Medical School and School of Psychiatry and Clinical Neurosciences, University of Western Australia
Alex Hatzimanolis, Department of Psychiatry and Institute of Genetic Medicine, Johns Hopkins University, Baltimore, USA
Laura Mandelli, Department of Psychiatry, University of Bologna, Italy

The ASPIS examined 2243 randomly selected young male conscripts, ages 18–24 years, from the Greek Air Force in their first 2 weeks of obligatory military induction. Eight separate waves of conscripts were assessed between January 1999 and March 2000. Conscripts underwent an extensive interview of computerized neurocognitive abilities and a self-rated psychometric evaluation. 1911 conscripts provided DNA samples for analysis of the 5-HTTLPR polymorphism (biallelic and triallelic). 1594 conscripts had also valid responses to the SCL90-R (Derogatis et al., 1973).The SCL90-R is a 90-item multidimensional self-reported questionnaire designed to screen for a broad range of psychological problems within the last two week prior to assessment. The homogeneous exposure of all subjects to the same stressful environment represented strength of the study. The study was approved by the Bioethics and Medical Deontology Committee of the University Mental Health Research Institute (UMHRI) in Athens Greece. This study supported a role of 5-HTTLPR in modulating abnormal responses to environmental stress, and in particular paranoid/defensive reactions under the stressful conditions of military induction.

References

1. Stefanis NC, Mandelli L, Hatzimanolis A, Zaninotto L, Smyrnis N, Avramopoulos D, Evdokimidis I, Serretti A.Serotonin transporter gene variants and prediction of stress-induced risk for psychological distress. Genes Brain Behav. 2011 Jul;10(5):536-41.
2. Stefanis NC, Hatzimanolis A, Smyrnis N, Avramopoulos D, Evdokimidis I, van Os J, Stefanis CN, Straub RE, Weinberger DR. Schizophrenia Candidate Gene ERBB4: Covert Routes of Vulnerability to Psychosis Detected at the Population Level. Schizophr. Bull. 2011 Nov 24.
3. Stefanis NC, Trikalinos A., Dimitrios Avramopoulos, Nikos Smyrnis, Ioannis Evdokimidis, Evangelia E. Ntzani, John P. Ioannidis, and Costas N. Stefanis Impact of Schizophrenia Candidate Genes on Schizotypy and Cognitive Endophenotypes at the Population Level (2007) Biological Psychiatry 62(7):784-92.
4. van Winkel R, Stefanis NC, Myin-Germeys I. Psychosocial stress and psychosis. A review of the neurobiological mechanisms and the evidence for gene-stress interaction. Schizophr Bull. 2008 Nov;34(6):1095-105.

ATP (Australian Temperament Project)

Investigators collaborating on the 5-HTTLPR Meta-analysis:

Craig Olsson, Royal Children's Hospital, Victoria, Australia

The ATP is a longitudinal community study following the psychosocial development of a large, representative cohort of children born in the state of Victoria, Australia, between September 1982 and January 1983. The original ATP cohort comprised 2,443 4-8 month old infants and their families, recruited through Maternal and Child Health centers in 1983. Data has been collected via mail questionnaires roughly every 1-2 years, using a range of informants. 15 waves of data have now been collected, the most recent being at 27-28 years of age. Full descriptions of the background, sampling and design of the ATP can be found in Prior et al.[1]. Attrition has been slightly higher in families experiencing socio-economic disadvantage or with parents born outside Australia. Importantly, the retained and non-retained subsamples show no or only trivial differences in scores on the infancy characteristics measured at the study's commencement. The study thus continues to be representative of the diverse range of young people's attributes.

References

1. Prior M, Smart D, Sanson A, Oberklaid F. (2000). Does shy-inhibited temperament in childhood lead to anxiety problems in adolescence? J Am Acad Child Adolesc Psychiatry. Apr;39(4):461-468.

Bologna (University of Bologna) (5-HTTLPR, stressful life events and depression)

Investigators collaborating on the 5-HTTLPR Meta-analysis:

Laura Mandelli, University of Bologna, Bologna, Italy
Alessandro Serretti, University of Bologna, Bologna, Italy

670 patients at their first episode of Mood disorder (both Major depression and Bipolar disorder) evaluated for SLEs within the 12 preceding months by the Life-events and difficulty Schedule and the biallelic 5-HTTLPR (S/L)

CHDS (The Christchurch Health and Development Study)

Investigators collaborating on the 5-HTTLPR Meta-analysis:

David Fergusson, University of Otago Christchurch, New Zealand
John Horwood, University of Otago Christchurch, New Zealand
Martin Kennedy, University of Otago Christchurch, New Zealand

The Christchurch Health and Development Study (CHDS) is a longitudinal study of a birth cohort of 1265 children born in Christchurch (New Zealand) in mid-1977. This cohort has been studied on 22 occasions from birth to the age of 30.[1,2] As part of this study DNA is available and data on mental health outcomes, assessed using DSM criteria, have been gathered from 15 – 30 yrs. The study has published a paper[3] in which we attempted to replicate and extend the findings of Caspi et al. on the GxE interaction between 5HTTLPR and mental health. Despite extensive analysis involving the results of over 100 regression models we were unable to show that 5HTTLPR moderates the associations between life course adversity and mental health outcomes.

References

1. Fergusson DM, Horwood LJ. The Christchurch Health and Development Study. In P. Joyce, G. Nicholls, K. Thomas & T. Wilkinson (Eds.), *The Christchurch Experience: 40 Years of Research and Teaching.* Christchurch: University of Otago, 2013; 79-87.
2. Fergusson DM, Horwood LJ. The Christchurch Health and Development Study: Review of findings on child and adolescent mental health. *Australian and New Zealand Journal of Psychiatry,* 2001; 35(3): 287-296.
3. Fergusson DM, Horwood LJ, Miller A, Kennedy MA. Life Stress, 5HTTLPR and Mental Disorder: Findings from a 30 year longitudinal Study. *British Journal of Psychiatry,* 2011;

198(2): 129-135.

CoFaMS (Cognition and Function in Mood Disorder Study**)**

Investigators collaborating on the 5-HTTLPR Meta-analysis:

Bernhard Baune, Discipline of Psychiatry, University of Adelaide, Adelaide, Australia
Sarah Cohen-Woods, Discipline of Psychiatry, Flinders University, Adelaide, Australia
Grant Sinnamon, Discipline of Psychiatry, University of Adelaide, Adelaide, Australia
Tracy Air, Discipline of Psychiatry, University of Adelaide, Adelaide, Australia
David Stacey, Discipline of Psychiatry, University of Adelaide, Adelaide, Australia
Catharine Jawahar, Discipline of Psychiatry, University of Adelaide, Adelaide, Australia
Catherine Toben, Discipline of Psychiatry, University of Adelaide, Adelaide, Australia

The Cognition and Function in Mood Disorder Study (CoFaMS) aims to investigate the long-term clinical course of cognitive dimensions in depression and its functional (psychosocial) as well as biological genomic correlates. For the 5-HTTLPR meta-analysis, 120 MDD cases and 317 healthy controls were genotyped for 5-HTTLPR. Inclusion criteria consist of a primary diagnosis of MDD or bipolar disorder ascertained according to DSM IV criteria using MINI 6.0. Healthy control status was ascertained after diagnostic interview using DSM IV criteria (MINI 6.0). Exclusion criteria were previous diagnosis or high screening score of a psychotic disorder, dementia, learning disorder, eating disorder or autistic spectrum disorder or medical conditions affecting the central nervous system (CNS) (e.g. Multiple Sclerosis, Parkinson's Disease, brain tumor). Healthy controls were required to have no previous or current psychiatric morbidity. Clinical assessments included the MINI600 diagnostic interview, SIGH-AD, the combined Hamilton Depression and Anxiety scale, extensive psychiatric history (e.g. number of episodes of depression, age of onset, duration of illness, medication history, education), the Functioning Assessment Short Test (FAST), the Childhood Trauma Questionnaire (CTQ), Life events questionnaire (LEQ), Perceived Stress Scale (PSS), a comprehensive cognitive test battery and other scales.

COGA (Collaborative Study on the Genetics of Alcoholism)

Investigators collaborating on the 5-HTTLPR Meta-analysis:

John Nurnberger, Indiana University, Indianapolis, IN, USA
Laura Bierut, Washington University Medical School, St. Louis, MO, USA
John Kramer, University of Iowa, Carver College of Medicine, Iowa City, IA, USA
Alison Goate, Icahan School of Medicine at Mount Sinai, New York, NY, USA
Jen-Chyong Wang, Icahan School of Medicine at Mount Sinai, New York, NY, USA

Subjects for 5-HTTLPR meta-analysis: 1408 (73% European American, 27% African American)

This case-control study of alcoholism drew its subjects from the Collaborative Study on the Genetics of Alcoholism (COGA), a large, ongoing family-based study that includes subjects from seven sites around the US [1]. COGA has gathered detailed, standardized data on study participants, including diagnostic and neurophysiological assessments. This sample has already proved successful in identifying several genes that influence the risk for alcoholism and neurophysiological endophenotypes, which have been independently replicated.[2,3]
Alcoholic probands were recruited from treatment facilities, assessed by personal interview, and after securing permission, other family members were also assessed. A set of comparison families was drawn from the same communities as the families recruited through an alcoholic proband. Assessment involved a detailed personal interview developed for this project, the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA), which gathers detailed information on alcoholism-related symptoms along with other drugs and psychiatric symptoms.

References

1. Edenberg, H. J. (2002) The Collaborative Study on the Genetics of Alcoholism: an update. Alcohol Res Health 26, 214-218.
2. Bierut, LJ, NL Saccone, JP Rice, A Goate, T Foroud, HJ Edenberg, L Almasy, PM

Conneally, R Crowe, V Hesselbrock, T-K Li, JI Nurnberger, Jr, B Porjesz, MA Schuckit, J Tischfield, H Begleiter, and T Reich (2002) Defining alcohol-related phenotypes in humans: The Collaborative Study on the Genetics of Alcoholism. Alcohol Res Health 26, 208-213.
3. Edenberg HJ and Foroud T (2006) The genetics of alcoholism: identifying specific genes through family studies. Addiction Biology 11, 386-396.

COGEND (Collaborative Genetic Study of Nicotine Dependence)

Investigators collaborating on the 5-HTTLPR Meta-analysis:

Naomi Breslau, Michigan State University, East Lansing, MI, USA
Laura Bierut, Washington University Medical School, St. Louis, MO, USA
Eric Johnson, RTI International, Research Triangle Park, NC, USA
Robert Culverhouse, Washington University Medical School, St. Louis, MO, USA
Nancy Saccone, Washington University Medical School, St. Louis, MO, USA

Subjects for 5-HTTLPR meta-analysis: 2783 (74% European American, 26% African American)

The Collaborative Genetic Study of Nicotine Dependence (COGEND) is a United States multi-site project. Subjects were recruited from St. Louis, Detroit, and Minneapolis through community-based telephone screening to determine eligibility for the study. Cases were required to have current Fagerström Test for Nicotine Dependence (FTND) ≥ 4 and controls were required to have a lifetime maximum FTND of 0 or 1, even during the period of heaviest smoking. The number of cigarettes per day (CPD) was assessed for the period of heaviest smoking as well as for current and other time points; the maximum of these values was used to define the CPD trait for analysis.

All subjects were smokers and reported smoking ≥ 100 cigarettes lifetime. Assessment involved a detailed semi-structured personal interview developed for this project from the SSAGA which gathers detailed information on smoking-related symptoms along with other drugs and psychiatric symptoms.

Reference

1. Bierut, L. J. *et al.* Novel genes identified in a high-density genome wide association study for nicotine dependence. *Hum Mol Genet* **16**, 24-35, doi:ddl441 [pii]10.1093/hmg/ddl441 (2007).

DeCC (Depression Case-Control study)

Investigators collaborating on the 5-HTTLPR Meta-analysis:

Peter McGuffin, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK
Helen L. Fisher, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK
Sarah Cohen-Woods, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK
Anne Farmer, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK

Individuals with recurrent unipolar depression and healthy controls were drawn from the Birmingham, Cardiff and London sites of the Depression Case-Control (DeCC) multi-centre study[1]. Additional controls from London were obtained from the Bipolar Affective Case-Control study (BACCs[2]). All participants were Caucasian, with parents and grandparents of white European origin, and aged 18 years or over. Patients were identified through psychiatric clinics, hospitals, general medical practitioner surgeries, and respondents to media advertisements. Patients must have experienced no less than 2 episodes of unipolar depression of at least moderate severity and separated by 2 or more months of remission, as defined by DSM-IV and/or the ICD-10. Exclusion criteria included: history of mania or hypomania, mood-incongruent psychosis, or a first or second-degree relative with bipolar or psychotic disorder. Controls were recruited through UK general medical practices across the UK (DeCC) or via internal emails at King's College London and newspaper advertisements (BACCs). Controls

were excluded if they had a personal or first-degree relative with a history of psychiatric disorder.

The List of Threatening Experiences Questionnaire (LTE-Q) was used to record 11 stressful life events that occurred 6 months before unipolar cases' most severe episode of depression and 6 months prior to interview for both cases and controls. Depressed cases and controls completed the Beck Depression Inventory – Second Edition (BDI-II[3]) to ascertain their mood state at the time of completing the LTE-Q. A subset of these participants (227 cases and 228 controls) also completed the Childhood Trauma Questionnaire[4].

References

1. Cohen-Woods S, Gaysina D, Craddock N, et al. Depression Case Control (DeCC) Study fails to support involvement of the muscarinic acetylcholine receptor M2 (CHRM2) gene in recurrent major depressive disorder. Hum. Mol. Genet. 2009;18(8):1504–1509.
2. Gaysina D, Cohen-Woods S, Chow PC, et al. Association of the dystrobrevin binding protein 1 gene (DTNBP1) in a bipolar case-control study (BACCS) Am. J. Med. Genet. B. Neuropsychiatr. Genet. 2009;150B(6):836–844.
3. Beck AT, Steer RA, Brown GK. *Beck Depression Inventory – Second Edition Manual.* The Psychological Corporation; San Antonio, TX: 1996.
4. Bernstein, D.P., Stein, J.A., Newcomb, M.D., et al. Development and validation of a brief screening version of the Childhood Trauma Questionnaire. Child Abuse Negl. 2003;27: 169–190

EPIC-Norfolk (European Prospective Investigation into Cancer – Norfolk)

Investigators collaborating on the 5-HTTLPR Meta-analysis:

Nick Wainwright, University of Cambridge, UK
Paul Surtees, University of Cambridge, UK

Subjects for 5-HTTLPR meta-analysis: 4175 (100% White European)

EPIC-Norfolk is a population-based cohort study initially set up to investigate the dietary causes of cancer as part of a Europe-wide collaboration. A total of 30,414 men and women (then) aged 40 to 74 years and resident in Norfolk, England were recruited between 1993 and 1997 through general practice age-gender registers[1].

Between 1996 and 2000, an assessment of social and psychological circumstances, the Health and Life Experiences Questionnaire (HLEQ), was completed by a total of 20,921 participants, representing a response rate of 73.2% of the total eligible EPIC-Norfolk sample. The HLEQ included a detailed assessment of social adversity, defined by adverse experience in childhood (0–16 years) and in adulthood (represented by stressful life events and enduring personal difficulties) [2] and a structured self-assessment approach to psychiatric symptoms embodying restricted DSM-IV criteria for MDD[3].

Subsequently, a sample of 5000 participants was selected from the EPIC-Norfolk HLEQ cohort. This sample was originally designed for a study of neuroticism and included 2500 men and 2500 women with DNA available, selected according to extremes of high and low neuroticism scores[4]. The length polymorphism *SLC6A4* in the promoter region of 5-HTT (5-HTTLPR) was successfully genotyped in 4175 participants (of 4416 individuals genotyped, a 94.5% genotype call rate), 2225 men and 1950 women.

References:

1. Day N., Oakes S., Luben R., Khaw K-T, Bingham S., Welch A., et al (1999): EPIC-Norfolk: Study design and characteristics of the cohort. Br J Cancer 80(suppl 1):95–103.
2. Surtees P. G. and Wainwright N. W. J. (2007) The shackles of misfortune: social adversity assessment and representation in a chronic disease epidemiology setting. Social Science and Medicine 64: 95-111.
3. Surtees P. G., Wainwright N. W. J., Luben R., Wareham N. J., Bingham S. A. and Khaw K-T. (2008) Depression and ischemic heart disease mortality: Evidence from the EPIC-Norfolk United Kingdom prospective cohort study. American Journal of Psychiatry 165: 515-523.

4. Willis-Owen S. A. G, Turri M. G., Munafo M. R., Surtees P. G., Wainwright N. W. J., Brixey R. D. and Flint J., (2005) The serotonin transporter length polymorphism, neuroticism and depression: a comprehensive assessment of association. Biological Psychiatry 58, 451-456

ESPRIT: The Enquête de Santé Psychologique – Risques, Incidence et Traitement Project

Investigators collaborating on the 5-HTTLPR Meta-analysis:

Karen Ritchie, Inserm, U1061 Montpellier, France
Isabelle Jaussent, Inserm, U1061 Montpellier, France

Subjects for 5-HTTLPR meta-analysis: 1648

The ESPRIT Project is the first longitudinal study of psychiatric disorder undertaken in France. Its principal aim is the construction of a comprehensive database incorporating clinical, biological, genetic and environmental risk factors. Participants were recruited from people aged 65 years and over by random selection from the fifteen electoral roles of the Montpellier district between March 1999 and February 2001. They were subjected to a base-line examination and re-examined on five further occasions at two-yearly intervals. At follow-up, the neurological, cognitive and psychiatric examinations were repeated and medication use and incident illness were recorded. Blood samples for DNA collection for *5-HTTLPR* genotyping were taken after the base-line clinical interview. Cortisol readings are also available for a sub-sample, taken on both a normal and stressful day.

References

1. Ritchie K, Artero S, Beluche I, Ancelin ML, Mann A, Dupuy AM, Malafosse A, Boulenger JP. Prevalence of DSM-IV psychiatric disorder in the French elderly population. British Journal of Psychiatry 2004; 184: 147-152
2. Ritchie K, Jaussent I, Stewart R, Dupuy AM, Courtet P, Ancelin ML, Malafosse A. Association of adverse childhood environment and 5-HTTLPR genotype with late-life depression. Journal of Clinical Psychiatry 2009; 70: 1281-1288

G1219

Investigators collaborating on the 5-HTTLPR Meta-analysis:

Thalia C Eley, Institute of Psychiatry, Kings College London, UK

Subjects for 5-HTTLPR meta-analysis: 377 (100% White)
This sample was selected from a larger sample of adolescent offspring taking part in an adult study of depression (GENESiS[1]). Adults were unselected and reported if they had children living in the home. All families reporting children in the home were sent booklets and asked to pass them on to any children aged 12-19 years. The booklet contained the Mood and Feelings Questionnaire (SMFQ).[2] Completed questionnaire booklets were returned by 1900 adolescents. Those with scores greater than 12 or less than 3 on the SMFQ (roughly the top and bottom 15%, N=560) were selected for follow-up and sent buccal swab kits. In all, 377 adolescents provided DNA (67%). Of this sample, 295 adolescents were unrelated and the remaining 82 were from sibling pairs.

Family environmental risk was assessed using three variables. First, the level of family social adversity was assessed using the Social Problems Questionnaire (SPQ[3]), which has a four-point rating scale. The scale assesses problems relating to finances, housing, work, relationships and social difficulties. Second, parental educational level was assessed using an eight-point scale ranging from 'No qualifications' to 'Postgraduate degree', which was recoded such that higher scores reflected a poorer level of education. Third, adverse life events were assessed with the 12-item 'List of Threatening Events' (LTE[4]), which relates to the previous 6 months. These events related to the parent or family as a whole and included items relating to serious illness, bereavement, relationship breakdowns, unemployment and financial crisis. A composite environmental measure was created by standardizing and combining the individual environmental measures, and this was dichotomized into above and below the entire sample mean.

References
1. Sham PC, Sterne A, Purcell S, Cherny SS, Webster M, Rijsdijk FV et al. GENESiS: creating a composite index of the vulnerability to anxiety and depression in a community-based sample of siblings. Twin Res 2000; 3: 316–322.
2. Angold A, Costello EJ, Messer SC, Pickles A, Winder F, Silver D. The development of a short questionnaire for use in epidemiological studies of depression in children and adolescents. Int J Methods Psychiatr Res 1995; 5: 1–12.
3. Corney R. Development and use of a short self-rating instrument to screen for psychosocial disorder. J R College Practioners 1988; 38: 263–266.
4. Brugha TS, Cragg D. The List of Threatening Experiences: the reliability and validity of a brief life events questionnaire. Acta Psychiatr Scand 1990; 82: 77–81.

GAN12 France (Genetic, Actigraphy and Neuropsychology in Bipolar Disorders)

Principal Investigator of GAN12: F. Bellivier (INSERM UMRS1144, Paris, France)
Scientific coordinators of GAN12: B. Etain, M. Leboyer (INSERM U955, Creteil, France)

Investigators collaborating on the 5-HTTLPR Meta-analysis:

Frank Bellivier, Sorbonne Paris Cité, Université Paris Diderot, Paris, France
Bruno Etain, Sorbonne Paris Cité, Université Paris Diderot, Paris, France
Mohamed Lajnef, INSERM U955, Creteil, France

The GAN research protocol has been set up to investigate the genetic and environmental risk factors to bipolar disorders. Patients fulfilled DSM-IV criteria (American Psychiatric Association 1994) for bipolar disorder (BD) type I or II and were recruited during their follow-up at three university-affiliated psychiatric departments in France (Paris/Créteil, Bordeaux, Nancy). Patients were interviewed by trained psychiatrists or psychologists, using the French version (Preisig, Fenton et al. 1999) of the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger, Blehar et al. 1994). The following inclusion criteria were used: older than 18 years and currently normothymic (i.e., to have a Montgomery-Asberg Depression Rating Scale score and a Mania Rating Scale score below 5) (Bech, Rafaelsen et al. 1978, Montgomery and Asberg 1979). All included individuals were of Caucasian origin. DNA samples and Childhood Trauma Questionnaire have been obtained for participants. This research protocol received appropriate Ethical Committee and institutional review board approvals. We obtained written informed consent from all study participants before inclusion. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

References
1. Etain B, Lajnef M, Henrion A, Dargél AA, Stertz L, Kapczinski F, Mathieu F, Henry C, Gard S, Kahn JP, Leboyer M, Jamain S, Bellivier F. Interaction between SLC6A4 promoter variants and childhood trauma on the age at onset of bipolar disorders. Sci Rep. 2015 Nov 6;5:16301.
2. Mathieu F, Etain B, Dizier MH, Lajnef M, Lathrop M, Cabon C, Leboyer M, Henry C, Bellivier F. Genetics of emotional reactivity in bipolar disorders. J Affect Disord. 2015 Dec 1;188:101-6.
3. Oliveira J, Etain B, Lajnef M, Hamdani N, Bennabi M, Bengoufa D, Sundaresh A, Chaabane AB, Bellivier F, Henry C, Kahn JP, Charron D, Krishnamoorthy R, Leboyer M, Tamouza R. Combined effect of TLR2 gene polymorphism and early life stress on the age at onset of bipolar disorders. PLoS One. 2015 Mar 19;10(3):e0119702.
4. Etain B, Aas M, Andreassen OA, Lorentzen S, Dieset I, Gard S, Kahn JP,Bellivier F, Leboyer M, Melle I, Henry C. Childhood trauma is associated withsevere clinical characteristics of bipolar disorders. J Clin Psychiatry. 2013 Oct;74(10):991-8.
5. Aas M, Etain B, Bellivier F, Henry C, Lagerberg T, Ringen A, Agartz I, Gard S, Kahn JP, Leboyer M, Andreassen OA, Melle I. Additive effects of childhood abuse and cannabis abuse on clinical expressions of bipolar disorders. Psychol Med. 2014 Jun;44(8):1653-62.

6. Etain B, Mathieu F, Henry C, Raust A, Roy I, Germain A, Leboyer M, Bellivier F. Preferential association between childhood emotional abuse and bipolar disorder. J Trauma Stress. 2010 Jun;23(3):376-83.

GENESIS

Investigators collaborating on the 5-HTTLPR Meta-analysis:

Phillipe Courtet, Université de Montpellier, INSERM U1061, France
Sébastien Guillaume, Université de Montpellier, INSERM U1061, France
Emilie Olié, Université de Montpellier, INSERM U1061, France

The GENESIS (GEnetics, NEuropSychology, functional neuroImaging of Suicidal behaviour) research protocol has been set up to investigate the genetic and environmental risk factors to suicidal behaviour. Patients were recruited in the Psychiatry Departement of Montpellier when they presented a lifetime history of suicide attempt ("a potentially self-injurious behaviour with a nonfatal outcome, for which there is evidence (either explicit or implicit) that the person intended at some (nonzero) level to kill himself/herself"). The following inclusion criteria were used: 18 - 75 years old; lifetime history of suicide attempt; West-European Caucasian origin for at least two generations. Patients were interviewed by trained psychiatrists or psychologists, using the French versions of the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al. 1994) or the Mini International Neuropsychiatric Interview (Sheehan et al. J Clin Psychiatry 1998; 59: 22-33). DNA samples and Childhood Trauma Questionnaire have been obtained for participants. This research protocol received appropriate Ethical Committee and institutional review board approvals. We obtained written informed consent from all study participants before inclusion. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

References

1. Lopez-Castroman J, Cerrato L, Beziat S, Jaussent I, Guillaume S, Courtet P. Heavy tobacco dependence in suicide attempters making recurrent and medically serious attempts. Drug Alcohol Depend. 2016 Mar 1;160:177-82
2. Richard-Devantoy S, Olié E, Guillaume S, Courtet P. Decision-making in unipolar or bipolar suicide attempters. J Affect Disord. 2016 Jan 15;190:128-36
3. Peñas-Lledó E, Guillaume S, Delgado A, Naranjo ME, Jaussent I, LLerena A, Courtet P. ABCB1 gene polymorphisms and violent suicide attempt among survivors. J Psychiatr Res. 2015 Feb;61:52-6.
4. Peñas-Lledó E, Guillaume S, Naranjo ME, Delgado A, Jaussent I, Blasco-Fontecilla H, Courtet P, LLerena A. A combined high CYP2D6-CYP2C19 metabolic capacity is associated with the severity of suicide attempt as measured by objective circumstances. Pharmacogenomics J. 2015 Apr;15(2):172-6.
5. Lopez-Castroman J, Jaussent I, Beziat S, Guillaume S, Baca-Garcia E, Genty C, Olié E, Courtet P. Increased severity of suicidal behavior in impulsive aggressive patients exposed to familial adversities. Psychol Med. 2014 Oct;44(14):3059-68.
6. Blasco-Fontecilla H, Jaussent I, Olié E, Garcia EB, Beziat S, Malafosse A, Guillaume S, Courtet P. Additive effects between prematurity and postnatal risk factors of suicidal behavior. J Psychiatr Res. 2013 Jul;47(7):937-43.
7. Guillaume S, Perroud N, Jollant F, Jaussent I, Olié E, Malafosse A, Courtet P. HPA axis genes may modulate the effect of childhood adversities on decision-making in suicide attempters. J Psychiatr Res. 2013 Feb;47(2):259-65
8. Lopez-Castroman J, Perez-Rodriguez Mde L, Jaussent I, Alegria AA, Artes-Rodriguez A, Freed P, Guillaume S, Jollant F, Leiva-Murillo JM, Malafosse A, Oquendo MA, de Prado-Cumplido M, Saiz-Ruiz J, Baca-Garcia E, Courtet P; European Research Consortium for Suicide (EURECA). Distinguishing the relevant features of frequent suicide attempters. J Psychiatr Res. 2011 May;45(5):619-25.
9. Perroud N, Jaussent I, Guillaume S, Bellivier F, Baud P, Jollant F, Leboyer M, Lewis CM, Malafosse A, Courtet P. COMT but not serotonin-related genes modulates the influence of

childhood abuse on anger traits. Genes Brain Behav. 2010 Mar 1;9(2):193-202.
10. Sarchiapone M, Jaussent I, Roy A, Carli V, Guillaume S, Jollant F, Malafosse A, Courtet P. Childhood trauma as a correlative factor of suicidal behavior - via aggression traits. Similar results in an Italian and in a French sample. Eur Psychiatry. 2009 Jan;24(1):57-62.

Heart & Soul

Investigators collaborating on the 5-HTTLPR Meta-analysis:

Mary Whooley, University of California, San Francisco (PI Heart & Soul Study)
Christian Otte, Charité University Medical School Berlin, Germany

Overview

To determine the mechanisms of association between depression and coronary heart disease (CHD), we performed a prospective cohort study of 1024 subjects with known CHD who were recruited between 9/00 and 12/02 and followed for 10 years. At the baseline examination, participants completed a structured diagnostic interview for depression, extensive questionnaire, EKG, 6-minute walk test, and full exercise treadmill testing with stress echocardiography. Participants were instructed to bring their medication bottles to the study appointment, and study personnel recorded all current medications. Participants also completed 24-hour ambulatory Holter monitoring to determine heart rate variability and collected 24-hour urine for measurement of creatinine, free cortisol, and catecholamines. Fasting blood was drawn, and samples of serum, plasma, DNA, and 24-hour urine were stored and remain in a specimen biorepository at –80 degrees Celsius. After 5 years of follow-up, 667 participants (>80% of survivors) completed a repeat examination that included a structured diagnostic interview for depression, questionnaire, EKG, exercise treadmill test, fasting blood draw and 24-hour urine. In addition, participants have been contacted annually to inquire about cardiovascular events, which are confirmed by review of medical records. Follow-up information is available for >99% of study participants.

Inclusion criteria

We used administrative databases to identify outpatients with documented coronary artery disease at two Department of Veterans Affairs Medical Centers (San Francisco VA Medical Center and the VA Palo Alto Health Care System, California), one University medical center (University of California, San Francisco), and nine public health clinics in the Community Health Network of San Francisco. Patients were eligible to participate if they had known CHD documented by at least one of the following: a history of myocardial infarction, angiographic evidence of at least 50% stenosis in one or more coronary vessels, prior evidence of inducible ischemia by treadmill or nuclear testing, or a history of coronary revascularization.

Participant characteristics

Between September 2000 and December 2002, a total of 1024 participants enrolled, including 385 from the San Francisco VA Medical Center, 55 from the VA Palo Alto Health Care System, 344 from the University of California, San Francisco, and 240 from the Community Health Network of San Francisco. Of the 1024 participants, 181 (18%) were women. There were 549 (54%) with a history of myocardial infarction, 237 (23%) with a history of revascularization but not myocardial infarction, and 238 (23%) with a diagnosis of coronary disease that was documented by their physician based on a positive angiogram or treadmill test. Participants were 60% non-Hispanic white, 9% Hispanic white, 17% African American, 11% Asian, and 3% other. The mean age was 67 (range 45-90) years at baseline.

References

1. Otte C, McCaffery J, Ali S, et al. Association of a Serotonin Transporter Polymorphism (5-HTTLPR) With Depression, Perceived Stress, and Norepinephrine in Patients With Coronary Disease: The Heart and Soul Study. *Am J Psychiatry* 2007;164:1379-1384.
2. Whooley MA, de Jonge P, Vittinghoff E, et al. Depressive Symptoms, Health Behaviors, and Risk of Cardiovascular Events in Patients With Coronary Heart Disease. *JAMA* 2008;300:2379-2388.

MARS (Mannheim Study of Children at Risk)

Investigators collaborating on the 5-HTTLPR Meta-analysis:

Manfred Laucht, Central Institute of Mental Health, Mannheim, Germany
Tobias Banaschewski, Central Institute of Mental Health, Mannheim, Germany
Daniel Brandeis, Central Institute of Mental Health, Mannheim, Germany

The Mannheim Study of Children at Risk (MARS) is an ongoing epidemiological cohort study following the outcome of early risk factors from infancy into adulthood (Laucht et al., 2000). The initial sample comprised 384 children born between 1986-88, of predominantly (>99.0%) European descent. Infants were recruited from two obstetric and six children's hospitals of the Rhine-Neckar Region of Germany and were included consecutively into the sample according to a two-factorial design intended to enrich and control the status of the sample regarding obstetric and psychosocial risks (for more details, cf. (Laucht et al., 1997). Only firstborn children with singleton births and German-speaking parents were enrolled in the study. Furthermore, children with severe physical handicaps, obvious genetic defects, or metabolic diseases were excluded. Assessments of mental health and of social and psychological circumstances were conducted at regular intervals of 2-4 years throughout development, most recently at age 25 years. DNA is available of N=328 participants.

References

1. Laucht, M., Esser, G., Schmidt, M.H., Baving, L., Gerhold, M., Hoesch, I., Ihle, W., Steigleider, P., Stock, B., Stöhr, R.M., Weindrich, D. (2000). Behavioral sequelae of perinatal insults and early family adversity at 8 years of age. *Journal of the American Academy of Child and Adolescent Psychiatry, 39,* 1229-1237.
2. Laucht, M., Esser, G. & Schmidt, M.H. (1997). Developmental outcome of infants born with biological and psychosocial risks. *Journal of Child Psychology and Psychiatry, 38*, 843-854

MLS (Michigan Longitudinal Study)

Investigators collaborating on the 5-HTTLPR Meta-analysis:

Margit Burmeister, University of Michigan, Ann Arbor, MI, USA
Katerina Gawronski, University of Michigan, Ann Arbor, MI, USA
Sandra Villafuerte, University of Michigan, Ann Arbor, MI, USA

PI: Robert A. Zucker
MPI: Mary M. Heitzeg

This now 28 year longitudinal high risk for substance abuse and disorder family study of 466 families recruited a community based sample of 3 to 5 year old boys, their parents and all biological siblings within +/- 8 years. Assessment with broad spectrum of behavioral measures at 3 year intervals, yearly intervals within the 11-23 age range. For the past 8 years, recruitment for genetics was added, to which ~70% of the sample agreed.

Molise (University of Molise)

Investigators collaborating on the 5-HTTLPR Meta-analysis:

Marco Sarchiapone, University of Bologna, Bologna, Italy
Laura Mandelli, University of Bologna, Bologna, Italy

763 male prisoners evaluated by the childhood trauma questionnaire (CTQ) and current depressive scores by the Hamilton depression scale (HRSD).

Muenster (Moodinflame & Meunster Imaging)

Investigators collaborating on the 5-HTTLPR Meta-analysis:

Bernhard Baune, Discipline of Psychiatry, University of Adelaide, Australia
Volker Arolt, Department of Psychiatry and Psychotherapy, University of Münster, Germany
Udo Dannlowski, Department of Psychiatry and Psychotherapy, University of Münster, Germany; Department of Psychiatry, University of Marburg, Germany
Sarah Cohen-Woods, Discipline of Psychiatry, Flinders University, Adelaide, Australia

Data were pooled from the Münster Neuroimaging study and the Moodinflame study recruited from the same geographical area conducted at the Department of Psychiatry, University of Münster, Germany. From the Münster Neuroimaging Study, 313 healthy subjects, all adult, and 72 MDD patients were genotyped for 5-HTTLPR. All healthy subjects were thoroughly investigated by experienced psychologists and were free from any lifetime history of psychiatric disorders according to DSM-IV criteria, as ascertained by the SCID interview. Additional scales were employed (e.g., CTQ, LEQ, BDI). Patients were thoroughly investigated by experienced psychologists and major depressive disorder (MDD) was ascertained according to DSM-IV criteria, as diagnosed with the SCID interview. Patients were recruited from the inpatient service of the University of Münster's Department of Psychiatry and healthy controls were derived from the same geographical area. Exclusion criteria were any neurologic abnormalities; substance-related disorders; psychotic symptoms; a history of mania or hypomania; treatment with benzodiazepine; and previous electroconvulsive therapy; and usual MRI-contraindications. Clinical assessment included a minimum of measures such as HAM-D-21, BDI, number of episodes of depression, age of onset, duration of illness, medication history, education, age and gender. According to similar inclusion and exclusion criteria, a second cohort (Moodinflame) of 237 adult MDD cases and 138 healthy controls were recruited at the University of Münster, Germany and genotyped for 5-HTTLPR. Psychiatric diagnoses were ascertained using a structured clinical interview (SCID). Clinical and pathological features were assessed in a standardized manner using various scales among which were inventory for depressed symptoms (IDS-C), Young Mania Rating Scale (YMRS), Childhood Trauma Questionnaire (CTQ), HAM-D, medication and psychiatric history. In addition to age, gender, and education, clinical characteristics such as number of episodes of depression, age of onset of depression, duration of illness and medication history were assessed.

NESDA-NTR

Investigators collaborating on the 5-HTTLPR Meta-analysis:

Christel M Middeldorp, Vrije Universiteit Amsterdam, the Netherlands
Gonneke Willemsen, Vrije Universiteit Amsterdam, the Netherlands
Jouke-Jan Hottenga, Vrije Universiteit Amsterdam, the Netherlands
Eco J.C. de Geus, Vrije Universiteit Amsterdam, the Netherlands
Dorret I Boomsma, Vrije Universiteit Amsterdam, the Netherlands
Wouter J Peyrot , VU University Medical Center & GGZ inGeest, Amsterdam, the Netherlands
Johannes H Smit, VU University Medical Center & GGZ inGeest, Amsterdam, the Netherlands
Brenda WJH Penninx, VU University Medical Center & GGZ inGeest, Amsterdam, the Netherlands

5-HTTLPR was genotyped in ~1900 cases and ~1900 controls from the Netherlands Twin Register (NTR) and the Netherlands Study on Depression and Anxiety (NESDA). MDD was diagnosed with the CIDI, an interview designed for epidemiological studies. Controls were selected based on longitudinal low scores on a composite score, based on survey questions, reflecting an individual's vulnerability for anxiety and depression. Data on life events were collected in a series of longitudinal surveys (NTR) or interviews (NESDA).

References

1. D. I. Boomsma, P. F. Sullivan, E. J. de Geus, P. Heutink, P. Meijer, D. Sondervan, C. Kluft, G. Smit, W. A. Nolen, F. G. Zitman, J. H. Smit, W. J. Hoogendijk, R. Van Dyck, G. Willemsen, and B. W. J. H. Penninx. Genome-wide association of major depression:

description of samples for the GAIN major depressive disorder study: NTR and NESDA Biobank Projects. *Eur.J.Hum.Genet.* 16:335-342, 2008.
2. D.I. Boomsma, A.L. Beem, M. van den Berg, C.V. Dolan, J.R. Koopmans, J.M. Vink, E.J. de Geus, P.E. Slagboom. Netherlands twin family study of anxious depression (NETSAD). Twin Res. 3:323-334, 2000
3. C. M. Middeldorp, E. J. de Geus, G. Willemsen, J. J. Hottenga, P. E. Slagboom, and D. I. Boomsma. The serotonin transporter gene length polymorphism (5-HTTLPR) and life events: no evidence for an interaction effect on neuroticism and anxious depressive symptoms. *Twin.Res.Hum.Genet.* 13 (6):544-549, 2010.
4. B. W. Penninx, A. T. Beekman, J. H. Smit, F. G. Zitman, W. A. Nolen, P. Spinhoven, P. Cuijpers, P. J. De Jong, H. W. van Marwijk, W. J. Assendelft, Meer K. van der, P. Verhaak, M. Wensing, R. De Graaf, W. J. Hoogendijk, J. Ormel, and R. Van Dyck. The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. *Int.J Methods Psychiatr Res* 17 (3):121-140, 2008.
5. Peyrot WJ, Middeldorp CM, Jansen R, Smit JH, de Geus EJ, Hottenga JJ, Willemsen G, Vink JM, Virding S, Barragan I, Ingelman-Sundberg M, Sim SC, Boomsma DI, Penninx BW. Strong effects of environmental factors on prevalence and course of major depressive disorder are not moderated by 5-HTTLPR polymorphisms in a large Dutch sample. J Affect Disord. 2013 Mar 20;146(1):91-9.

NewMood (New Molecules for Mood Disorders)

Investigators collaborating on the 5-HTTLPR Meta-analysis:

Gyorgy Bagdy, Department of Pharmacodynamics, Faculty of Pharmacy, Semmelweis University, Budapest, Hungary; MTA-SE Neuropsychopharmacology and Neurochemistry Research Group, Hungarian Academy of Sciences, Semmelweis University, Budapest, Hungary; NAP A-SE Research Group, Semmelweis University, Budapest, Hungary
Xenia Gonda, Department of Psychiatry and Psychotherapy, Kutvolgyi Clinical Center, Semmelweis University, Budapest, Hungary
Peter Petschner, Department of Pharmacodynamics, Faculty of Pharmacy, Semmelweis University, Budapest, Hungary; MTA-SE Neuropsychopharmacology and Neurochemistry Research Group, Hungarian Academy of Sciences, Semmelweis University, Budapest, Hungary
John Francis William Deakin, Neuroscience and Psychiatry Unit, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK; Manchester Academic Health Sciences Centre, Manchester, UK
Ian Muir Anderson, Neuroscience and Psychiatry Unit, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK; Manchester Academic Health Sciences Centre, Manchester, UK
Gabriella Juhasz, MTA-SE-NAP B Genetic Brain Imaging Migraine Research Group, Hungarian Academy of Sciences, Semmelweis University; Department of Pharmacodynamics, Faculty of Pharmacy, Semmelweis University, Budapest, Hungary; Neuroscience and Psychiatry Unit, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK

Subjects for 5-HTTLPR meta-analysis:
Level 1 Budapest: 1003
Level 1 Manchester: 1218
Level 2 Manchester: 237

The NewMood (New Molecules for Mood Disorders) Study was an EU funded (Sixth Framework Program of the European Union, NewMood, LSHM-CT-2004-503474) project which major aim was to identify new molecular mechanisms contributing to the pathophysiology of Major Depressive Disorder (1). Recruitment strategies involved general practices, advertisements and a web-site from Greater Manchester, UK and general practices and advertisements from Budapest, Hungary. Consented participants aged 18-60 years filled out the NewMood questionnaire pack, English or Hungarian version as applicable, and provided DNA by using a

genetic saliva sampling kit. The carefully designed self-rating questionnaire pack collected detailed information about socio-demographic background, including childhood maltreatment and recent negative life events, together with medical and psychiatric history, and measured current depression and anxiety symptoms (Level 1). Reported lifetime depression was derived from this questionnaire. To validate the questionnaire data additional participants took part in face-to-face psychiatric interviews using the Structured Clinical Interview for DSM-IV (SCID; Level 2 phase in Manchester). The study was approved by the local Ethics Committees (North Manchester Local Research Ethics Committee, Manchester, UK; Scientific and Research Ethics Committee of the Medical Research Council, Budapest, Hungary) and carried out in accordance with the Declaration of Helsinki. All participants provided written informed consent before participating in the study. The primary findings regarding the 5HTTLPR x environment interaction were published in references (2-4).

The Level 1 and Level 2 NewMood samples in Manchester involved different ascertainment and assessments, and thus could not be analysed as a pooled sample.

References

1. Deakin JF, Harro J, & Anderson IM (2011) NewMood: a productive European model of collaboration for translational research in depression. *Eur Neuropsychopharmacol* 21(1):1-2.
2. Juhasz G*, et al.* (2015) Variability in the effect of 5-HTTLPR on depression in a large European population: the role of age, symptom profile, type and intensity of life stressors. *PLoS One* 10(3):e0116316.
3. Lazary J*, et al.* (2008) New evidence for the association of the serotonin transporter gene (SLC6A4) haplotypes, threatening life events, and depressive phenotype. *Biol Psychiatry* 64(6):498-504.
4. Gonda X*, et al.* (2016) Financial difficulties but not other types of recent negative life events show strong interactions with 5-HTTLPR genotype in the development of depressive symptoms. *Transl Psychiatry* 6:e798.

PATH (Personality and Total Health Through Life)

Investigators collaborating in the 5-HTTLPR Meta-analysis:
Simon Easteal, Australian National University, Canberra, ACT, Australia
Richard Burns, Australian National University, Canberra, ACT, Australia
Kaarin Anstey, Australian National University, Canberra, ACT, Australia

Sample: The sample is comprised of three cohorts aged 20-24, 40-44 and 60-64 at baseline and was drawn from the electoral rolls in Canberra which is in the Australian Capital Territory and Queanbeyan in the state of New South Wales. Voting is compulsory in Australia. Subjects for 5-HTTLPR meta-analysis: n = 1931 (96.8%). Caucasians drawn from the youngest cohort at Wave 2 with relevant data.

Measures: Demographic, mental health, lifestyle, physical health, substance use, cognitive function, physical performance and blood pressure were collected at baseline. Assessments were conducted face-to-face in participants' homes. The BPH-Q was used to assess depression for this analysis and data on childhood adversity and life events were collected. The study also includes the Goldberg depression and anxiety inventory at Wave 2 for this cohort.

Genomic DNA was isolated using QIAamp blood kits (QIAGEN, Hilden, Germany) from buccal epithelial cells obtained using cotton swabs. Polymerase chain reaction (PCR) primers and conditions were as described by Heils et al. (1996).

References

1. Anstey, K.J., Christensen, H., Butterworth, P., Easteal, S., Mackinnon, A., Jacomb, T., Maxwell, K., Rodgers, B., Windsor,T., Cherbuin, N., Jorm, A.F. (2012). Cohort Profile: The PATH through life project. International Journal of Epidemiology, 41(4), 951-60.
2. Chipman P, Jorm AF, Prior M, Sanson A, Smart D, Tan X, Easteal S. No interaction between the serotonin transporter polymorphism (5-HTTLPR) and childhood adversity or recent stressful life events on symptoms of depression: results from two community surveys. Am J Med Genet B Neuropsychiatr Genet. 2007 Jun 5;144B(4):561-5.

POUCH (Pregnancy Outcomes and Community Health Studies) and POUCH-CESD

Investigators collaborating on the 5-HTTLPR Meta-analysis:

Jeanette Scheid, Michigan State University, East Lansing, MI, USA
Claudia Holzman, Michigan State University, East Lansing, MI, USA
Nicole Jones, Michigan State University, East Lansing, MI, USA

The first of two studies included non-Hispanic white women (N=568) who were between 15-27 weeks gestation when recruited from 52 prenatal clinics in five Michigan communities. The sample included women who delivered preterm along with a subcohort of women who delivered at term. At the time of recruitment, the women provided blood samples for DNA analysis including the 5-HTTLPR polymorphism (l, s alleles), completed the Center for Epidemiological Studies Depression (CES-D) questionnaire, and completed a modified version of the Turner, Wheaton and Lloyd stressful life circumstances (SLE) questionnaire. The sample was stratified by CES-D score (<18 vs. ≥18 'elevated' depressive symptoms). Odds ratios were calculated to assess associations between lifetime exposure to SLE subconstructs (economic, abuse, substance use, legal problems, violence and loss) and 'elevated' depressive symptoms. Analyses were repeated after stratifying by 5-HTTLPR genotype. Effect modification by genotype was evaluated using the Breslow-Day test for homogeneity of odds ratios. There were no direct associations between 5-HTTLPR genotype and 'elevated' depressive symptoms. There was no evidence of effect modification by 5-HTTLPR genotype (s/s vs. s/l and l/l) when assessing the OR for 'elevated' depressive symptoms by SLE total score. Statistically significant effect modification by 5-HTTLPR genotype was seen for the SLE – abuse subconstruct after excluding the 13% of the sample (N=73) who reported recent use of psychotropic medications (the association between exposure to abuse and 'elevated' depressive symptoms during pregnancy was stronger for the s/s genotype compared to the group with either s/l or l/l genotypes)

The second of two studies included African American women (N=698) from the POUCH Study also recruited at mid-pregnancy from 52 prenatal clinics in five Michigan communities. The assessment of stressful life events (SLE) and 'elevated' depressive symptoms was the same as in the study of non-Hispanic white women. However, DNA analysis included assessment of the two forms of the l allele (La and Lg).The allelic frequency of the Lg allele is higher in African American populations and previous studies have shown that the expression of the SERT protein varies by genotype (La highest, Lg intermediate or equivalent to S allele and S lowest). Previous studies assessing gene-environment interactions have considered the expression of the Lg allele to be equivalent to the S allele. We chose to assess genotype modification considering the possibility that Lg and S alleles are not equivalent in expression. The relation between stressful life events and 'elevated' depressive symptoms was stronger in S/S compared with La/La genotype (interaction P=0.11). Similar to the results in the white women, effect modification by genotype (La/La vs S/S) was seen for relations between 'elevated' depressive symptoms and the abuse subconstruct of SLE (p=0.03) (strongest association between abuse and 'elevated' depressive symptoms in the S/S genotype compared to the La/La genotype).

References:

1. Scheid J.M., Holzman C.B., Jones N., et al. Depressive symptoms in mid pregnancy, lifetime stressors and the 5-HTTLPR genotype. Genes, Brain and Behavior 6: 453-464. 2007.
2. Scheid J.M., Holzman, C. B., Jones N. Friderci K.H.,Jernigan K.A., Symonds L.L., Sikorskii A.,Fisher R. Life stressors and 5-HTTLPR interaction in relation to midpregnancy depressive symptoms among African–American women. Psychiatric Genetics 21(6): 271-280. 2011.

QIMRtwin (Queensland Institute of Medical Research Twin and Family Study)

Investigators collaborating on the 5-HTTLPR Meta-analysis:

William Coventry, University of New England, Armidale, NSW, Australia
Nick Martin, Queensland Institute of Medical Research, Brisbane, QLD, Australia
Naomi Wray, University of Queensland, Brisbane, QLD, Australia

Enda Byrne, Queensland Institute of Medical Research, Brisbane, QLD, Australia

Subjects for 5-HTTLPR meta-analysis: 3,243 (97% Northern European ancestry)

Sample and measures: The sample was drawn from the Australian NHMRC Twin Register. A Health and Lifestyle Questionnaire (administered 1988–1990) assessed depression and SLEs in the preceding 12 months. A telephone interview using the SSAGA (administered 1992-2000) assessed lifetime DSM-IV depression and suicide ideation. Blood (or buccal/saliva in ~4% of cases) was also collected.

Genotyping: In pilot experiments conducted for this study, we recognized problems with the original PCR assay [Heils et al., 1996], as found by others [Kaiser et al., 2002; Yonan et al., 2006] and designed a new high-throughput assay [Wray et al., 2009]. The genotyping in duplicate of all samples, the genotyping of replicated samples, of MZ twins and of family members, all serve to provide a high level of quality control in our study. We found, in a subsample genotyped by our group [Gillespie et al., 2005] using the original assay, on which much of the literature is based, 16% showed inconsistencies with the new genotyping assay. Without our levels of quality control, it is likely other studies using the original assay will have suffered similar genotyping inaccuracy. The genotyping included subdivision of the 5HTTLPR L allele according to the SNP rs25531.

The primary GxE study from this dataset was published in (Coventry et al. 2010).

Reference

1. Coventry WL, James MR, Eaves LJ, Gillespie NA, Heath AC, Montgomery GW, Martin NG, & Wray NR. (2010). Do 5HTTLPR and stress interact in risk for depression and suicidality? Item response analyses of a large sample. American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics, 153B(3), 757-765.

SALVe 2001 (Survey of Adolescent Life in Vestmanland 2001)

Investigators collaborating on the 5-HTTLPR Meta-analysis:
Kent W Nilsson, Centre for Clinical Research, Uppsala University, Västmanland County Hospital, Västerås, Sweden

Subjects for 5-HTTLPR meta-analysis: **200** (Scandinavian ethnicity)

This is a cross-sectional study of Swedish adolescents ages 17-18.

All students in the ninth grade in primary school and third grade in secondary school in Västmanland completed the SALVe 2001 questionnaire during class hours. All students had the opportunity to give their informed consent to participate in an in-depth interview and agree to the donation of a blood sample, by including their full personal code number on the form's front page. Informed consent was received from 785 students who could be traced with valid names. All students were classified with a risk index, depending on their risk behaviours reported in the questionnaire, and divided into four groups according to their respective risk index. Randomized samples of 400 students, matched for age, sex and risk behaviour were drawn from the volunteers. Eighty-one of the boys and 119 of the girls agreed to give blood samples and to take part in an interview when asked for informed consent a second time.

Venous blood was drawn from all interviewed students for molecular genetic analyses. DNA was extracted from venous blood and 5-HTTLPR genotyping performed essentially according to the protocol by Collier et al. (1996). In order to confirm that the correct regions of the 5-HTT gene were amplified, PCR products representing all genotypes were sequenced using BigDye1 Terminator chemistry (Applied Biosystems, Foster City, CA, USA) and analysed by an automated ABI PRISMTM (PerkinElmer, Foster City, CA, USA). The DNA fragments were analysed using the SequencerTM 3.1.1 software (PerkinElmer).

All interviews were audio-taped and these tapes were used to code psychosocial variables.

The responses of the participants to these questions of psychosocial variables were then combined and transformed from a 'qualitative' to a 'quantitative' dichotomous measure.

The dichotomous psychosocial variables (fathers' and mothers' education, parental occupation, family economy, quality of family relationships and traumatic conflicts within the family) were merged into an index and then dichotomized to psychosocial risk (no and one risk/ two or more risks). Three years after the initial questionnaire and interviews an additional questionnaire was mailed to the participants including the Depression Self-Rating Scale (DSRS) of the DSM-IV (A-criterion) for major depression.

Several other candidate genes have been analyzed in the SALVe 2001 resulting in a number of publications (1, 2, 3).

References

1. Rickard L. Sjöberg, Kent W. Nilsson, Niklas Nordquist, John Öhrvik, Jerzy Leppert, Leif Lindström and Lars Oreland. Development of depression: sex and the interaction between environment and a promoter polymorphism of the serotonin transporter gene*. International Journal of Neuropsychopharmacology* (2005), 9, 1–7.
2. Nilsson KW, Sjoberg RL, Damberg M, Leppert J, Ohrvik J, Alm PO, Lindstrom L, Oreland L (2006) Role of monoamine oxidase A genotype and psychosocial factors in male adolescent criminal activity. Biol Psychiatry 59(2):121–127
3. Nilsson KW, Sjoberg RL, Wargelius HL, Leppert J, Lindstrom L, Oreland L (2007) The monoamine oxidase A (MAO-A) gene, family function and maltreatment as predictors of destructive behaviour during male adolescent alcohol consumption. Addiction 102(3):389–398.

SALVe 2006 (Survey of Adolescent Life in Vestmanland 2006)

Investigators collaborating on the 5-HTTLPR Meta-analysis:

Kent W Nilsson, Centre for Clinical Research, Uppsala University, Västmanland County Hospital, Västerås, Sweden
Cecilia Åslund, Centre for Clinical Research, Uppsala University, Västmanland County Hospital, Västerås, Sweden

Subjects for 5-HTTLPR meta-analysis: **1482** (Scandinavian ethnicity)
This is a cross-sectional study of Swedish adolescents ages 17-18.

Survey of Adolescent Life in Vestmanland is a survey distributed biennially by the County Council of Västmanland, Sweden, in order to monitor the psychosocial health of the county's adolescent population. Västmanland is a medium sized Swedish county, situated about 100 km west of Stockholm. All students in the second year of high school (17–18 years old) were asked to complete a questionnaire during class hours. In addition, participants were asked to provide a saliva sample for DNA extraction by rinsing their mouth for 30 s with a 0.9% sodium chloride solution. Participants answered questions about maltreatment (quarrel and violence between parents, psychological and physical maltreatment) and the depression self-rating scale (DSRS) of the DSM-IV (A + C-criterion), for major depression.

Polymerase chain reaction (PCR) was performed in a 10 µl reaction mixture containing 30 ng DNA, 1 mM PCR Buffer 109 with 1.5 mM MgCl2, 0.2 lM dNTPs, 0.8 lM of two primers, and 0.5 U FastStart Taq DNA polymerase (Roche Diagnostics GmbH, Mannheim, Germany).

The PCR products were analyzed by capillary electrophoresis using an ABI PRISM 3700 DNA Analyzer (Applied Biosystems, Inc., Foster City, California, USA) and allele sizes were determined manually on chromatograms using Gene Marker 1.5 AFLP/Genotyping software (SoftGenetics LLC, State College, PA, USA).

Several other candidate genes have been analyzed in the SALVe 2006, with a number of publications (see for example (1, 2, 3).

References

1. Cecilia Åslund, Jerzy Leppert, Erika Comasco, Niklas Nordquist, Lars Oreland, Kent W. Nilsson. Impact of the Interaction Between the 5HTTLPR Polymorphism and Maltreatment on Adolescent Depression. A Population-Based Study. Behavior Genetics 2009: 39(5); 524-531

2. C. Åslund, N. Nordquist, E. Comasco, J. Leppert, L. Oreland, K. W. Nilsson. Maltreatment, MAOA, and Delinquency: Sex Differences in Gene–Environment Interaction in a Large Population-Based Cohort of Adolescents. *Behavior Genetics* 2011: 41(2); 262-272.
3. Nilsson KW, Comasco E, Hodgins S, Oreland L, Åslund C. Genotypes do not confer risk for delinquency but rather alter susceptibility to positive and negative environmental factors: Gene-environment interactions of BDNF Val66Met, 5-HTTLPR, and MAOA-uVNTR. *The International Journal of Neuropsychopharmacology* 2014 Dec 10;18(5).

SEBAS (Social Environment and Biomarkers of Aging Study), Taiwan

Investigators collaborating on the 5-HTTLPR Meta-analysis:

Dana Glei, Georgetown University, Washington, DC, USA
Noreen Goldman, Princeton University, Princeton, NJ, USA
Maxine Weinstein, Georgetown University, Washington, DC, USA

Subjects for 5-HTTLPR meta-analysis:
877 in 2000 (70% Fukienese, 13% Hakka, 17% Mainlanders; 0.1% Aborigine)
1019 in 2006 (71% Fukienese, 15% Hakka, 13% Mainlanders; 0.5% Other)

The Social Environment and Biomarkers of Aging Study (SEBAS) in Taiwan is an extension of the Taiwan Longitudinal Study of Aging (TLSA) that began in 1989. The SEBAS builds on this longitudinal survey by including a collection of biomarkers and a medical examination, along with household interviews, in two waves: 2000 and 2006.[1]

The 2000 wave of the Social Environment and Biomarkers of Aging Study (SEBAS) comprised a nationally representative sample of Taiwanese aged 54 and older drawn from the TLSA sample; older persons (71+) and urban residents were oversampled. In-home interviews were completed with 1497 respondents (92% response rate), 1023 of whom also completed the physical examination. In 2006, a follow-up was conducted with those who completed the 2000 exam and survived to 2006. A refresher cohort of those aged 53-60 in 2006 was also added so that the 2006 SEBAS represents a cross-section of the Taiwanese population aged 53 and older. In-home interviews were completed by 1284 respondents (91% of survivors in the longitudinal cohort; 82% response rate for the younger cohort), 1036 of whom also completed the physical examination.

The household interview includes extensive information on self-reported measures of health and well-being, the social environment, health-related behaviors and life challenges. In 2006, an expanded set of health assessments was administered by the interviewers in the respondent's home. Several weeks after the household interview, participants visited a nearby hospital for a physical examination. The biomarker collection included seated blood pressure, anthropometric measurements, a fasting venous blood specimen, a spot urine sample, and a 12h overnight urine collection (7pm to 7am). Compliance was high: in 2000, 96 percent fasted overnight and provided a urine specimen deemed suitable for analysis; the comparable figure was 88 percent in 2006.

Reference

1. Chang M, Lin H, Chuang Y, et al. Social Environment and Biomarkers of Aging Study in Taiwan (SEBAS 2000 and SEBAS 2006): main documentation for SEBAS longitudinal public use data (released 2012-01-06). ICPSR03792-v5. Ann Arbor, MI: Inter-university Consortium for Political and Social Research [distributor], 2012. http://www.icpsr.umich.edu/icpsrweb/ICPSR/studies/3792/detail doi: 10.3886/ICPSR03792.v5

SHIP (Study of Health in Pomerania)

Investigators collaborating on the 5-HTTLPR Meta-analysis:

Hans Joergen Grabe, Dept of Psychiatry, Univ. Medicine Greifswald, Germany
Sandra Van der Auwera, Dept of Psychiatry, Univ. Medicine Greifswald, Germany
Christian Schwahn, Department of Oral Health, University Medicine Greifswald, Germany
Henry Völzke, Institute for Community Medicine, University Medicine Greifswald, Germany
Henriette Meyer zu Schwabedissen, Biopharmacy, Department Pharmaceutical Sciences, University of Basel, Switzerland
Matthias Nauck, Institute of Clinical Chemistry and Laboratory Medicine, University Medicine Greifswald, Germany

SHIP consists of an initial set of subjects (baseline: n = 4000) of which a subset received additional phenotyping appropriate for the current meta-analysis (LEGEND: n = 2152).

In the text and tables, the analysed data (SHIP LEGEND) will simply be referred to as SHIP.

Description of SHIP baseline
The target population was comprised of adult German residents in northeastern Germany living in 3 cities and 29 communities, with a total population of 212,157. A two-stage stratified cluster sample of adults aged 20 to 79 years at baseline had been drawn from local population registration files. Among the net sample of 6,267 eligible subjects, 4,308 Caucasian subjects participated in SHIP-0 between 1997 and 2001. SHIP was approved by the local Institutional Review Board and conformed to the principles of the Declaration of Helsinki.

Besides unemployment as putative stressor, the interview-rated number of chronic diseases (Myocardical infarction, stroke, diabetes, kidney disease, chronic bronchitis, arthritis and degenerative diseases of the joints and spine, osteoporosis, peptic ulcer, pancreatitis, gastrointestinal bleedings, migraine, thyroid disease, cancer, multiple sclerosis and parkinson´s disease) was taken as another stressor. The modified version of von Zerssen's complaints scale was used to assess psychological and somatic symptoms and complaints by self-report on 38 items. Complete genotype and clinical data were available for n=4000 subjects (2022 females).

Description of LEGEND (subsample of SHIP-baseline)
From 2007 to 2010, the "Life-Events and Gene-Environment Interaction in Depression" (LEGEND) study was conducted. In LEGEND a detailed psychometric assessment was performed.

Selection of Phenotype Measures
Current depressive symptoms were assessed in LEGEND using the Beck Depression Inventory (BDI-II).

The Childhood Trauma Questionnaire (CTQ) was used for self-report of childhood maltreatment including emotional, physical and sexual abuse.

Depressive disorders according to DSM-IV criteria were assessed by face-to face interview.

Reference

1. Völzke H, Alte D, Schmidt CO, Radke D, Lorbeer R, Friedrich N, Aumann N, Lau K, Piontek M, Born G, Havemann C, Ittermann T, Schipf S, Haring R, Baumeister SE, Wallaschofski H, Nauck M, Frick S, Arnold A, Jünger M, Mayerle J, Kraft M, Lerch MM, Dörr M, Reffelmann T, Empen K, Felix SB, Obst A, Koch B, Gläser S, Ewert R, Fietze I, Penzel T, Dören M, Rathmann W, Haerting J, Hannemann M, Röpcke J, Schminke U, Jürgens C, Tost F, Rettig R, Kors JA, Ungerer S, Hegenscheid K, Kühn JP, Kühn J, Hosten N, Puls R, Henke J, Gloger O, Teumer A, Homuth G, Völker U, Schwahn C, Holtfreter B, Polzer I, Kohlmann T, Grabe HJ, Rosskopf D, Kroemer HK, Kocher T, Biffar R, John U, Hoffmann W. Cohort profile: the study of health in Pomerania. Int J Epidemiol. 2011 Apr;40(2):294-307.

TRAILS (TRacking Adolescents' Individual Lives Survey)

Investigators collaborating on the 5-HTTLPR Meta-analysis:

Albertine Oldehinkel, University Medical Center Groningen, Netherlands
Esther Nederhof, University Medical Center Groningen, Netherlands
Johan Ormel, University Medical Center Groningen, Netherlands

The "TRacking Adolescents' Individual Lives Survey" (TRAILS) consists of two prospective cohort studies; a population-based cohort and a clinical cohort (1,2). The current meta-analysis used data from the first four assessment waves of the population cohort, which ran from March 2001 to July 2002 (T1), September 2003 to December 2004 (T2), September 2005 to August 2007 (T3), and October 2008 to September 2010 (T4). T4 included a CIDI interview assessing lifetime and 12-month diagnoses according to the DSM-IV diagnoses, while depressive symptoms were assessed at every wave, by the Youth Self-Report (T1-T3) and Adult Self-Report (T4). Information on both DSM-IV diagnoses and 5-HTTLPR (including rs25531) is available of 1230 participants, of whom 1108 are of Dutch origin.

The study area is well defined by postal codes and covers about 1,717,000 inhabitants. There is a mixture of economic activities including (light) industry, services, educational facilities, and a variety of agricultural activities. Almost 90% of the population sample was recruited in the three largest towns in the area: Groningen (190,000 inhabitants), Leeuwarden (95,000), and Assen (67,000). The rest lives in rural areas. The largest ethnic group is the Dutch (89.7%). TRAILS studies have been approved by the National Dutch Central Committee on Research Involving Human Subjects by the Medical Ethical Committee of the University Medical Center Groningen. For each assessment wave, participants are asked for their written informed consent.

References

1. Huisman M, Oldehinkel AJ, De Winter AF, Minderaa RB, De Bildt A, Huizink AC, et al. Cohort profile: The Dutch "TRacking Adolescents' Individual Lives' Survey"; TRAILS. Int J Epidemiol 2008; 37: 1227-35.
2. Oldehinkel AJ, Rosmalen JGM, Buitelaar JK, Hoek HW, Ormel J, Raven D, et al. Cohort Profile update. The TRacking Adolescents' Individual Lives Survey (TRAILS). Int J Epidemiol 2015; 44(1):76-76n.

TREND (SHIP-TREND; Study of Health in Pomerania-TREND)

Investigators collaborating on the 5-HTTLPR Meta-analysis:

Hans Joergen Grabe, Dept of Psychiatry, Univ. Medicine Greifswald, Germany
Sandra Van der Auwera, Dept of Psychiatry, Univ. Medicine Greifswald, Germany
Christian Schwahn, Department of Oral Health, University Medicine Greifswald, Germany
Henry Völzke, Institute for Community Medicine, University Medicine Greifswald, Germany
Henriette Meyer zu Schwabedissen, Biopharmacy, Department Pharmaceutical Sciences, University of Basel, Switzerland
Matthias Nauck, Institute of Clinical Chemistry and Laboratory Medicine, University Medicine Greifswald, Germany

In 2008, a new sample called SHIP–TREND (*n* = 4,420) from the same area as SHIP-baseline was drawn and similar examinations like in SHIP-baseline were undertaken. The objective was to compare two samples from the same target population but from different time periods (1997 and 2008) concerning disease prevalence and risk behavior.

Selection of Phenotype Measures
Current depressive symptoms were assessed in TREND using the Patient Health Questionnaire (PHQ-9).

The Childhood Trauma Questionnaire (CTQ) was used for self-report of childhood maltreatment including emotional, physical and sexual abuse.

Depressive disorders according to DSM-IV criteria were assessed by face-to face interview.

Subjects for meta-analysis in TREND: n= 3499

Reference

1. Völzke H, Alte D, Schmidt CO, Radke D, Lorbeer R, Friedrich N, Aumann N, Lau K, Piontek M, Born G, Havemann C, Ittermann T, Schipf S, Haring R, Baumeister SE, Wallaschofski H, Nauck M, Frick S, Arnold A, Jünger M, Mayerle J, Kraft M, Lerch MM, Dörr M, Reffelmann T, Empen K, Felix SB, Obst A, Koch B, Gläser S, Ewert R, Fietze I, Penzel T, Dören M, Rathmann W, Haerting J, Hannemann M, Röpcke J, Schminke U, Jürgens C, Tost F, Rettig R, Kors JA, Ungerer S, Hegenscheid K, Kühn JP, Kühn J, Hosten N, Puls R, Henke J, Gloger O, Teumer A, Homuth G, Völker U, Schwahn C, Holtfreter B, Polzer I, Kohlmann T, Grabe HJ, Rosskopf D, Kroemer HK, Kocher T, Biffar R, John U, Hoffmann W. Cohort profile: the study of health in Pomerania. Int J Epidemiol. 2011 Apr;40(2):294-307.

VAHCS (Victoria Adolescent Health Care Study)

Investigators collaborating on the 5-HTTLPR Meta-analysis:

George Patton, Royal Children's Hospital & University of Melbourne
Craig Olsson, Centre for Social and Early Emotional Development, Deakin University; Centre for Adolescent Health, Murdoch Childrens Research Institute; Department of Paediatrics and School of Psychological Sciences, The University of Melbourne
Carolyn Coffey, Murdoch Childrens Research Centre

Participants were drawn from the Victorian Adolescent Health Cohort Study, a longitudinal study of 1943 young people from adolescence to adulthood, focusing on the continuity and consequences of adolescent mental health and health risk behaviours in adulthood. The sample is a representative of Victorian (Australia) population in 1992, when the participants were 14 years. Within the VAHCS we conducted a nested case control study of depression (n=406) which included measurement of life events (LTE_Q). Current major depression disorder was assessed using ICD-10 criteria. The data from participants from this study who had also provided genetic samples (n=210) and were uniformly Caucasian were available for inclusion in the meta-analysis.

Young Adult Analyses:

Primary Analyses **1Ai** and **1Bi** focused on individuals assessed during **young adulthood** (ages 21 to 30). This time period is of particular interest because the study originally reporting the 5-HTTLPR by stress interaction[2] consisted of individuals assessed during young adulthood, and it was hypothesized that individuals could be particularly vulnerable at this stage of development. Studies with longitudinal data selected information provided from assessments when subjects were in the young adult age range.

Both of these analyses used **diagnosis of a major depressive episode** as the outcome variable and a **dichotomous exposure to stress** as a predictor variable (exposure to childhood maltreatment in analysis 1Ai and combined exposure to childhood maltreatment or other life stress in analysis 1Bi). Results from these meta-analyses are listed in Supplemental **Table S9**.

When the dataset level results were meta-analyzed, we learned that in spite of our large cumulate sample, some of the proposed meta-analyses were not possible due to insufficient data (i.e. fewer than 2 datasets passing quality control checks). Nonetheless, the results of the young-adult meta-analyses of dichotomous phenotypes that could be performed (Table S9) are consistent with the findings presented in Table 1, in that they provide no statistical support for an interaction effect in the hypothesized direction.

Primary analyses **1Aii** and **1Bii** of the young adults examined **quantitative measures for stress and depression**. For both sets of analyses, the designated quantitative depression variable was the number of DSM symptoms endorsed by the subject. The quantitative measure for childhood maltreatment used was the score from the Childhood Trauma Questionnaire (CTQ), the most common assessment of childhood maltreatment among the members of our consortium. The most common assessment of other life stress in our consortium was the Lifetime Traumatic Events Questionnaire (LTEQ). Because this has a different scale than the CTQ, we could not combine these into a single quantitative stress variable. As a consequence, in the quantitative stress analyses we examined childhood maltreatment (CTQ score) and *other life stress **(LTE-Q score)*** as the second stress phenotype (rather than broad stress).

We did not have sufficient data to analyze both quantitative depression and quantitative stress in a single meta-analysis. As a consequence, we separately present results based on **depression diagnosis as the outcome with quantitative stress** (Supplemental Table S10a) and **quantitative depression outcome with dichotomous stress exposure** (Supplemental Table S10b). In Supplemental Table S10b, because the outcome is quantitative, the effect sizes are indicated by a beta coefficient, rather than an odds ratio.

Supplemental Table S9: Meta-analyses of Young Adults (age 21 to 30) based on depression diagnosis and dichotomous stress exposure

Young adults; Stress = Childhood Maltreatment (Primary Analysis 1Ai)

Depression	Stress	Studies	Subjects	Covariate	OR	95% CI	p-value
Lifetime	Childhood maltreatment			Sex	0.65	(0.41 , 1.02)	0.06
				Stress	0.93	(0.43 , 2.02)	0.85
				Gene	0.90	(0.66 , 1.22)	0.49
				Gene x stress	0.79	(0.40 , 1.58)	0.51
Current	Childhood maltreatment			Sex	-	-	-
				Stress	-	-	-
				Gene	-	-	-
				Gene x stress	-	-	-

Young adults; Stress = Childhood maltreatment or other life stress (Primary Analysis 1Bi)
Includes studies assessing only one of the stressors

Depression	Stress	Studies	Subjects	Covariate	OR	95% CI	p-value
Lifetime	Broad stress (Other life stress < 5 years prior or childhood maltreatment)	5	886	Sex	0.74	(0.46 , 1.19)	0.22
				Stress	0.88	(0.43 , 1.80)	0.73
				Gene	0.79	(0.54 , 1.14)	0.21
				Gene x stress	1.37	(0.53 , 3.49)	0.52
Current	Broad stress (Other life stress < 5 years prior or childhood maltreatment)			Sex	-	-	-
				Stress	-	-	-
				Gene	-	-	-
				Gene x stress	-	-	-
Lifetime	Broad stress (Other life stress or childhood maltreatment)	9	1675	Sex	0.66	(0.49 , 0.89)	0.01
				Stress	0.86	(0.51 , 1.45)	0.57
				Gene	0.78	(0.55 , 1.10)	0.16
				Gene x stress	1.19	(0.72 , 1.97)	0.50
Current	Broad stress (Other life stress or childhood maltreatment)			Sex	-	-	-
				Stress	-	-	-
				Gene	-	-	-
				Gene x stress	-	-	-

Sex (female = 0; male = 1)
Stress (not exposed = 0; exposed = 1)
Gene (additive coding in number of S alleles for 5-HTTLPR (LL = 0; LS=1; SS=2))
Broad stress does not require both stressors to be assessed.

MODEL: $depression = \beta_0 + \beta_1(age) + \beta_2(sex) + \beta_3(stress) + \beta_4(gene) + \beta_5(gene \times stress)$
Depression variable: **depression diagnosis**
Stress variable: **dichotomous stress exposure**
Meta-analyses 1Ai and 1Bi from our protocol[1]
Age was not significant in any of the models
Blank results indicate insufficient data to perform a meta-analysis

Forest plots for the interaction terms for these analyses are in Figure S6.

Supplemental Table S10a: Meta-analyses of Young Adults (age 21 to 30) based on depression diagnosis and quantitative measures of stress

Primary Analysis 1Aii

Depression	Stress	Studies	Subjects	Covariate	OR	95% CI	p-value
Lifetime	Childhood Maltreatment	6	830	Sex	0.61	(0.36 , 1.02)	0.06
				Stress	1.02	(0.95 , 1.09)	0.62
				Gene	0.72	(0.20 , 2.62)	0.61
				Gene x stress	1.00	(0.95 , 1.06)	0.93
Current	Childhood Maltreatment			Sex	-	-	-
				Stress	-	-	-
				Gene	-	-	-
				Gene x stress	-	-	-

Primary Analysis 1Bii

Depression	Stress	Studies	Subjects	Covariate	OR	95% CI	p-value
Lifetime	Other life stress (Life stress < 5 years prior)	2	317	Sex	1.68	(0.31 , 9.07)	0.55
				Stress	1.66	(1.20 , 2.38)	0.01
				Gene	1.32	(0.49 , 3.58)	0.59
				Gene x stress	1.01	(0.73 , 1.41)	0.94
Current	Other life stress (Life stress < 5 years prior)			Sex	-	-	-
				Stress	-	-	-
				Gene	-	-	-
				Gene x stress	-	-	-
Lifetime	Other life stress (Life stress at any time)	4	870	Sex	0.90	(0.51 , 1.60)	0.72
				Stress	1.62	(1.20 , 2.10)	2.8E-4
				Gene	1.03	(0.57 , 1.87)	0.92
				Gene x stress	0.97	(0.78 , 1.21)	0.79
Current	Other life stress (Life stress at any time)			Sex	-	-	-
				Stress	-	-	-
				Gene	-	-	-
				Gene x stress	-	-	-

Sex (female = 0; male = 1)
Stress (CTQ-score for childhood maltreatment, LTE-Q score for other life stress)
Gene (additive coding in number of S alleles for 5-HTTLPR (LL = 0; LS=1; SS=2))
Quantitative stress is based on a single assessed stress

MODEL: $depression = \beta_0 + \beta_1(age) + \beta_2(sex) + \beta_3(stress) + \beta_4(gene) + \beta_5(gene \times stress)$
Depression variable: **depression diagnosis**
Stress variable: **quantitative stress**
Age was not significant in any of the models
Blank results indicate insufficient data to perform a meta-analysis

Forest plots for the interaction terms for these analyses are in Figure S7.

Supplemental Table S10b: Meta-analyses of Young Adults (age 21 to 30) based on DSM-IV symptom count and dichotomous stress exposure

Primary Analysis 1Aii

Depression	Stress	Studies	Subjects	Covariate	β	95% CI	p-value
Lifetime	Childhood Maltreatment	2	524	Sex	-0.87	(-2.00 , 0.27)	0.14
				Stress	-0.04	(-1.10 , 0.98)	0.95
				Gene	-0.07	(-0.38 , 0.23)	0.63
				Gene x stress	0.12	(-1.00 , 1.25)	0.83
Current	Childhood Maltreatment			Sex	-	-	-
				Stress	-	-	-
				Gene	-	-	-
				Gene x stress	-	-	-

Primary Analysis 1Aii

Depression	Stress	Studies	Subjects	Covariate	β	95% CI	p-value
Lifetime	Broad Stress (Other life stress < 5 years prior or childhood maltreatment)	3	583	Sex	-0.53	(-1.47 , 0.40)	0.26
				Stress	-0.17	(-1.07 , 0.73)	0.71
				Gene	-0.50	(-0.95 , -0.04)	0.03
				Gene x stress*	0.93	(0.27 , 1.59)	0.006
Current	Broad Stress (Other life stress < 5 years prior or childhood maltreatment)			Sex	-	-	-
				Stress	-	-	-
				Gene	-	-	-
				Gene x stress	-	-	-
Lifetime	Broad Stress (Other life stress or childhood maltreatment)	4	1142	Sex	-0.45	(-0.78 , -0.12)	0.01
				Stress	-0.17	(-0.94 , 0.59)	0.66
				Gene	-0.44	(-0.87 , -0.01)	0.05
				Gene x stress*	0.77	(0.21 , 1.33)	0.007
Current	Broad Stress (Other life stress or childhood maltreatment)			Sex	-	-	-
				Stress	-	-	-
				Gene	-	-	-
				Gene x stress	-	-	-

Sex (female = 0; male = 1)
Stress (not exposed = 0; exposed = 1)
Gene (additive coding in number of S alleles for 5-HTTLPR (LL = 0; LS=1; SS=2))

Broad stress does not require both stressors to be assessed.

MODEL: $depression = \beta_0 + \beta_1(age) + \beta_2(sex) + \beta_3(stress) + \beta_4(gene) + \beta_5(gene \times stress)$

Depression variable: **DSM symptom count**
Stress variable: **dichotomous stress exposure**

Age was not significant in any of the models
Blank results indicate insufficient data to perform a meta-analysis

Forest plots for the interaction terms for these analyses are in Figure S8.

*Nominally significant interaction in the hypothesized direction. Note that stress is not significant in either and has a protective point estimate in both. Sex is not significant in the first analysis.

All Age Analyses:

The remaining analyses laid out in our protocol[1] used subjects of all ages. The first set of these, Primary Analyses 2Ai and 2Bi, were full interaction models using **major depression diagnosis** as the outcome and **dichotomous stress exposures** for the stress variable. The results from these analyses were presented in **Table 1** in the main body of the manuscript.

Primary Analyses, **2Aii** and **2Bii** used quantitative measures of depression and stress. The phenotype definitions were the same as in the Young Adult analyses: the **quantitative depression** variable was the **number of DSM symptoms** endorsed by the subject; the quantitative measure for childhood maltreatment was the score from the **Childhood Trauma Questionnaire (CTQ)**; other life stress was the Lifetime Traumatic Events Questionnaire (LTE-Q score). Because LTE-Q has a different scale than the CTQ, for these analyses **other life stress (LTE-Q score)** was used rather than broad stress.

We did not have sufficient data to analyze both quantitative depression and quantitative stress in a single meta-analysis. As a consequence, we present results based on **depression diagnosis with quantitative stress** (Supplemental Table S11a) and **quantitative depression with dichotomous stress exposure** (Supplemental Table S11b). Because the outcome is quantitative in Supplemental Table S11b, the effect sizes are indicated by a beta coefficient, rather than an odds ratio.

Supplemental Table S11a. Meta-analyses of subjects of all ages based on depression diagnosis and quantitative measures of stress

Primary Analysis 2Aii

Depression	Stress	Studies	Subjects	Covariate	OR	95% CI	p-value
Lifetime	Childhood maltreatment	10	9928	Sex	0.61	(0.50 , 0.74)	1.2E-6
				Stress	1.06	(1.00 , 1.10)	1.1E-3
				Gene	0.82	(0.56 , 1.21)	0.32
				Gene x stress	1.01	(0.99 , 1.03)	0.47
Current	Childhood maltreatment	4	2322	Sex	0.77	(0.63 , 0.96)	0.02
				Stress	1.08	(1.00 , 1.18)	0.07
				Gene	0.84	(0.33 , 2.15)	0.72
				Gene x stress	1.01	(0.96 , 1.06)	0.65

Primary Analysis 2Bii

Depression	Stress	Studies	Subjects	Covariate	OR	95% CI	p-value
Lifetime	Other life stress (Life stress < 5 years prior)	2	1669	Sex	0.75	(0.57 , 0.99)	0.04
				Stress	1.19	(0.95 , 1.49)	0.13
				Gene	1.13	(0.91 , 1.41)	0.26
				Gene x stress	1.03	(0.93 , 1.14)	0.60
Current	Other life stress (Life stress < 5 years prior)			Sex		-	
				Stress		-	
				Gene		-	
				Gene x stress		-	
Lifetime	Other life stress (Life stress at any time)	7	9065	Sex	0.64	(0.52 , 0.80)	6.0E-5
				Stress	1.48	(1.30 , 1.74)	1.8E-6
				Gene	1.02	(0.92 , 1.13)	0.71
				Gene x stress	1.03	(0.98 , 1.09)	0.25
Current	Other life stress (Life stress at any time)	5	2952	Sex	0.72	(0.39 , 1.33)	0.29
				Stress	1.42	(1.30 , 1.58)	2.5E-10
				Gene	0.91	(0.69 , 1.20)	0.50
				Gene x stress	1.04	(0.95 , 1.15)	0.41

Sex (female = 0; male = 1)
Stress (CTQ-score for childhood maltreatment, LTE-Q score for other life stress)
Gene (additive coding in number of S alleles for 5-HTTLPR (LL = 0; LS=1; SS=2))
Quantitative stress is based on a single assessed stress.

MODEL: $depression = \beta_0 + \beta_1(age) + \beta_2(sex) + \beta_3(stress) + \beta_4(gene) + \beta_5(gene \times stress)$
Depression variable: **depression diagnosis**
Stress variable: **quantitative stress**

Age was not significant in any of the models
Blank results indicate insufficient data to perform a meta-analysis

Forest plots for the interaction terms for these analyses are in Figure S9.

Supplemental Table S11b: Meta-analyses of subjects of all ages based on DSM-IV symptom count and dichotomous stress exposure

Primary Analysis 2Aii

Depression	Stress	Studies	Subjects	Covariate	β	95% CI	p-value
Lifetime	Childhood Maltreatment	4	6878	Sex	-0.78	(-1.00 , -0.54)	3.3E-10
				Stress	1.75	(0.80 , 2.70)	3.0E-4
				Gene	0.03	(-0.09 , 0.14)	0.67
				Gene x stress	-0.26	(-0.61 , 0.09)	0.15
Current	Childhood Maltreatment	4	5723	Sex	-0.91	(-1.20 , -0.62)	6.5E-10
				Stress	1.82	(1.30 , 2.33)	2.4E-12
				Gene	-0.01	(-0.13 , 0.11)	0.87
				Gene x stress	-0.28	(-0.71 , 0.15)	0.20

Primary Analysis 2Bii

Depression	Stress	Studies	Subjects	Covariate	β	95% CI	p-value
Lifetime	Broad stress (Other life stress <5 years prior or childhood maltreatment)	5	7840	Sex	-0.66	(-0.98 , -0.35)	2.9E-5
				Stress	1.31	(0.75 , 1.86)	3.4E-6
				Gene	0.08	(-0.03 , 0.20)	0.16
				Gene x stress	-0.16	(-0.39 , 0.07)	0.17
Current	Broad stress (Other life stress <5 years prior or childhood maltreatment)	4	5645	Sex	-0.94	(-1.28 , -0.60)	5.3E-8
				Stress	1.60	(1.10 , 2.10)	4.5E-10
				Gene	0.00	(-0.14 , 0.14)	1.00
				Gene x stress	-0.07	(-0.35 , 0.20)	0.59
Lifetime	Broad stress (Other life stress or childhood maltreatment)	6	13337	Sex	-0.70	(-0.97 , -0.43)	5.6E-07
				Stress	1.30	(0.74 , 1.86)	6.2E-06
				Gene	0.11	(-0.02 , 0.25)	0.09
				Gene x stress	-0.07	(-0.33 , 0.19)	0.59
Current	Broad stress (Other life stress or childhood maltreatment)	4	6909	Sex	-0.91	(-1.26 , -0.55)	4.1E-7
				Stress	0.99	(-0.30 , 2.28)	0.13
				Gene	0.06	(-0.45 , 0.58)	0.81
				Gene x stress	-0.16	(-0.70 , 0.38)	0.57

Sex (female = 0; male = 1)
Stress (not exposed = 0; exposed = 1)
Gene (additive coding in number of S alleles for 5-HTTLPR (LL = 0; LS=1; SS=2))
Broad stress does not require both stressors to be assessed.

MODEL: $depression = \beta_0 + \beta_1(age) + \beta_2(sex) + \beta_3(stress) + \beta_4(gene) + \beta_5(gene \times stress)$

Depression variable: **DSM symptom count**
Stress variable: **dichotomous stress exposure**
Age was not significant in any of the models

Forest plots for the interaction terms for these analyses are in Figure S10.

Broad Analyses (Primary Analyses 2C from our protocol[1]): In our final primary analyses, we estimated the allele frequency distribution for each individual substratum of the analysis using all available data. In this way, we were able to include information from studies with incomplete strata (e.g. studies where all subjects were female, studies where all subjects were exposed to stress). Combining cell counts across every study, we performed omnibus analyses of the data with study as a covariate. Results from the primary analysis models using the broad data are listed in Supplemental Table S12.

The p-value for sex and stress exposure are generally more extreme in these analyses using more subjects than in the more refined analyses, with generally consistent OR. This is what would be expected for robust effects. In contrast, despite the larger sample sizes, the p-values for the gene and gene-by-stress interaction terms remain non-significant, suggesting that the interaction must require more specific circumstances to be seen.

Supplemental Table S12: Pooled data analyses of subjects of all ages based on depression diagnosis and exposure to stress

Primary Analysis 2C

Depression	Stress	Studies	Subjects	Covariate	OR	95% CI	p-value
Lifetime	Childhood maltreatment	20	21398	Sex	0.55	(0.52 , 0.59)	2.2E-61
				Stress	2.29	(1.98 , 2.64)	2.8E-29
				Gene	1.00	(0.95 , 1.05)	0.98
				Gene x stress	0.99	(0.87 , 1.13)	0.90
Current	Childhood maltreatment	16	15494	Sex	0.62	(0.56 , 0.69)	6.6E-19
				Stress	2.52	(2.07 , 3.07)	2.1E-20
				Gene	1.02	(0.94 , 1.11)	0.57
				Gene x stress	0.91	(0.77 , 1.08)	0.29
Lifetime	Broad Stress (Other life stress <5 years prior or childhood maltreatment)	21	24557	Sex	0.59	(0.55 , 0.63)	1.3E-54
				Stress	2.32	(2.07 , 2.60)	1.2E-46
				Gene	1.01	(0.95 , 1.07)	0.74
				Gene x stress	1.01	(0.92 , 1.11)	0.82
Current	Broad Stress (Other life stress <5 years prior or childhood maltreatment)	16	15068	Sex	0.62	(0.55 , 0.69)	7.0E-19
				Stress	2.75	(2.27 , 3.31)	7.3E-26
				Gene	1.04	(0.94 , 1.16)	0.43
				Gene x stress	0.93	(0.80 , 1.07)	0.31
Lifetime	Broad Stress (Other life stress or Childhood maltreatment)	25	30286	Sex	0.61	(0.57 , 0.65)	8.8E-62
				Stress	2.14	(1.94 , 2.35)	4.4E-53
				Gene	1.01	(0.95 , 1.07)	0.77
				Gene x stress	1.01	(0.94 , 1.10)	0.74
Current	Broad Stress (Other life stress or Childhood maltreatment)	18	17432	Sex	0.62	(0.56 , 0.68)	2.0E-24
				Stress	2.46	(2.04 , 2.96)	3.6E-21
				Gene	1.08	(0.95 , 1.23)	0.27
				Gene x stress	0.91	(0.78 , 1.06)	0.22

Sex (female = 0; male = 1)
Stress (not exposed = 0; exposed = 1)
Gene (additive coding in number of S alleles for 5-HTTLPR (LL = 0; LS=1; SS=2))
Broad stress does not require both stressors to be assessed.

MODEL: $depression = \beta_0 + \beta_1(study) + \beta_2(sex) + \beta_3(stress) + \beta_4(gene) + \beta_5(gene \times stress)$

Depression variable: **depression diagnosis**
Stress variable: **dichotomous stress exposure**

Because these were not meta-analyses, there are no forest plots for these analyses.

Secondary Analyses: As outlined in our protocol,[1] we performed secondary analyses to aid our interpretation of our primary results. In these analyses we varied several factors that might be expected to impact the relationship between stress, 5-HTTLPR variation, and depression outcomes. Secondary analyses investigated the following: (1) narrower diagnostic criteria for major depression, (2) analyses stratified by sex, (3) alternatives to coding the genetic term as additive in the number of S alleles, and (4) limiting analyses to data from longitudinal studies, which might be expected to minimize effects of recall bias.

Secondary Analysis 1: Restricting diagnosis to DSM or ICD criteria. All the studies that assessed lifetime depression used DSM or ICD criteria. However, several studies that assessed current depression could not be harmonized to one of these two systems. Supplemental Table S13 presents the analog of Table 1 if we restrict the data to subjects with depression diagnosis based on DSM-IV or ICD-10. The findings are essentially the same as the meta-analysis results using all studies that were able to construct a depression diagnosis. One interaction term is nominally significant, but the direction of effect is opposite of the hypothesis.

Supplemental Table S13. Meta-analysis of subjects of all ages based on depression diagnosis limited to DSM-IV or ICD-10 criteria and stress exposure

Depression	Stress	Studies	Subjects	Covariate	OR	95% CI	p-value
Lifetime	Child Maltreatment	18	21135	Sex	0.57	(0.50 , 0.66)	1.4E-15
				Stress	2.16	(1.70 , 2.82)	1.7E-8
				Gene	1.00	(0.95 , 1.05)	0.95
				Gene x stress	1.05	(0.91 , 1.21)	0.49
Current	Child Maltreatment	9	10081	Sex	0.61	(0.49 , 0.74)	9.8E-7
				Stress	2.71	(1.50 , 4.88)	8.7E-4
				Gene	1.03	(0.93 , 1.13)	0.61
				Gene x stress	0.88	(0.70 , 1.13)	0.32
Lifetime	Broad stress (Other life stress <5 years prior or childhood maltreatment)	19	21938	Sex	0.58	(0.51 , 0.67)	2.9E-15
				Stress	1.82	(1.39 , 2.39)	1.4E-05
				Gene	1.00	(0.95 , 1.06)	0.95
				Gene x stress	1.06	(0.93 , 1.20)	0.40
Current	Broad stress (Other life stress <5 years prior or childhood maltreatment)	10	9960	Sex	0.61	(0.51 , 0.73)	2.0E-7
				Stress	3.18	(1.76 , 5.73)	1.3E-4
				Gene	1.05	(0.92 , 1.19)	0.47
				Gene x stress	0.88	(0.71 , 1.09)	0.24
Lifetime	Broad stress (Other life stress or childhood maltreatment)	21	28252	Sex	0.60	(0.53 , 0.67)	1.1E-16
				Stress	2.00	(1.56 , 2.56)	3.8E-8
				Gene	1.00	(0.94 , 1.07)	0.92
				Gene x stress	1.05	(0.94 , 1.16)	0.38
Current	Broad stress (Other life stress or childhood maltreatment)	12	12936	Sex	0.54	(0.44 , 0.68)	5.3E-8
				Stress	2.74	(1.45 , 5.16)	1.9E-3
				Gene	1.26	(1.05 , 1.52)	0.01
				Gene x stress*	0.74	(0.59 , 0.93)	0.01

Sex (female = 0; male = 1)
Stress (not exposed = 0; exposed = 1)
Gene (additive coding in number of S alleles for 5-HTTLPR (LL = 0; LS=1; SS=2))
Broad stress does not require both stressors to be assessed.

MODEL: $depression = \beta_0 + \beta_1(age) + \beta_2(sex) + \beta_3(stress) + \beta_4(gene) + \beta_5(gene \times stress)$

Depression variable: **depression diagnosis**
Stress variable: **dichotomous stress exposure**
Age was not significant in any of the models

Forest plots for the interaction terms for these analyses are in Figure S11.

*Nominally significant, but ***NOT*** in the hypothesized direction of effect

Secondary Analysis 2: Analyses stratified by sex. Stratified analyses examined whether the hypothesized interaction might be stronger in a single sex (**Supplemental Table S14)**. Although the impact of stress on the diagnosis of depression is strong and consistent across analyses in both sex strata, we do not observe a statistically significant interaction in any of these analyses.

Supplemental Table S14: Stratified (by sex) meta-analyses of subjects of all ages based on depression diagnosis and stress exposure

S14a: Females Only

Depression	Stress	Studies	Subjects	Covariate	OR	95% CI	p-value
Lifetime	Child Maltreatment	19	12484	Stress	2.09	(1.50 , 2.82)	1.6E-6
				Gene	0.97	(0.90 , 1.03)	0.32
				Gene x stress	1.09	(0.92 , 1.30)	0.31
Current	Child Maltreatment	13	7471	Stress	3.14	(1.90 , 5.32)	2.1E-5
				Gene	1.01	(0.90 , 1.14)	0.81
				Gene x stress	0.90	(0.70 , 1.15)	0.4
Lifetime	Broad stress (Other life stress <5 years prior or childhood maltreatment)	20	13074	Stress	1.80	(1.33 , 2.44)	1.5E-4
				Gene	0.97	(0.90 , 1.03)	0.32
				Gene x stress	1.09	(0.94 , 1.28)	0.25
Current	Broad stress (Other life stress <5 years prior or childhood maltreatment)	13	7286	Stress	3.18	(1.90 , 5.33)	1.1E-5
				Gene	1.06	(0.89 , 1.26)	0.51
				Gene x stress	0.85	(0.68 , 1.08)	0.19
Lifetime	Broad stress (Other life stress or childhood maltreatment)	23	17721	Stress	2.06	(1.58 , 2.67)	6.5E-08
				Gene	0.99	(0.91 , 1.07)	0.76
				Gene x stress	1.05	(0.92 , 1.21)	0.44
Current	Broad stress (Other life stress or childhood maltreatment)	17	9334	Stress	2.44	(1.41 , 4.23)	1.5E-3
				Gene	1.14	(0.89 , 1.46)	0.29
				Gene x stress	0.82	(0.58 , 1.14)	0.23

S14b: Males Only

Depression	Stress	Studies	Subjects	Covariate	OR	95% CI	p-value
Lifetime	Child Maltreatment	15	8665	Stress	2.27	(1.72 , 3.00)	8.8E-9
				Gene	1.05	(0.96 , 1.14)	0.30
				Gene x stress	0.97	(0.75 , 1.26)	0.84
Current	Child Maltreatment	13	6485	Stress	2.30	(1.47 , 3.62)	2.9E-4
				Gene	0.99	(0.86 , 1.13)	0.84
				Gene x stress	1.03	(0.72 , 1.48)	0.88
Lifetime	Broad stress (Other life stress <5 years prior or childhood maltreatment)	17	9012	Stress	1.77	(1.25 , 2.51)	1.2E-3
				Gene	1.05	(0.96 , 1.15)	0.25
				Gene x stress	1.00	(0.81 , 1.24)	0.99
Current	Broad stress (Other life stress <5 years prior or childhood maltreatment)	14	6407	Stress	2.36	(1.61 , 3.46)	1.2E-5
				Gene	1.00	(0.84 , 1.18)	0.97
				Gene x stress	1.00	(0.74 , 1.36)	0.98
Lifetime	Broad stress (Other life stress or childhood maltreatment)	20	11442	Stress	2.08	(1.61 , 2.67)	1.3E-8
				Gene	1.04	(0.94 , 1.16)	0.46
				Gene x stress	1.04	(0.87 , 1.24)	0.68
Current	Broad stress (Other life stress or childhood maltreatment)	17	7690	Stress	2.52	(1.70 , 3.73)	3.9E-6
				Gene	1.12	(0.89 , 1.40)	0.34
				Gene x stress	0.91	(0.65 , 1.28)	0.61

Stress (not exposed = 0; exposed = 1)
Gene (additive coding in number of S alleles for 5-HTTLPR (LL = 0; LS=1; SS=2))
Broad stress does not require both stressors to be assessed.
MODEL: $depression = \beta_0 + \beta_1(age) + \beta_2(stress) + \beta_3(gene) + \beta_4(gene \times stress)$
Depression variable: **depression diagnosis**
Stress variable: **dichotomous stress exposure**
Age was not significant in any of the models

Forest plots for the interaction terms for these analyses are in Figure S12

Secondary Analysis 3: Alternate Genetic Coding. Our primary analyses were based on an additive coding of the 5-HTTLPR L vs S genotypes (coded as the number of S alleles carried).

Coding the S allele as dominant contrasts the carriers of L/L to individuals who carry at least 1 copy of the S allele (L/S or S/S). Coding the S allele as recessive contrasts the carriers of S/S to individuals who carry at least 1 copy of the L allele (L/S or L/L). Our third alternate genetic coding used haplotypes based on the L/S variant and the single nucleotide polymorphism rs25531: This coding contrasts the L variant that also carries the A allele for rs25531 (L_A) with all others (L_G, S_A, S_G). To be analogous to the coding for the Primary Analyses, L_A/L_A was coded = 0, L_A/other = 1, and other/other = 2. Results analogous to those listed in Table 1, but using these three alternate codings for the genetic term are listed in Supplemental Table S15.

All of the analyses using dominant coding resulted in non-significant point estimates for the interaction term in the opposite direction from the hypothesis. One recessive analysis (Lifetime depression diagnosis; broad stress (childhood maltreatment or other life stress where the relative timing of life stress and depression may be unknown), resulted in a nominally significant interaction term (p = 0.02) in the hypothesized direction of effect (OR = 1.25). For all the recessive coding analyses examining current depression diagnosis as the outcome, the point estimates of the interaction terms were in the reverse direction (but not nominally significant). None of the analyses based on additive coding of the L_A haplotype were even nominally significant.

Supplemental Table S15: Meta-analysis of subjects of all ages based on depression diagnosis and stress exposure using alternate coding for the genetic term

S15a: Coding S allele as dominant

Depression	Stress	Studies	Subjects	Covariate	OR	95% CI	p-value
Lifetime	Child Maltreatment	17	20858	Sex	0.569	(0.50 , 0.65)	1.1E-15
				Stress	2.26	(1.70 , 2.98)	5.6E-9
				Gene	0.99	(0.91 , 1.07)	0.72
				Gene x stress	0.99	(0.81 , 1.22)	0.95
Current	Child Maltreatment	13	13956	Sex	0.63	(0.51 , 0.79)	4.2E-5
				Stress	2.83	(1.85 , 4.35)	1.9E-6
				Gene	1.00	(0.88 , 1.15)	0.96
				Gene x stress	0.85	(0.63 , 1.15)	0.29
Lifetime	Broad stress (Other life stress <5 years prior or childhood maltreatment)	18	21661	Sex	0.58	(0.51 , 0.66)	2.8E-15
				Stress	1.94	(1.47 , 2.57)	3.7E-6
				Gene	1.00	(0.93 , 1.09)	0.92
				Gene x stress	0.97	(0.80 , 1.16)	0.70
Current	Broad stress (Other life stress <5 years prior or childhood maltreatment)	13	13556	Sex	0.63	(0.51 , 0.79)	4.0E-5
				Stress	3.05	(2.03 , 4.58)	6.9E-8
				Gene	1.02	(0.85 , 1.23)	0.82
				Gene x stress	0.87	(0.66 , 1.15)	0.33
Lifetime	Broad stress (Other life stress or childhood maltreatment)	20	27975	Sex	0.59	(0.53 , 0.67)	5.3E-17
				Stress	2.15	(1.67 , 2.77)	3.4E-9
				Gene	1.03	(0.93 , 1.14)	0.52
				Gene x stress	0.95	(0.82 , 1.11)	0.54
Current	Broad stress (Other life stress or childhood maltreatment)	16	16715	Sex	0.60	(0.49 , 0.75)	7.4E-6
				Stress	2.57	(1.62 , 4.08)	6.0E-5
				Gene	1.07	(0.78 , 1.46)	0.69
				Gene x stress	0.84	(0.56 , 1.26)	0.39

S15b: Coding S allele as recessive

Depression	Stress	Studies	Subjects	Covariate	OR	95% CI	p-value
Lifetime	Child Maltreatment	16	20605	Sex	0.59	(0.51 , 0.67)	6.9E-14
				Stress	2.14	(1.67 , 2.89)	2.1E-8
				Gene	1.00	(0.89 , 1.12)	0.99
				Gene x stress	1.18	(0.90 , 1.53)	0.23
Current	Child Maltreatment	10	12802	Sex	0.61	(0.48 , 0.78)	4.7E-5
				Stress	2.43	(1.52 , 3.88)	2.0E-4
				Gene	1.00	(0.85 , 1.18)	1.00
				Gene x stress	1.10	(0.75 , 1.62)	0.61
Lifetime	Broad stress (Other life stress <5 years prior or childhood maltreatment)	17	21431	Sex	0.59	(0.52 , 0.68)	6.7E-14
				Stress	1.89	(1.40 , 2.55)	3.0E-5
				Gene	0.99	(0.89 , 1.11)	0.91
				Gene x stress	1.24	(0.99 , 1.56)	0.06
Current	Broad stress (Other life stress <5 years prior or childhood maltreatment)	10	12426	Sex	0.61	(0.49 , 0.77)	4.1E-5
				Stress	2.34	(1.38 , 3.96)	1.6E-03
				Gene	0.99	(0.81 , 1.21)	0.94
				Gene x stress	0.97	(0.69 , 1.38)	0.88
Lifetime	Broad stress (Other life stress or childhood maltreatment)	20	28084	Sex	0.61	(0.53 , 0.69)	3.0E-15
				Stress	1.96	(1.53 , 2.52)	1.0E-7
				Gene	0.98	(0.86 , 1.12)	0.75
				Gene x stress*	1.25	(1.04 , 1.51)	0.02
Current	Broad stress (Other life stress or childhood maltreatment)	15	16337	Sex	0.58	(0.46 , 0.72)	1.2E-6
				Stress	2.14	(1.25 , 3.68)	0.01
				Gene	1.17	(0.92 , 1.49)	0.20
				Gene x stress	0.85	(0.61 , 1.18)	0.33

S15c: Coding L_A haplotype as additive

Depression	Stress	Studies	Subjects	Covariate	OR	95% CI	p-value
Lifetime	Child Maltreatment	13	14530	Sex	0.55	(0.46 , 0.65)	2.1E-12
				Stress	2.19	(1.50 , 3.12)	1.5E-5
				Gene	1.00	(0.94 , 1.06)	0.90
				Gene x stress	1.03	(0.87 , 1.21)	0.75
Current	Child Maltreatment	6	5743	Sex	0.59	(0.44 , 0.80)	5.8E-4
				Stress	2.66	(1.20 , 6.05)	0.02
				Gene	1.01	(0.89 , 1.14)	0.89
				Gene x stress	0.89	(0.62 , 1.29)	0.55
Lifetime	Broad stress (Other life stress <5 years prior or childhood maltreatment)	14	15423	Sex	0.56	(0.48 , 0.66)	7.3E-12
				Stress	1.86	(1.35 , 2.57)	1.5E-4
				Gene	1.00	(0.94 , 1.06)	1.00
				Gene x stress	1.06	(0.91 , 1.24)	0.44
Current	Broad stress (Other life stress <5 years prior or childhood maltreatment)	7	5547	Sex	0.60	(0.46 , 0.79)	2.8E-4
				Stress	3.14	(1.33 , 7.41)	0.01
				Gene	1.02	(0.89 , 1.17)	0.79
				Gene x stress	0.77	(0.53 , 1.11)	0.16
Lifetime	Broad stress (Other life stress or childhood maltreatment)	15	19664	Sex	0.58	(0.49 , 0.68)	1.7E-11
				Stress	2.03	(1.46 , 2.82)	2.8E-5
				Gene	1.01	(0.94 , 1.08)	0.80
				Gene x stress	1.05	(0.93 , 1.18)	0.44
Current	Broad stress (Other life stress or childhood maltreatment)	8	7028	Sex	0.65	(0.49 , 0.86)	2.3E-3
				Stress	1.97	(0.80 , 4.83)	0.14
				Gene	1.16	(0.95 , 1.42)	0.16
				Gene x stress	0.76	(0.54 , 1.09)	0.14

Sex (female = 0; male = 1)
Stress (not exposed = 0; exposed = 1)
Broad stress does not require both stressors to be assessed.

MODEL: $depression = \beta_0 + \beta_1(age) + \beta_2(sex) + \beta_3(stress) + \beta_4(gene) + \beta_5(gene \times stress)$

Depression variable: **depression diagnosis**
Stress variable: **dichotomous stress exposure**

Age was not significant in any of the models

Forest plots for the interaction terms for these analyses are in Figure S13.

*Nominally significant **with** the hypothesized direction of effect.

Secondary Analysis 4: Analyses based on data from longitudinal studies only. It is necessary for stress to precede depression in order for it to cause a depressive episode. Because longitudinal studies have the potential to minimize noise from recall bias and otherwise provide cleaner historical information on subjects, we investigated whether analyzing only the longitudinal dataset would increase power to detect the hypothesized interaction (Supplemental Table S16). None of the interaction terms were statistically significant and for 4 of the 6 meta-analyses, the point estimates were not in the hypothesized direction.

Supplemental Table S16: Meta-analyses of subjects of all ages based on depression diagnosis and stress exposure using only longitudinal study data

Depression	Stress	Studies	Subjects	Covariate	OR	95% CI	p-value
Lifetime	Child Maltreatment	5	4711	Sex	0.47	(0.38 , 0.59)	9.6E-12
				Stress	2.87	(2.10 , 4.00)	7.0E-10
				Gene	1.03	(0.93 , 1.14)	0.62
				Gene x stress	0.87	(0.65 , 1.17)	0.36
Current	Child Maltreatment	6	5534	Sex	0.55	(0.36 , 0.82)	3.9E-3
				Stress	3.10	(2.10 , 4.50)	2.8E-9
				Gene	1.07	(0.91 , 1.27)	0.42
				Gene x stress	0.96	(0.69 , 1.33)	0.79
Lifetime	Broad stress (Other life stress <5 years prior or childhood maltreatment)	5	4408	Sex	0.51	(0.37 , 0.71)	5.1E-5
				Stress	1.71	(1.21 , 2.43)	2.6E-3
				Gene	0.98	(0.86 , 1.13)	0.81
				Gene x stress	1.08	(0.85 , 1.39)	0.52
Current	Broad stress (Other life stress <5 years prior or childhood maltreatment)	7	5422	Sex	0.57	(0.40 , 0.82)	2.5E-3
				Stress	3.90	(2.43 , 6.24)	1.5E-08
				Gene	1.17	(0.88 , 1.55)	0.28
				Gene x stress	0.85	(0.59 , 1.21)	0.36
Lifetime	Broad stress (Other life stress or childhood maltreatment)	5	6868	Sex	0.52	(0.35 , 0.78)	1.3E-3
				Stress	2.36	(1.73 , 3.21)	5.7E-08
				Gene	0.99	(0.81 , 1.21)	0.92
				Gene x stress	1.05	(0.87 , 1.26)	0.64
Current	Broad stress (Other life stress or childhood maltreatment)	7	5527	Sex	0.57	(0.40 , 0.81)	2.0E-3
				Stress	3.92	(2.54 , 6.03)	5.4E-10
				Gene	1.15	(0.82 , 1.63)	0.41
				Gene x stress	0.88	(0.60 , 1.29)	0.50

Sex (female = 0; male = 1)
Stress (not exposed = 0; exposed = 1)
Gene (additive coding in number of S alleles for 5-HTTLPR (LL = 0; LS=1; SS=2))
Broad stress does not require both stressors to be assessed.

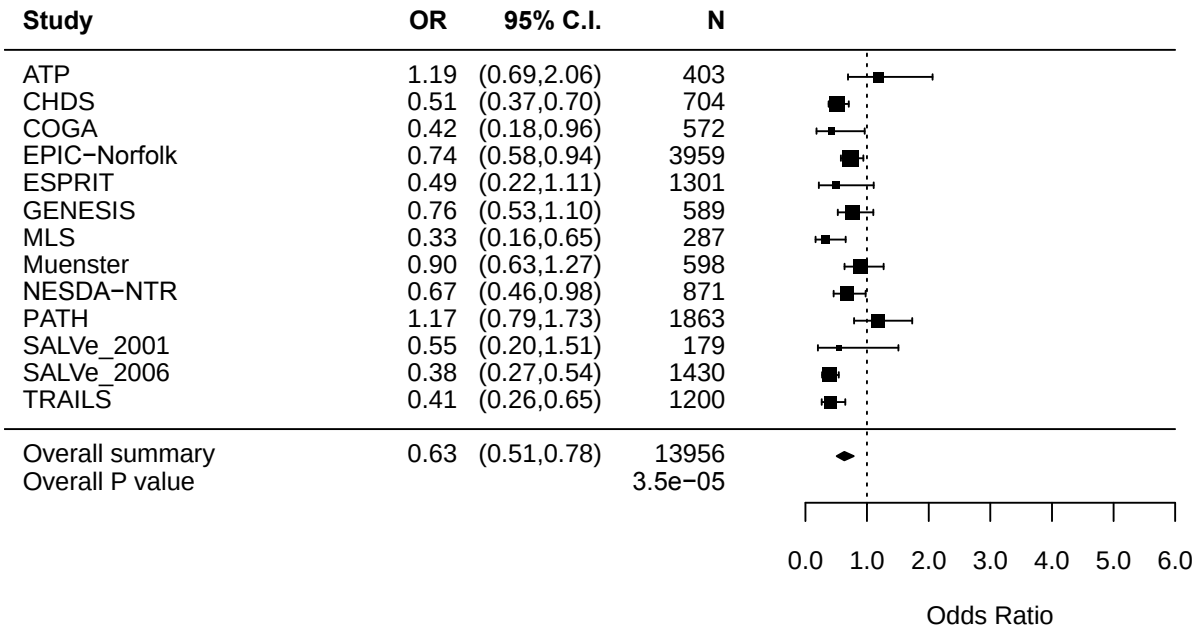
MODEL: $depression = \beta_0 + \beta_1(age) + \beta_2(sex) + \beta_3(stress) + \beta_4(gene) + \beta_5(gene \times stress)$

Depression variable: **depression diagnosis**
Stress variable: **dichotomous stress exposure**
Age was not significant in any of the models

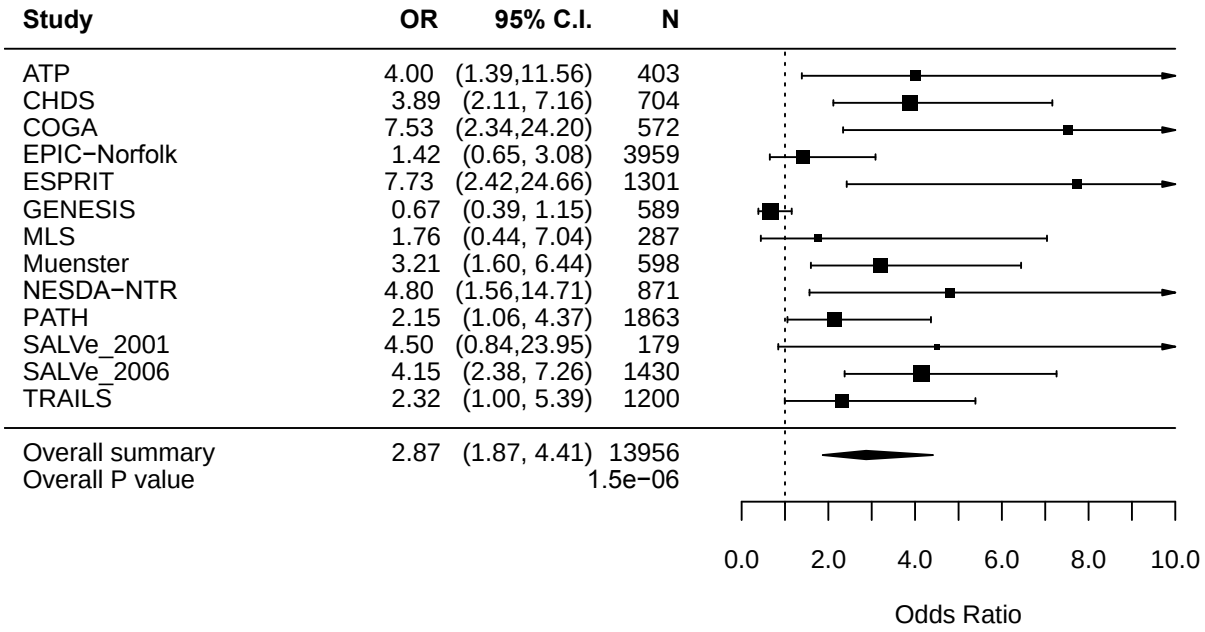
Forest plots for the interaction terms for these analyses are in Figure S14.

Supplemental Figures:

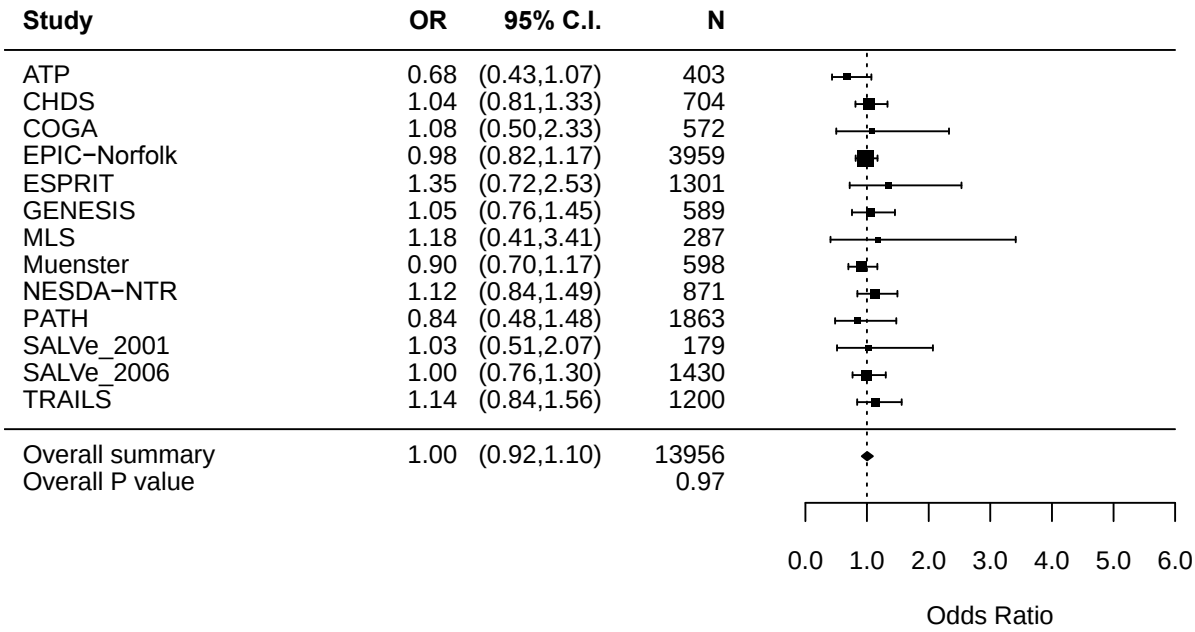
Figure S1: Forest plots for sex, stress, gene, and gene x stress terms from the model based on current depression diagnosis, exposure to childhood maltreatment, and subjects of all ages. (Corresponds to an analysis in Table 1)



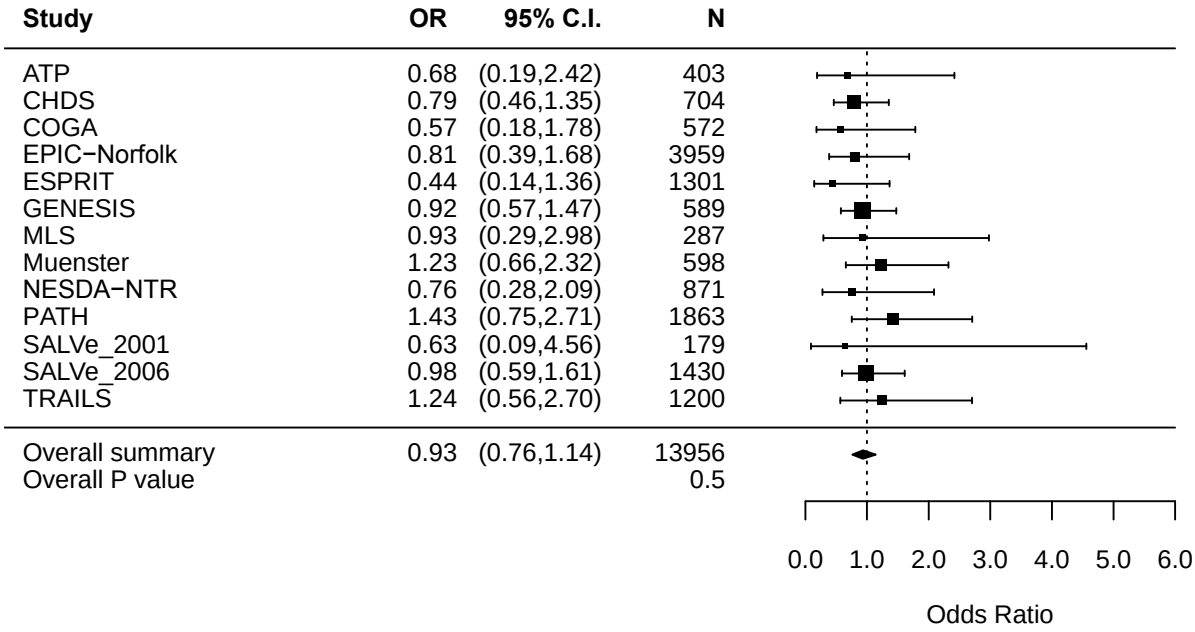
S1a. **Sex** (female = 0; male = 1) Thus, female is the reference.
Being male is associated with a lower risk of developing depression.



S1b. **Stress** (childhood maltreatment)
Exposure to stress is associated with a higher risk of developing depression.



S1c. **Gene** (additively coded for number of S alleles) Thus, LL is the reference. The number of S alleles is not associated with risk for depression.



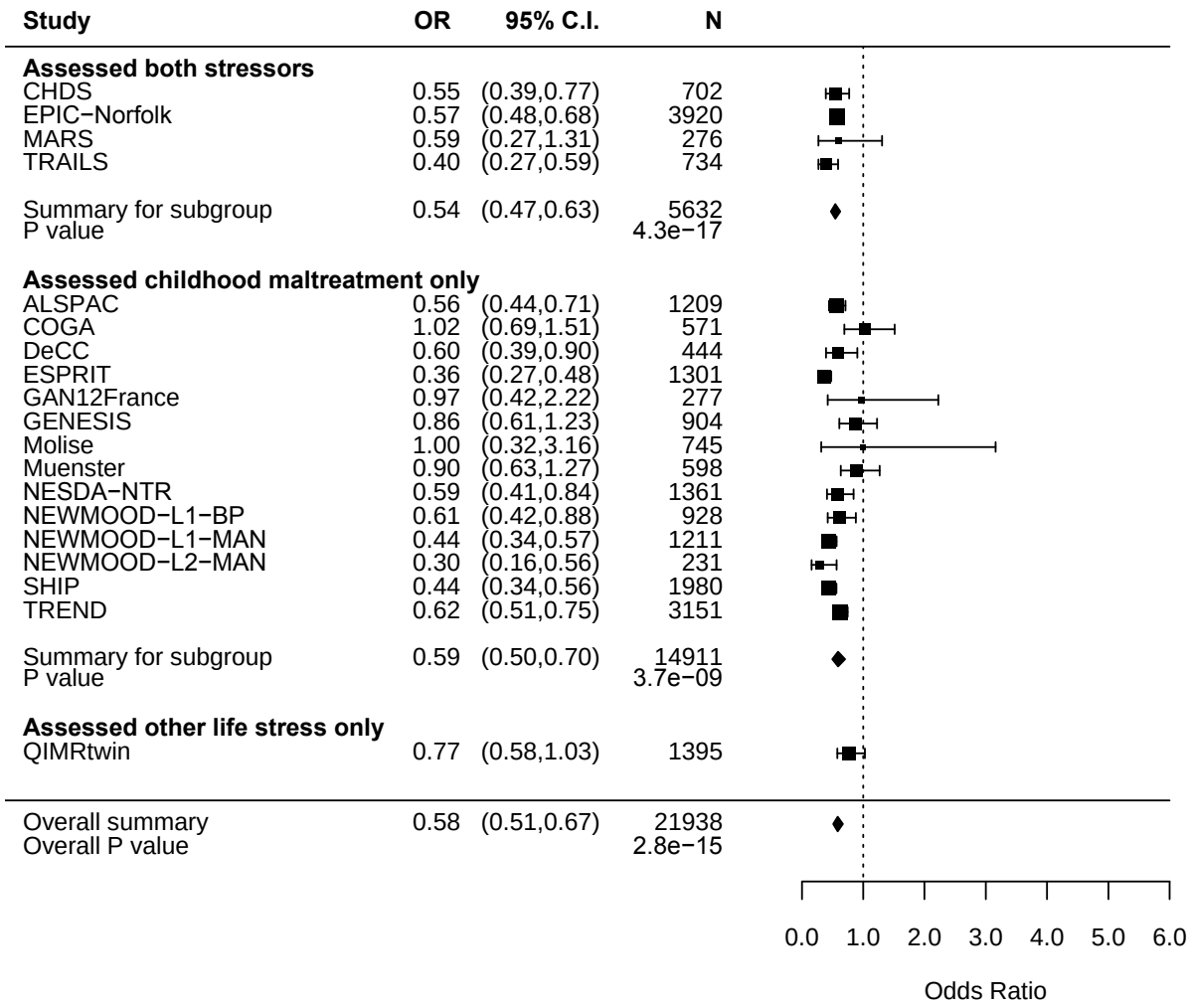
S1d. **Gene x Stress** (Note: the hypothesized direction of effect is an OR > 1)

Supplemental Figure S1: Forest plots for current depression diagnosis in subjects of all ages based on exposure to childhood maltreatment as the stressor (2nd analysis listed in Table 1)

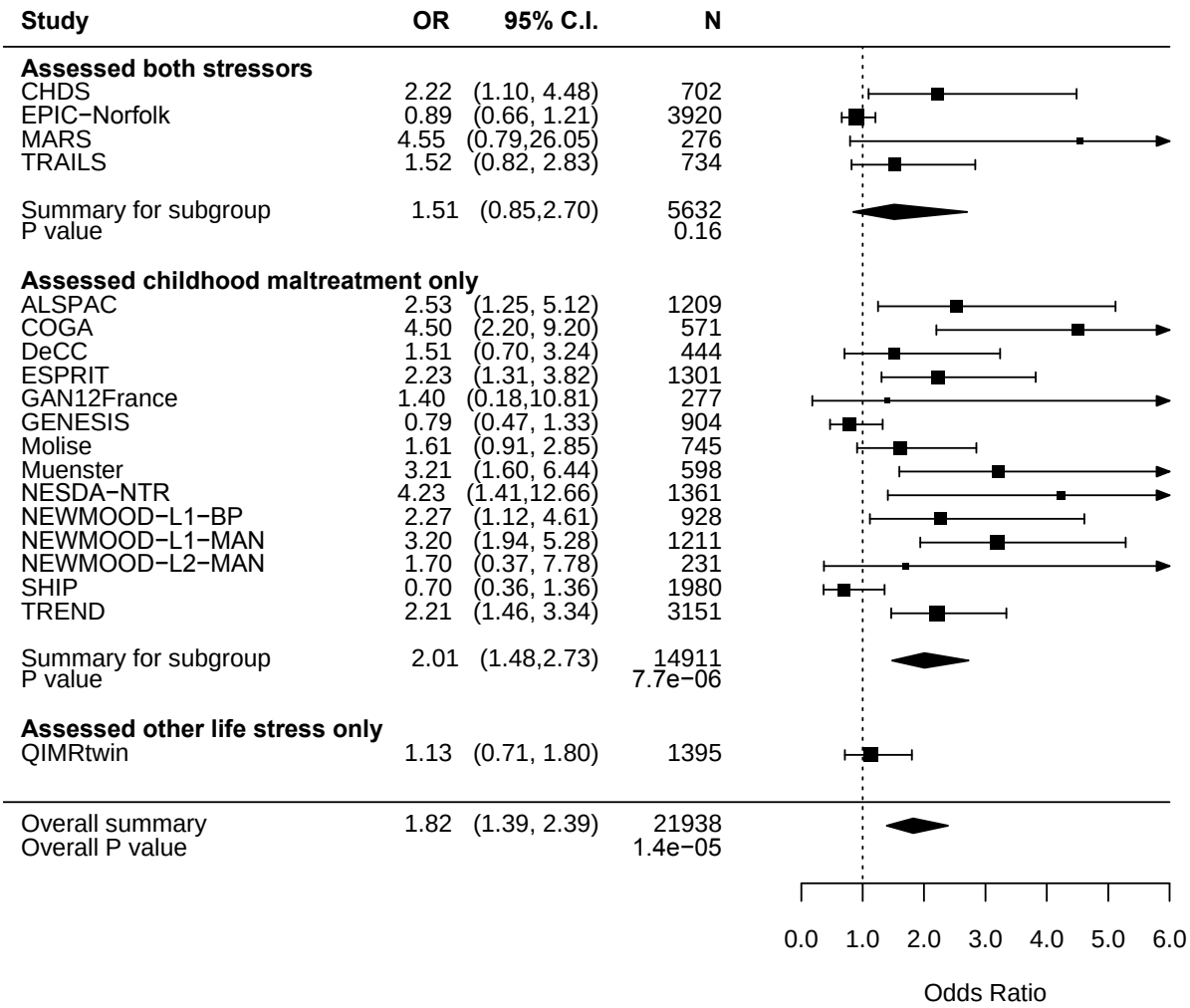
MODEL: $depression = \beta_0 + \beta_1(age) + \beta_2(sex) + \beta_3(stress) + \beta_4(gene) + \beta_5(gene \times stress)$

Depression (current depression diagnosis)
Sex (female = 0; male = 1)
Stress (childhood maltreatment)
Gene (additive coding in number of S alleles for 5-HTTLPR (LL = 0; LS=1; SS=2))

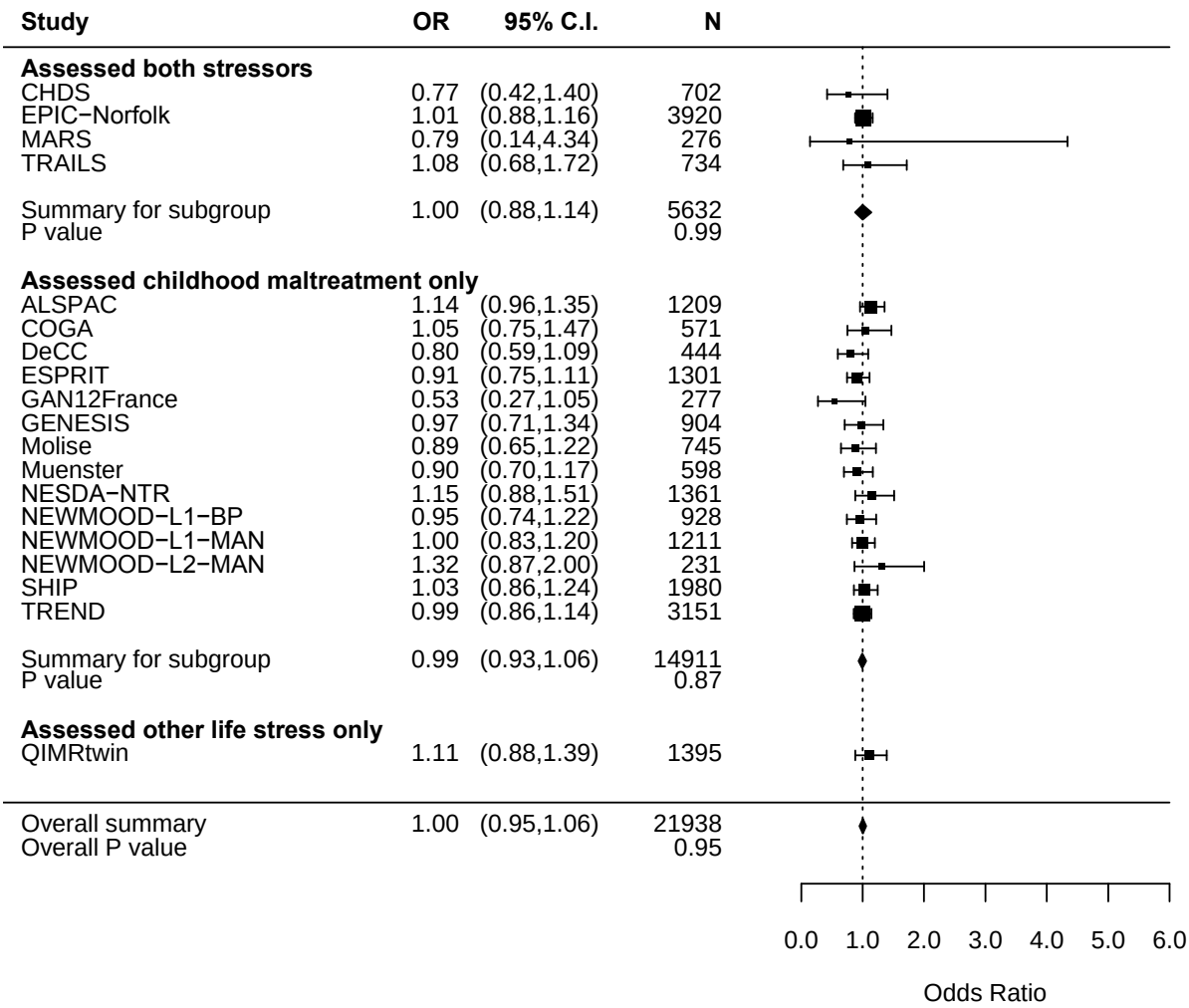
Figure S2: Forest plots for sex, stress, gene, and gene x stress terms from the model based on lifetime depression diagnosis, exposure to childhood maltreatment or other life stress known to have occurred in the 5 years prior to first depressive episode (or assessment if no depression), and subjects of all ages. (Corresponds to an analysis in Table 1)



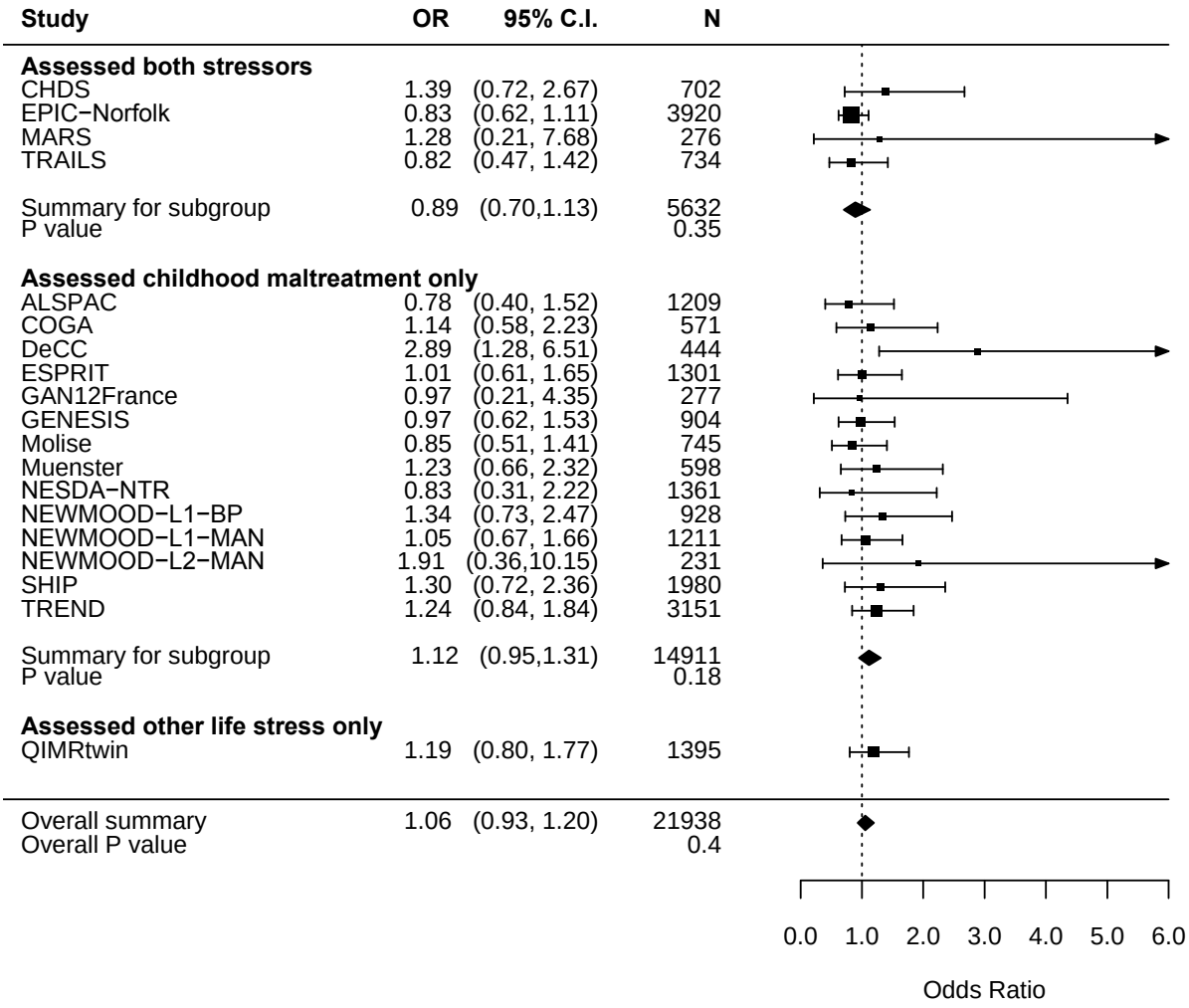
S2a. **Sex** (female = 0; male = 1) Thus, female is the reference.
Being male is associated with a lower risk of developing depression.



S2b. **Broad Stress** (other life stress < 5 years prior or childhood maltreatment) Exposure to stress is associated with a higher risk of developing depression.



S2c. **Gene** (additively coded for number of S alleles) Thus LL is the reference. The number of S alleles is not associated with risk for depression.



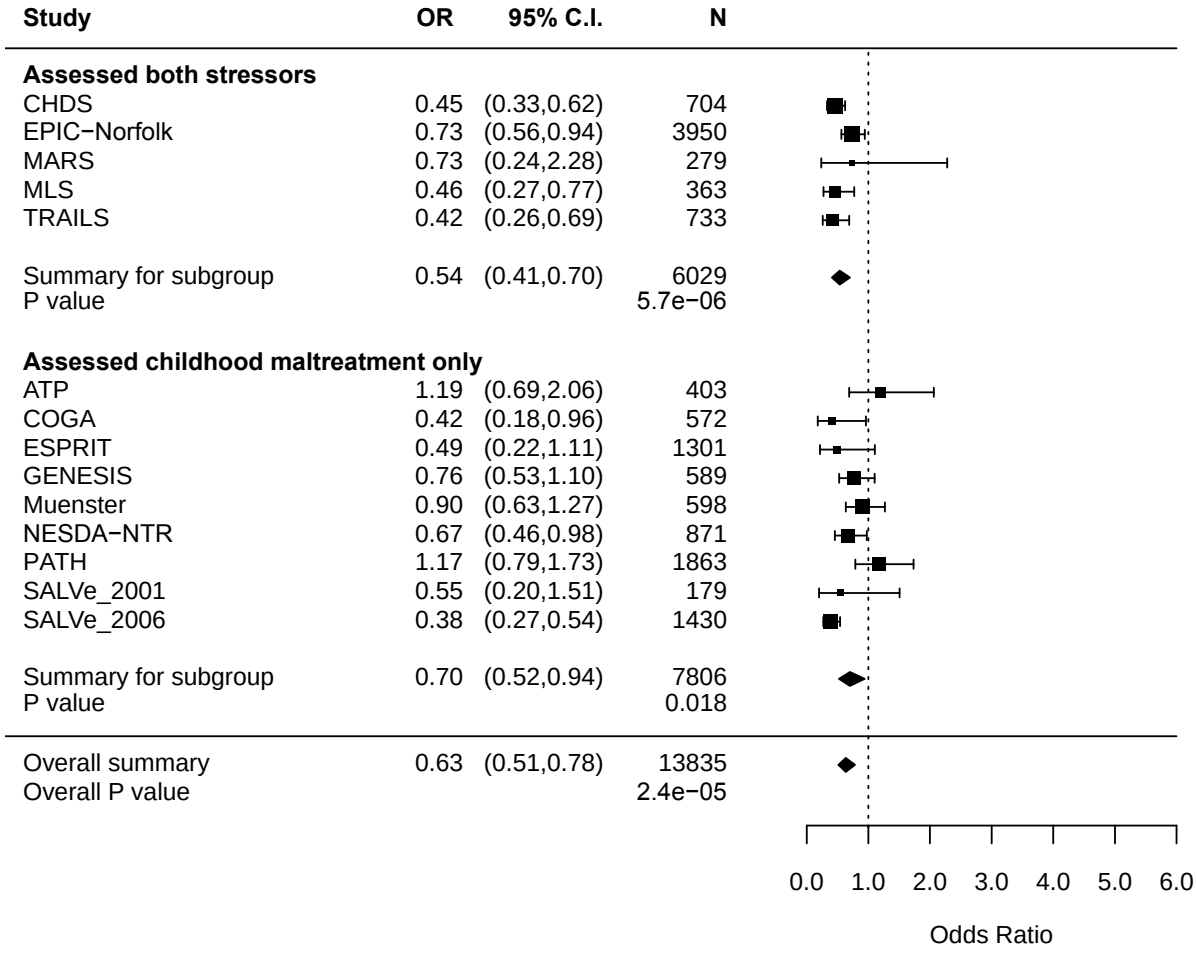
S2d. **Gene x Stress** (Note: the hypothesized direction of effect is an OR > 1)

Supplemental Figure S2: Forest plots for lifetime depression diagnosis in subjects of all ages based on exposure to broad stress (childhood maltreatment or other life stress) **where any other life stress must have occurred in the 5-years prior to first depressive episode** (or assessment, if no depression) (3rd analysis listed in Table 1)

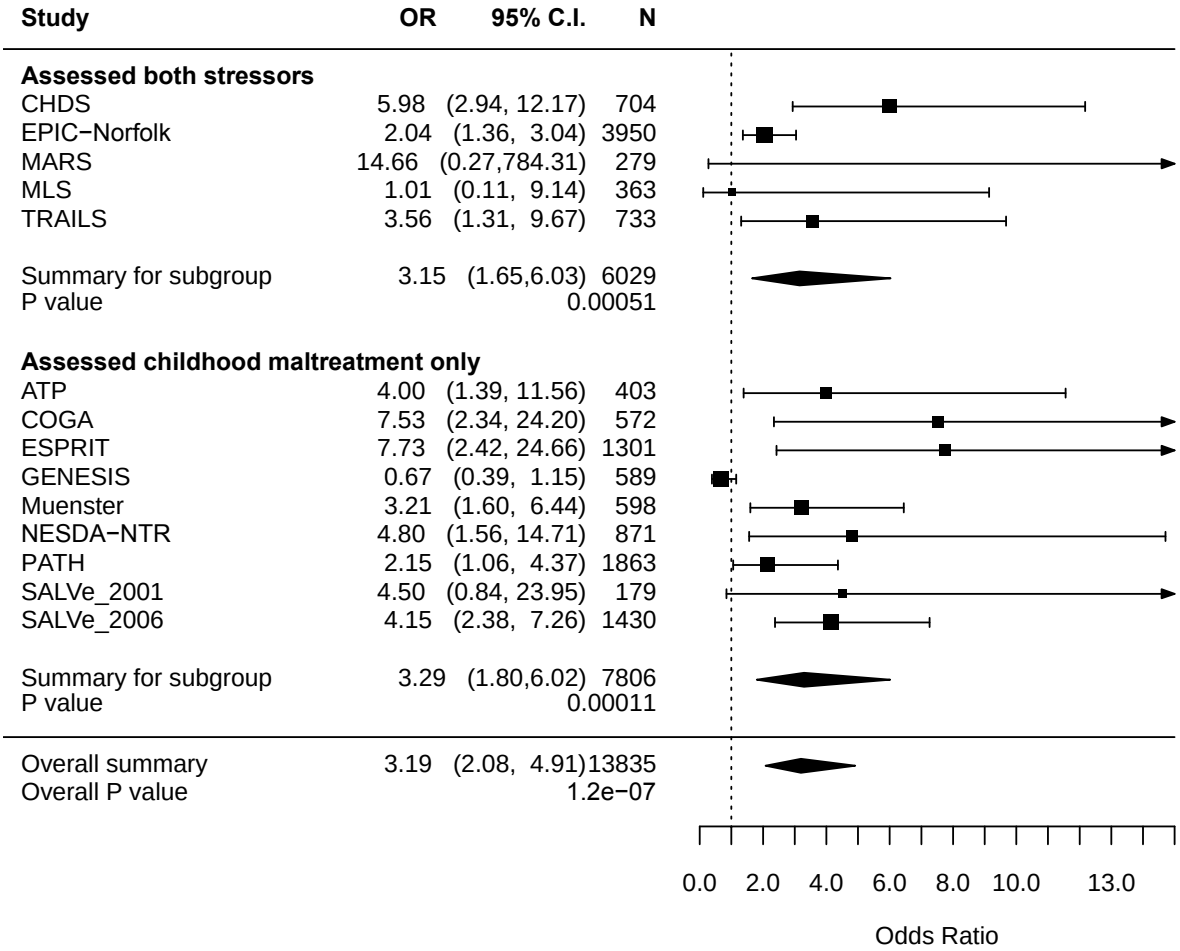
MODEL: $depression = \beta_0 + \beta_1(age) + \beta_2(sex) + \beta_3(stress) + \beta_4(gene) + \beta_5(gene \times stress)$

Depression (lifetime depression diagnosis)
Sex (female = 0; male = 1)
Stress (broad stress exposure; other life stress < 5 years prior or childhood maltreatment)
Gene (additive coding in number of S alleles for 5-HTTLPR (LL = 0; LS=1; SS=2))

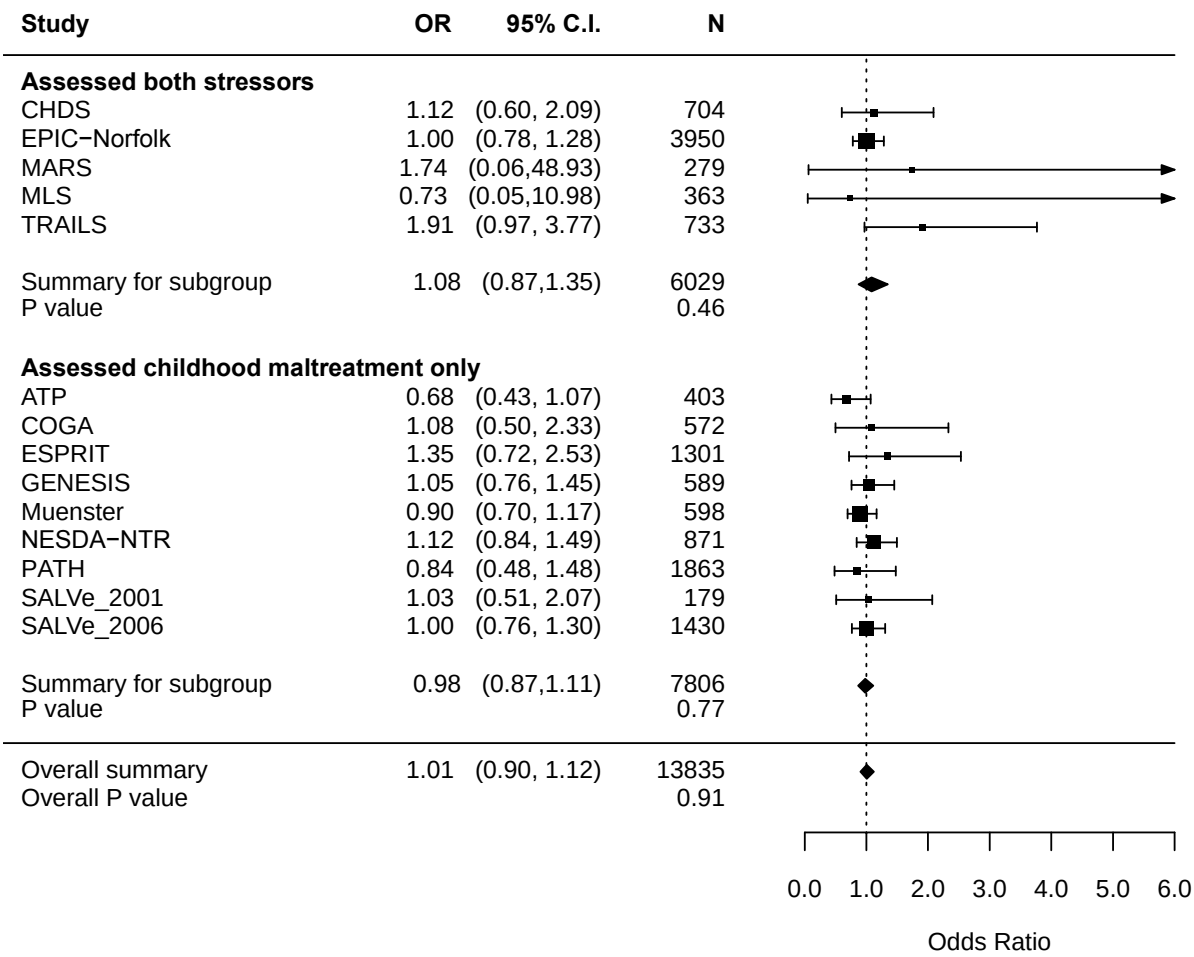
Figure S3: Forest plots for sex, stress, gene, and gene x stress terms from the model based on current depression diagnosis, exposure to childhood maltreatment or other life stress known to have occurred in the 5 years prior to the first depressive episode (or assessment if no depression), and subjects of all ages. (Corresponds to an analysis in Table 1)



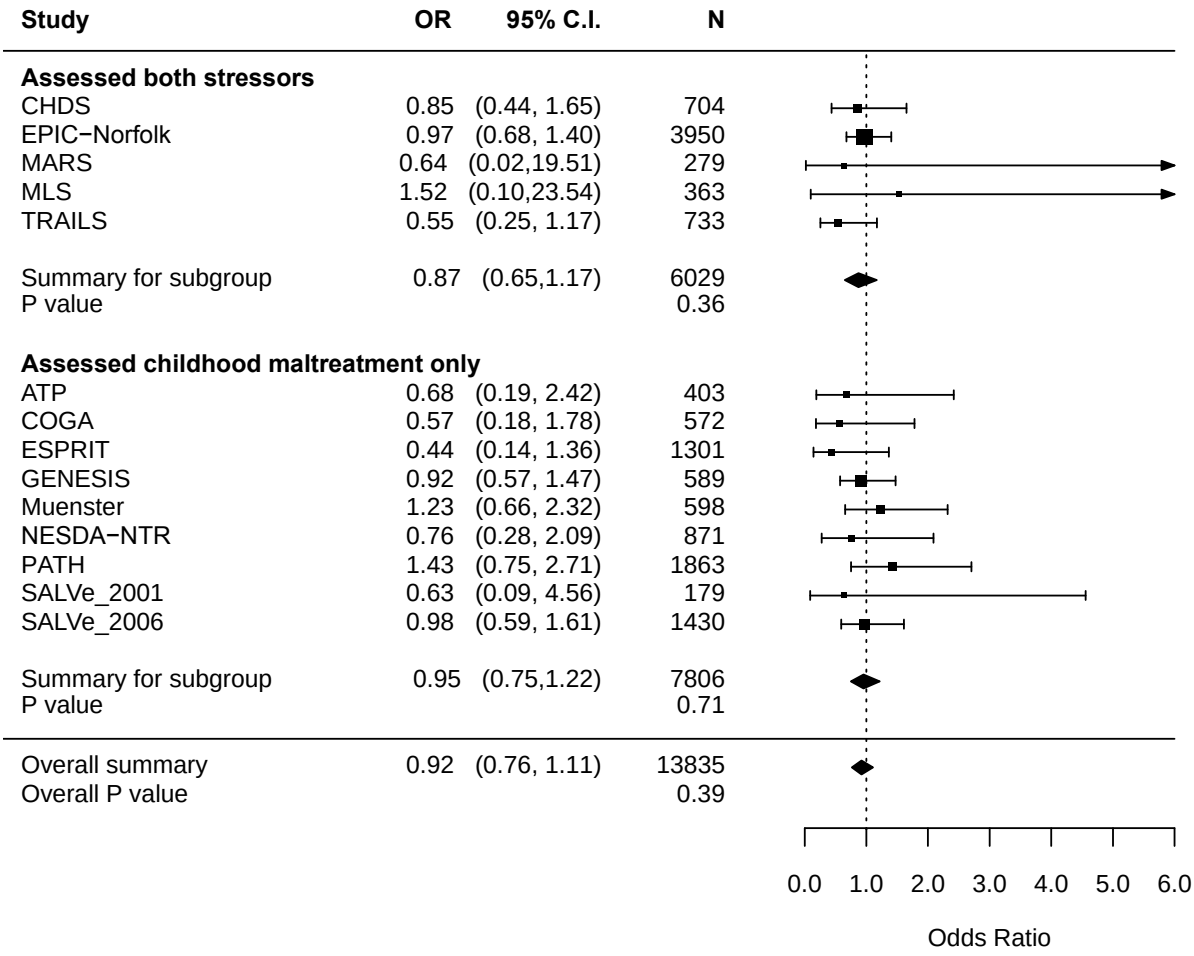
S3a. **Sex** (female = 0; male = 1) Thus, female is the reference.
Being male is associated with a lower risk of developing depression.



S3b. **Broad Stress** (other life stress < 5 years prior or childhood maltreatment) Exposure to stress is associated with a higher risk of developing depression.



S3c. **Gene** (additively coded for number of S alleles) Thus, LL is the reference. The number of S alleles is not associated with risk for depression.



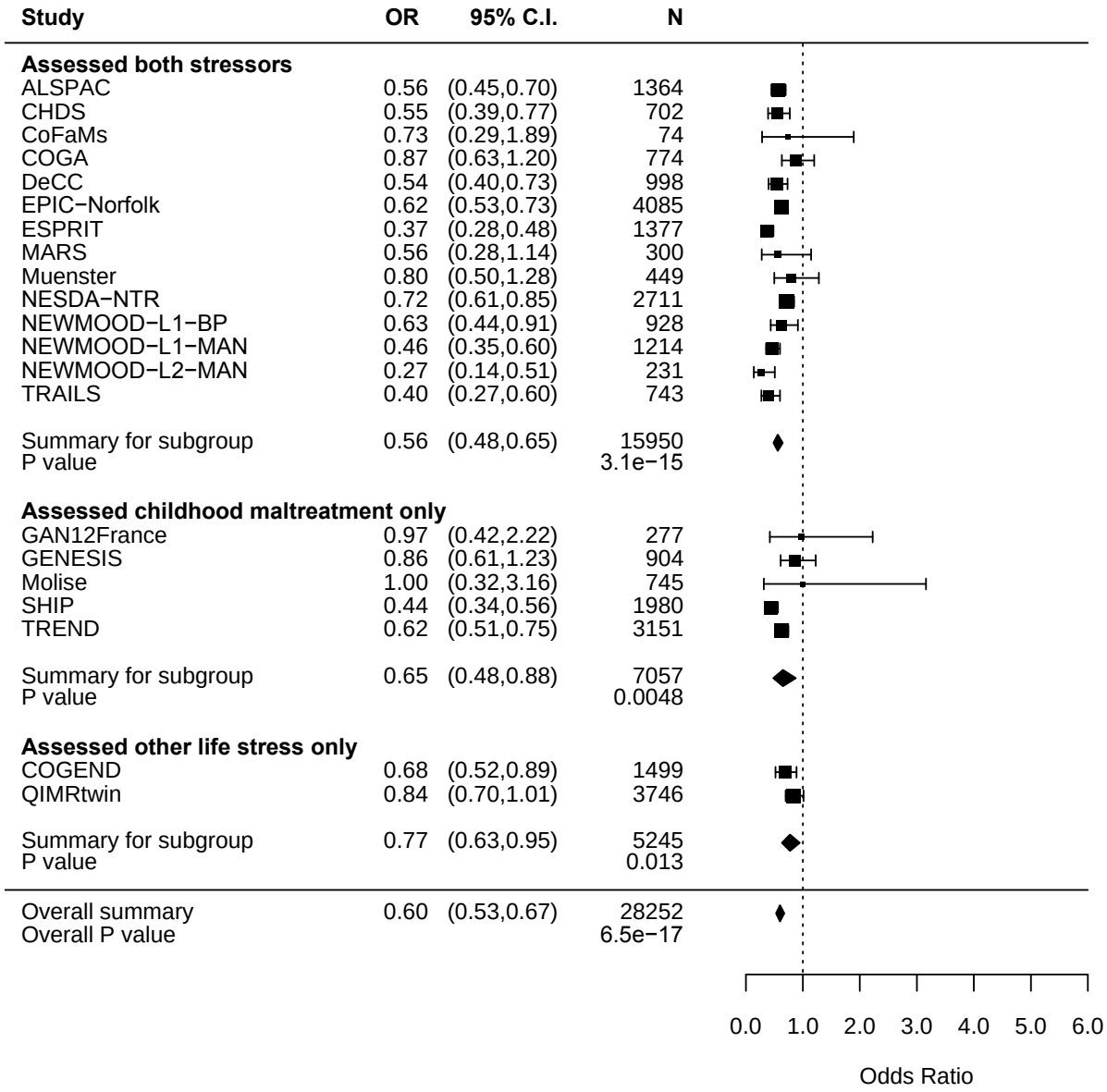
S3d. **Gene x Stress** (Note: the hypothesized direction of effect is an OR > 1)

Supplemental Figure S3: Forest plots for current depression diagnosis in subjects of all ages based on exposure to broad stress (childhood maltreatment or other life stress) where any other life stress must have occurred in the 5-years prior to first depressive episode (or assessment, if no depression) (4^{th} analysis listed in Table 1)

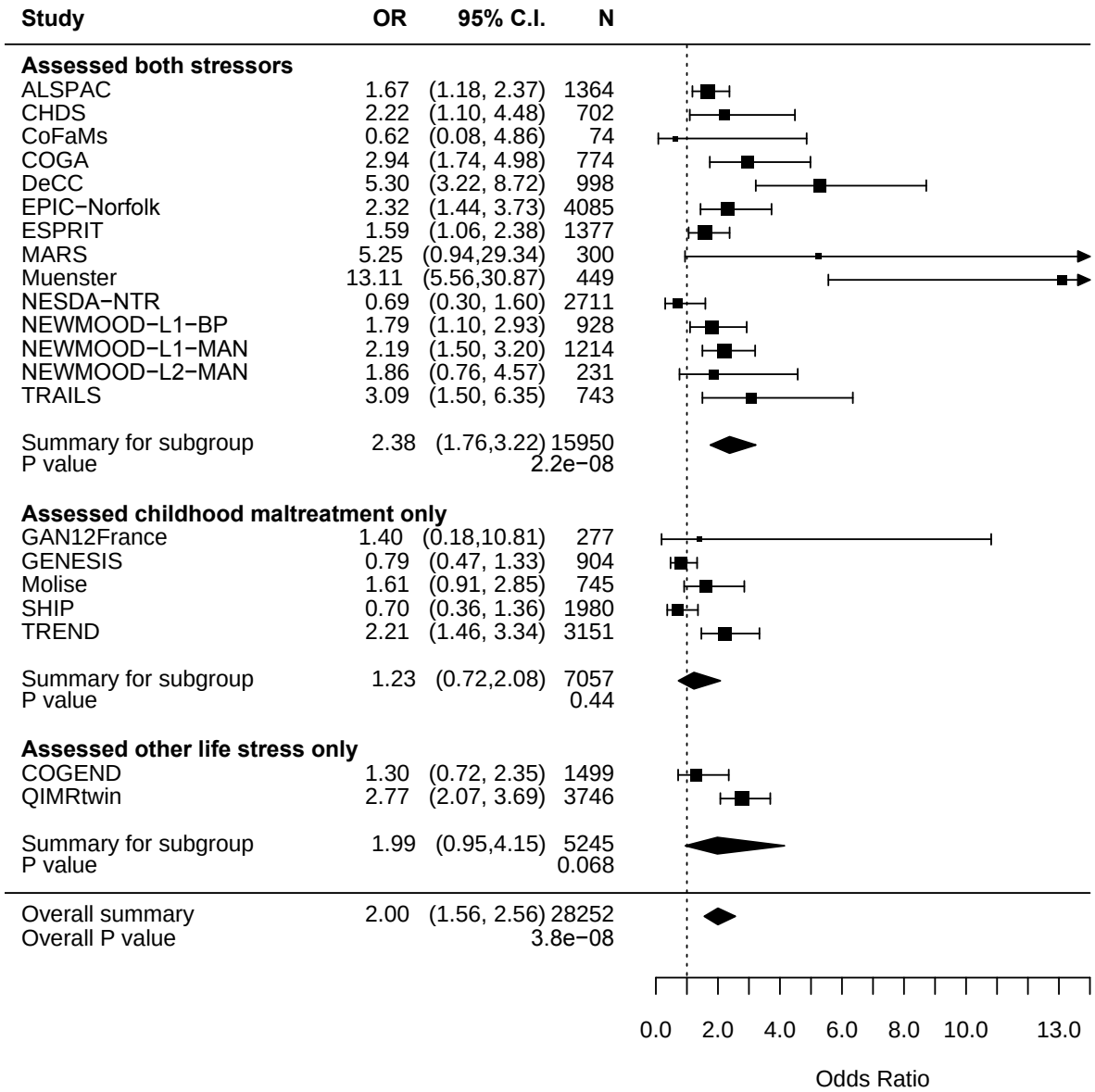
MODEL: $depression = \beta_0 + \beta_1(age) + \beta_2(sex) + \beta_3(stress) + \beta_4(gene) + \beta_5(gene \times stress)$

Depression (current depression diagnosis)
Sex (female = 0; male = 1)
Stress (broad stress; or other life stress < 5 year prior or childhood maltreatment)
Gene (additive coding in number of S alleles for 5-HTTLPR (LL = 0; LS=1; SS=2))

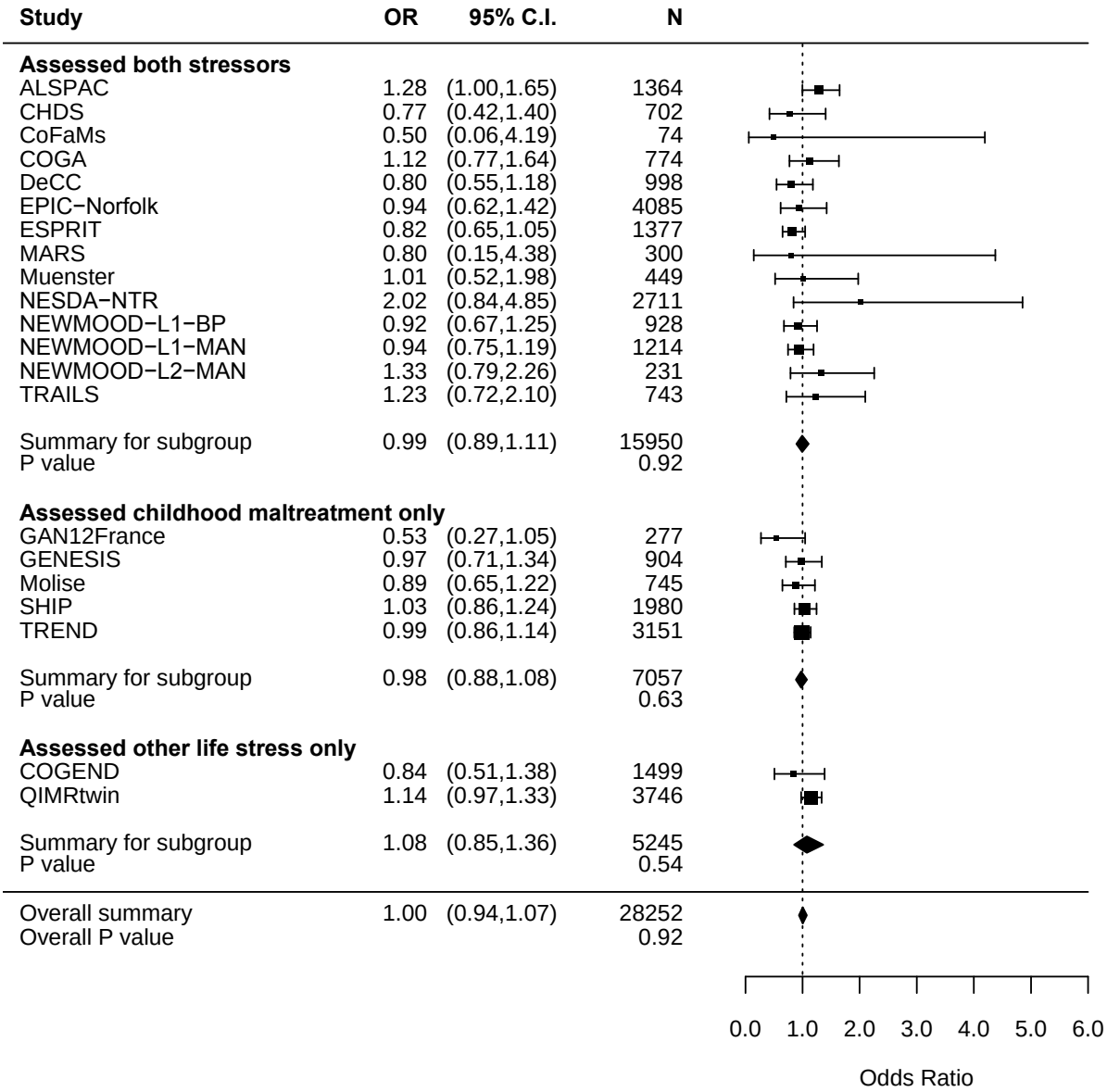
Figure S4: Forest plots for sex, stress, gene, and gene x stress terms from the model based on lifetime depression diagnosis, exposure to childhood maltreatment or other life stress occurring at any time, and subjects of all ages. (Corresponds to an analysis in Table 1)



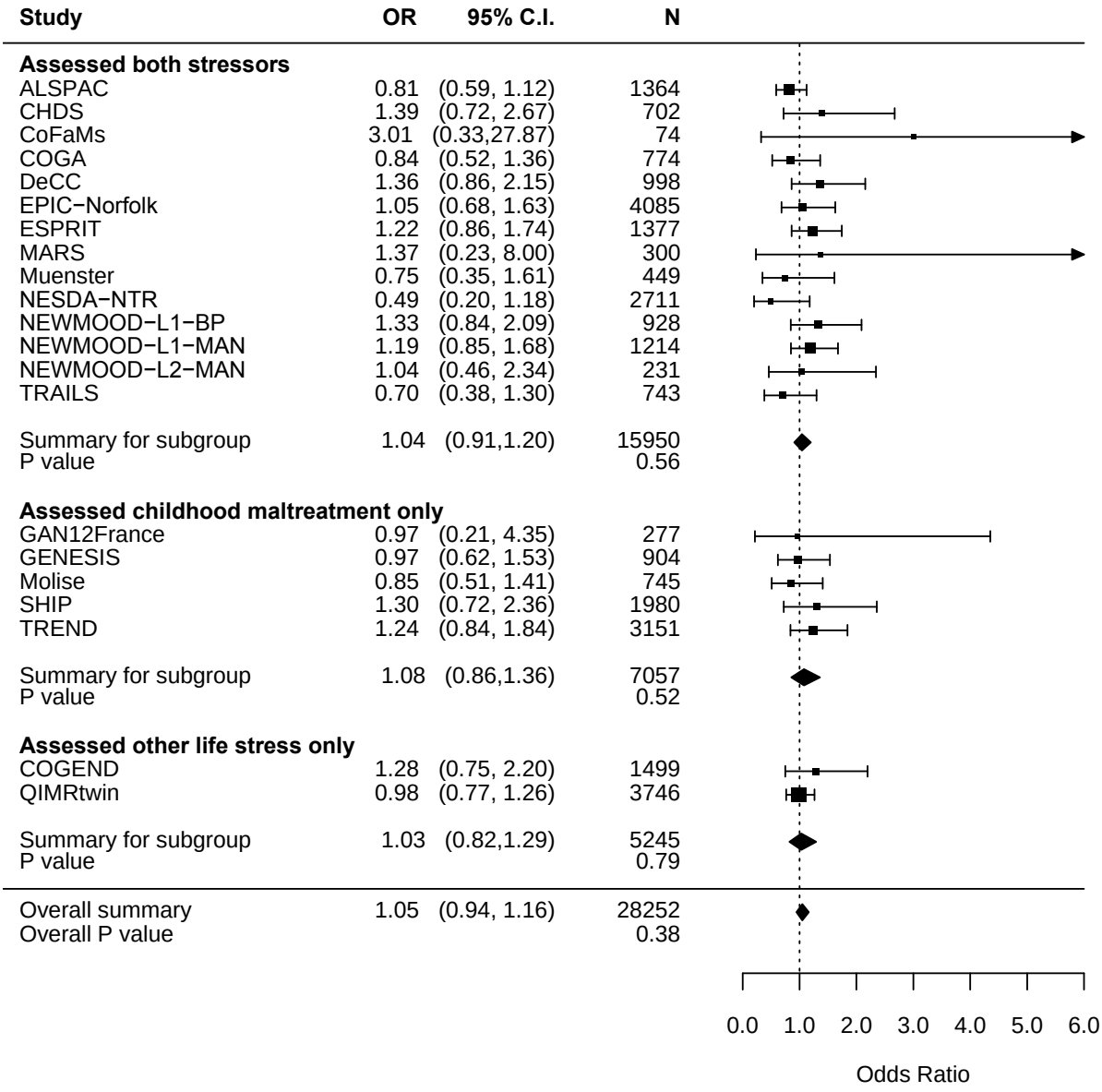
S4a. **Sex** (female = 0; male = 1) Thus, female is the reference.
Being male is associated with a lower risk of developing depression.



S4b. **Stress** (childhood maltreatment or other life stress (any time))
Exposure to stress is associated with a higher risk of developing depression.



S4c. **Gene** (additively coded for number of S alleles) Thus, LL is the reference. The number of S alleles is not associated with risk for depression.



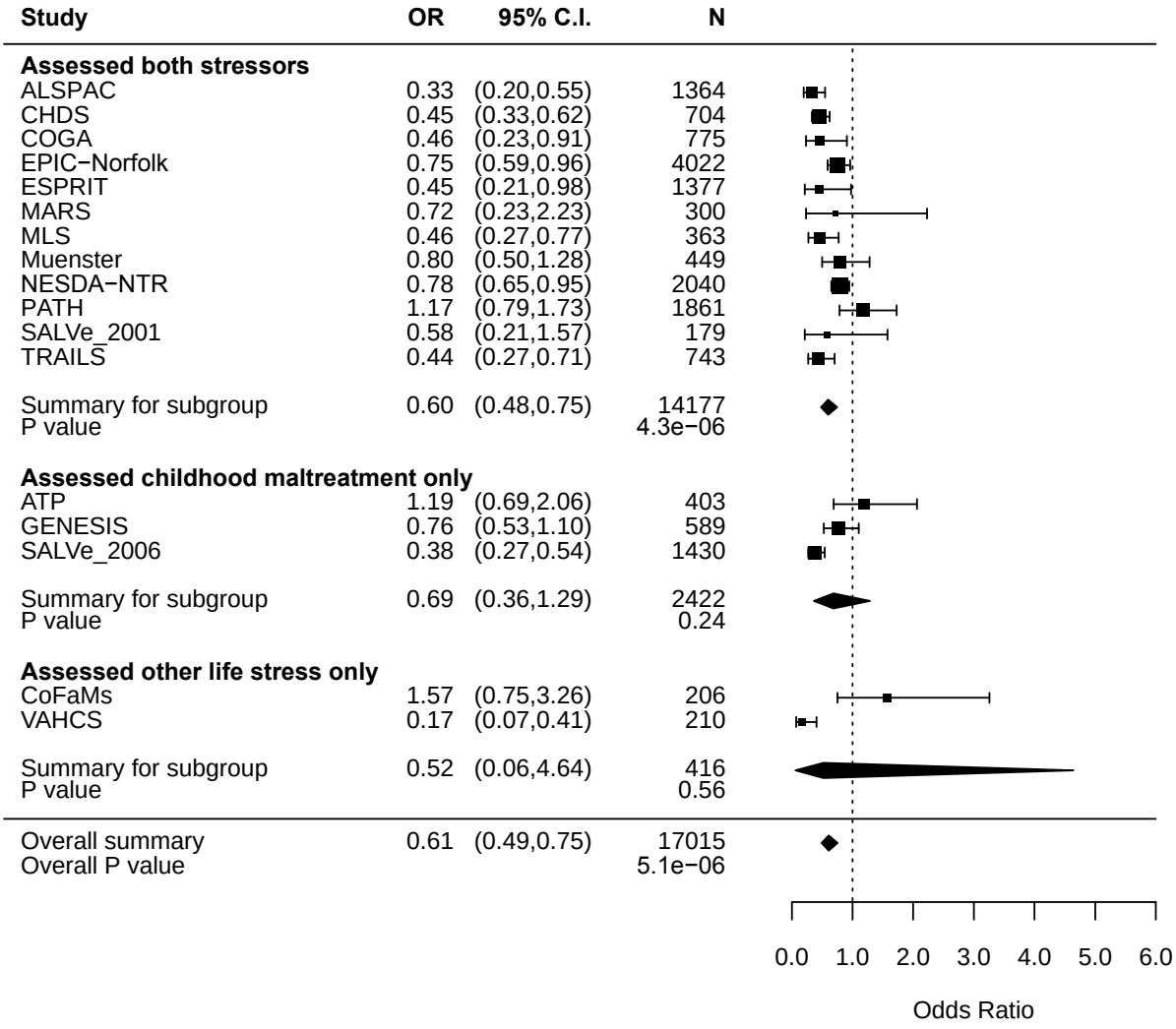
S4d. **Gene x Stress** (Note: the hypothesized direction of effect is an OR > 1)

Supplemental Figure S4: Forest plots for lifetime depression diagnosis in subjects of all ages based on exposure to broad stress (childhood maltreatment or other life stress) where timing of life stress other than childhood maltreatment may be unknown (5th analysis listed in Table 1)

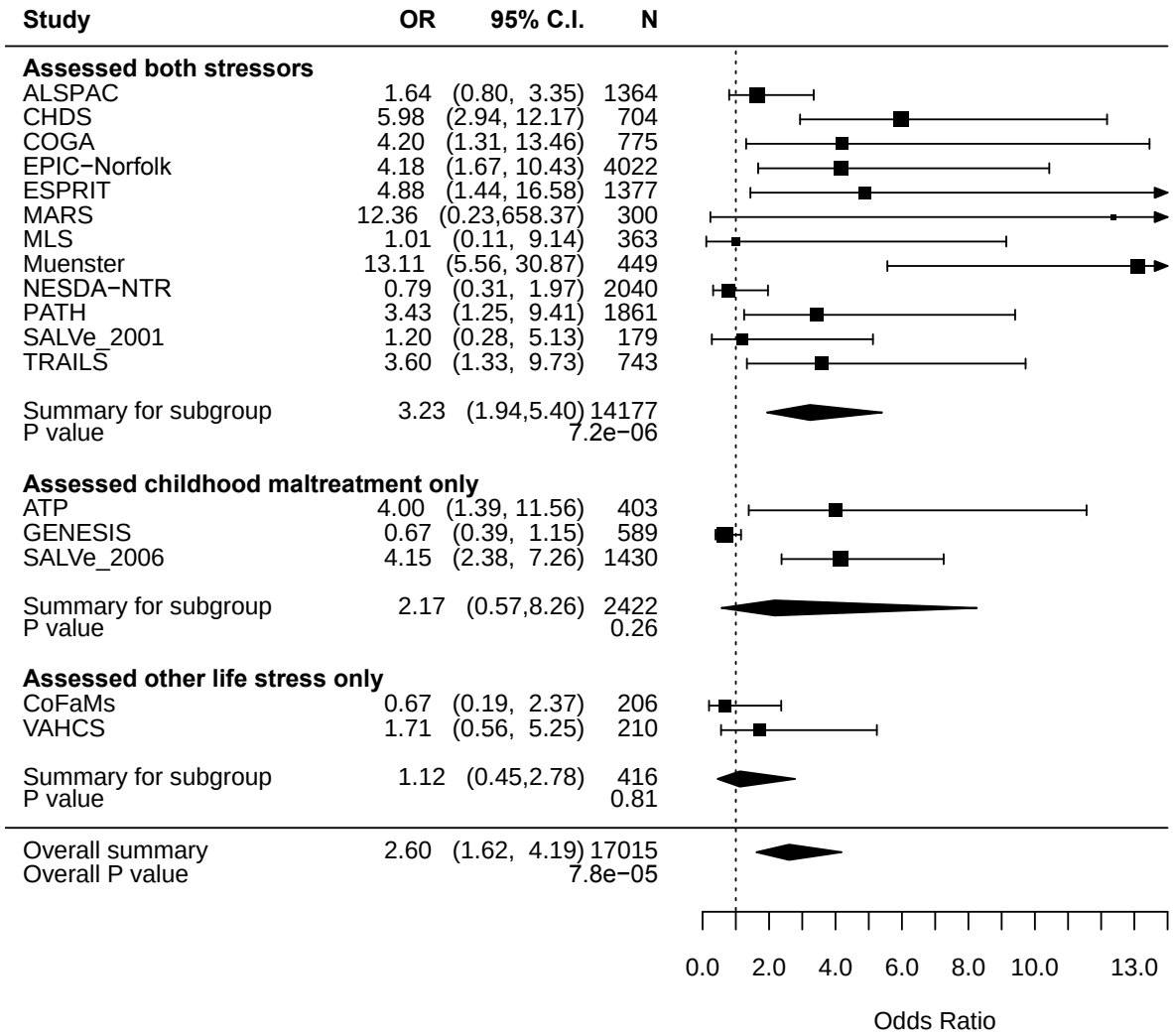
MODEL: $depression = \beta_0 + \beta_1(age) + \beta_2(sex) + \beta_3(stress) + \beta_4(gene) + \beta_5(gene \times stress)$

Depression (lifetime depression diagnosis)
Sex (female = 0; male = 1)
Stress (broad stress; childhood maltreatment or other life stress at any time)
Gene (additive coding in number of S alleles for 5-HTTLPR (LL = 0; LS=1; SS=2))

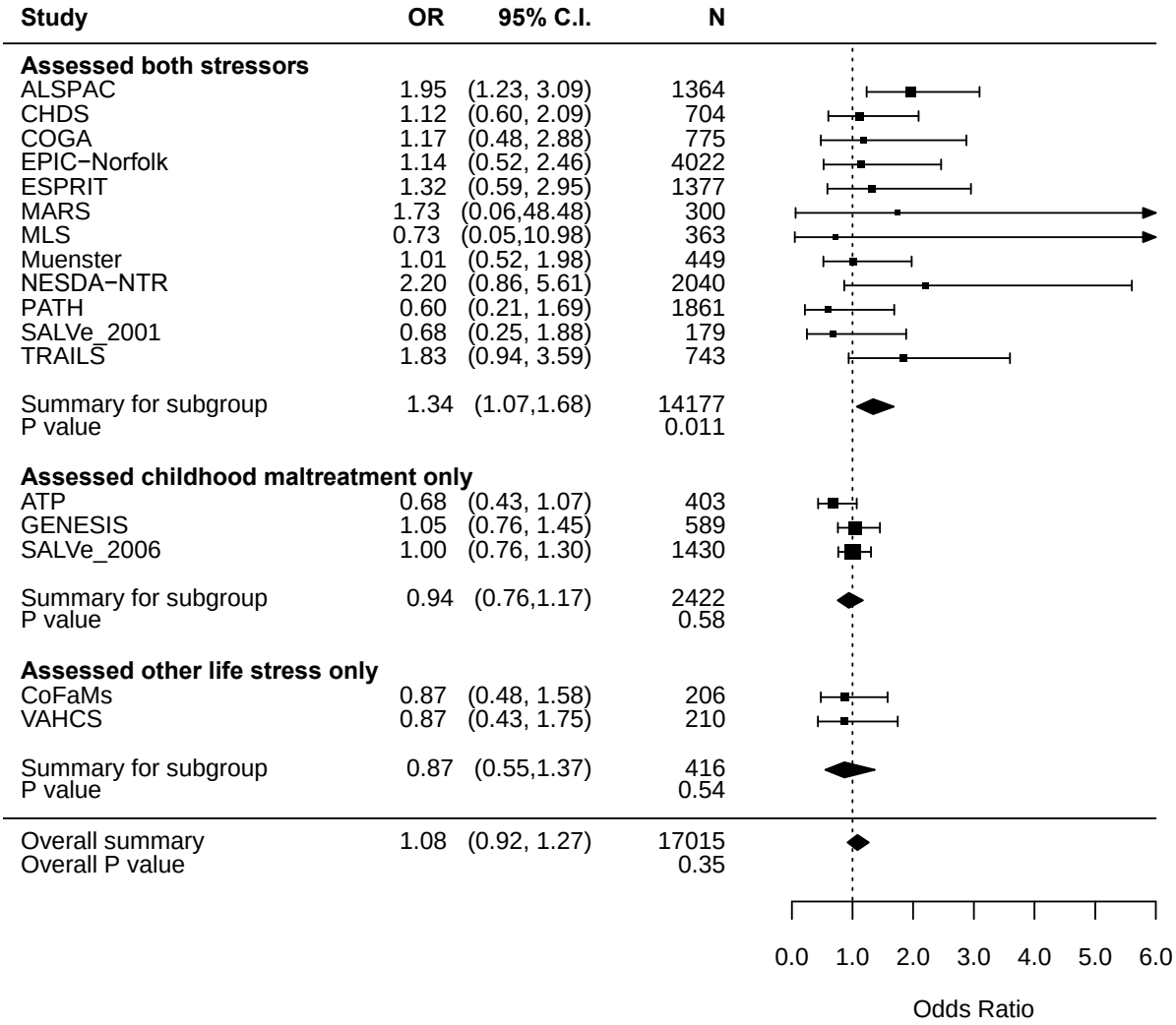
Figure S5: Forest plots for sex, stress, gene, and gene x stress terms from the model based on current depression diagnosis, exposure to childhood maltreatment or other life stress occurring at any time, and subjects of all ages. (Corresponds to an analysis in Table 1)



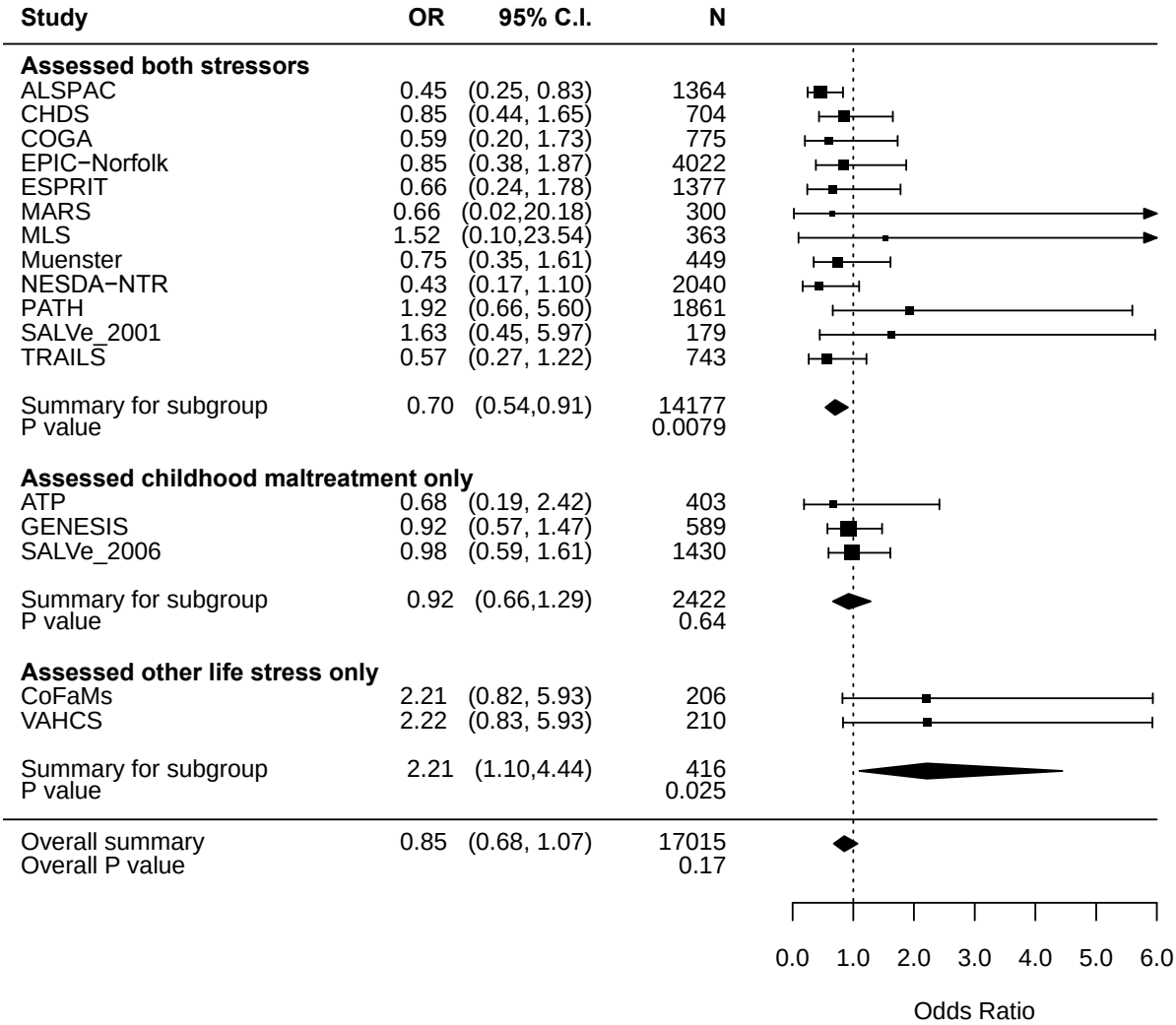
S5a. **Sex** (female = 0; male = 1) Thus, female is the reference.
Being male is associated with a lower risk of developing depression.



S5b. **Broad Stress** (childhood maltreatment or other life stress (any time)) Exposure to stress is associated with a higher risk of developing depression.



S5c. **Gene** (additively coded for number of S alleles) Thus, LL is the reference. The number of S alleles is not associated with risk for depression.



S5d. **Gene x Stress** (Note: the hypothesized direction of effect is an OR > 1)

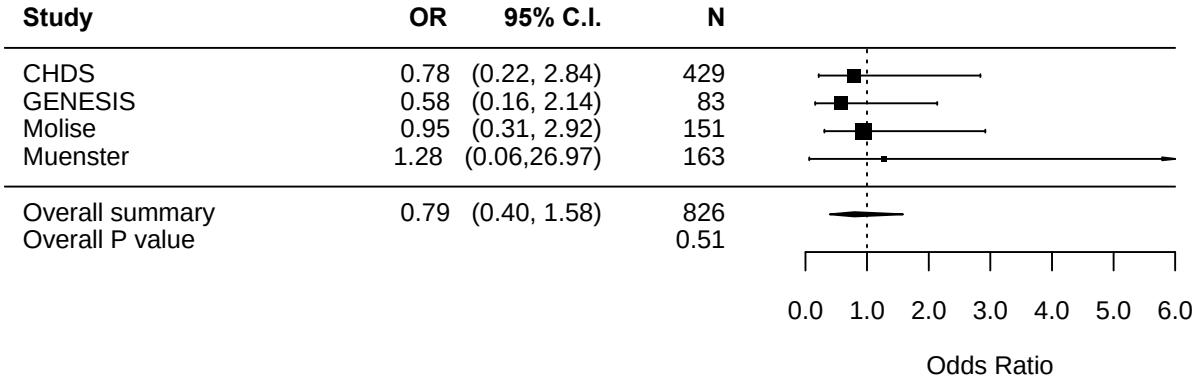
Supplemental Figure S5: Forest plots for current depression diagnosis in subjects of all ages based on exposure to broad stress (childhood maltreatment or other life stress) where timing of life stress other than childhood maltreatment may be unknown (6th analysis listed in Table 1)

MODEL: $depression = \beta_0 + \beta_1(age) + \beta_2(sex) + \beta_3(stress) + \beta_4(gene) + \beta_5(gene \times stress)$

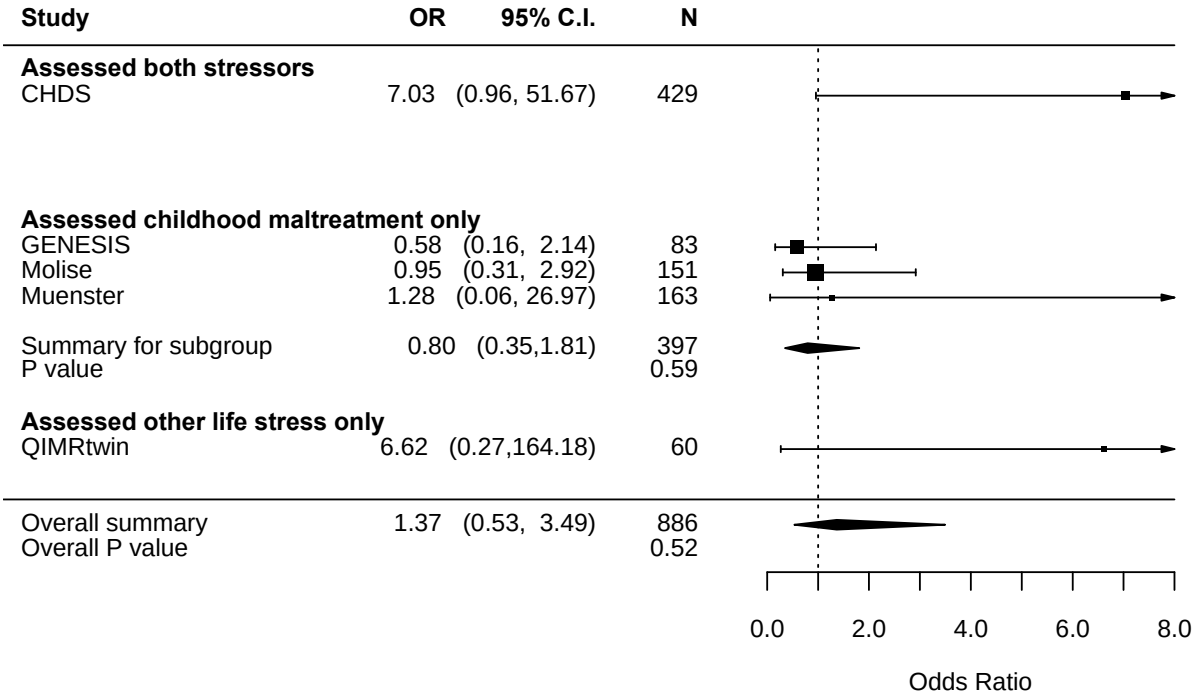
Depression (current depression diagnosis)
Sex (female = 0; male = 1)
Stress (broad stress; childhood maltreatment or other life stress at any time)
Gene (additive coding in number of S alleles for 5-HTTLPR (LL = 0; LS=1; SS=2))

Forest plots for interaction terms from the remaining primary analyses
Plots correspond to results listed in Supplemental Tables S9 through S11)

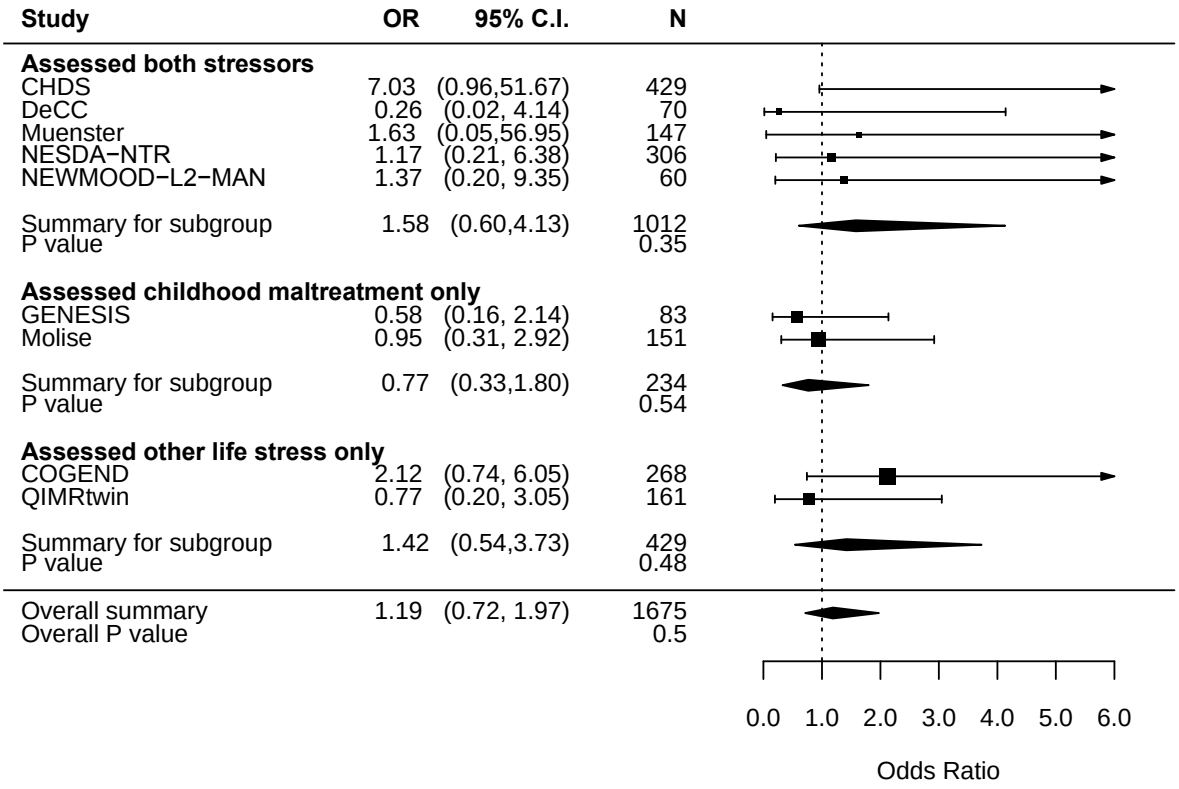
Figure S6: Forest plots for the gene x stress terms from the models based on depression diagnoses, stress exposure, and young adult subjects (ages 21 to 30). (Corresponds to the analyses in Supplemental Table S9)



S6a. **GxE interaction term**
Lifetime depression diagnosis; Childhood maltreatment



S6b. **GxE interaction term**
Lifetime depression diagnosis; Broad stress (other life stress < 5 years prior or childhood maltreatment)



S6c. **GxE interaction term**

Lifetime depression diagnosis; Broad Stress (childhood maltreatment or other life stress at any time)

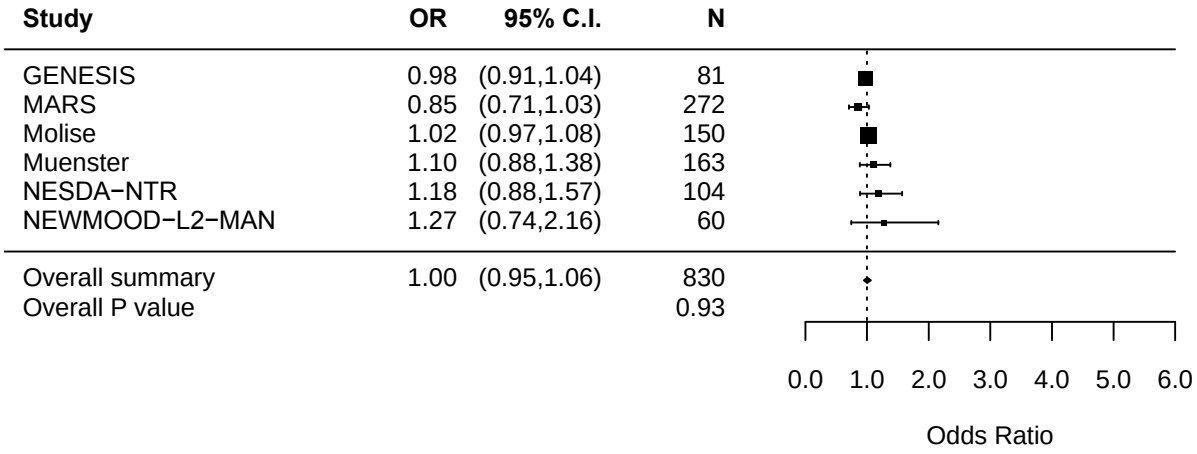
Figure S6: Forest plots for the **interaction term** from meta-analyses of Young Adults (ages 21 to 30 at assessment) based on depression diagnosis and dichotomous stress exposure
(Primary analysis models 1Ai and 1Bi with results listed in Supplemental Table S9)

MODEL: $depression = \beta_0 + \beta_1(age) + \beta_2(sex) + \beta_3(stress) + \beta_4(gene) + \beta_5(gene \times stress)$

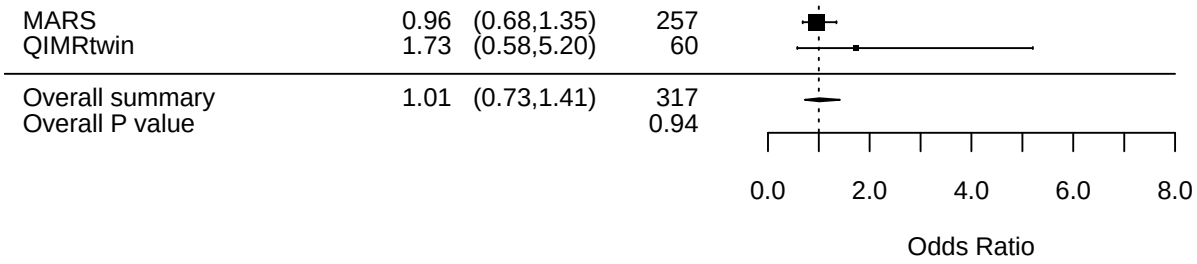
Sex (female = 0; male = 1)
Gene (additive coding in number of S alleles for 5-HTTLPR (LL = 0; LS=1; SS=2))

Hypothesized direction of effect is OR > 1

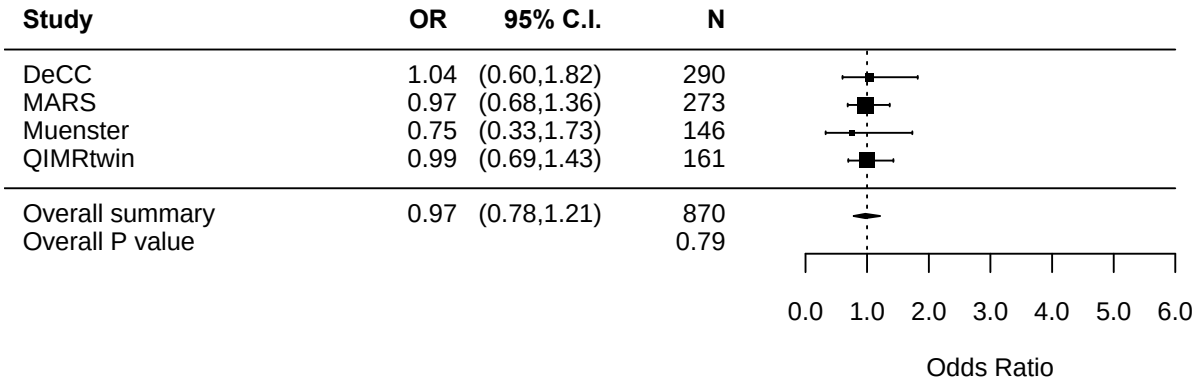
Figure S7: Forest plots for the gene x stress terms from the models based on depression diagnoses, quantitative assessments of stress, and young adult subjects (ages 21 to 30). (Corresponds to the analyses in Supplemental Table S10a)



S7a. **GxE Interaction term**
Lifetime depression diagnosis; Quantitative childhood maltreatment (CTQ score)



S7b. **GxE Interaction term**
Lifetime depression diagnosis; Quantitative other life stress (LTE-Q score) < 5 years prior



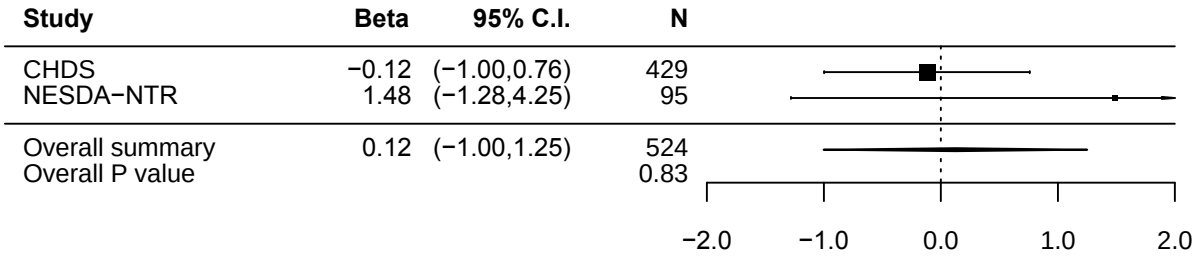
S7b. **GxE Interaction term**
Lifetime depression diagnosis; Quantitative other life stress (LTE-Q score) any time

Figure S7: Forest plots for the **interaction term** from meta-analyses of Young Adults (ages 21 and 30 at assessment) based on depression diagnosis and quantitative stress
(Primary analysis models 1Aii and 1Bii with results listed in Supplemental Table S10a)

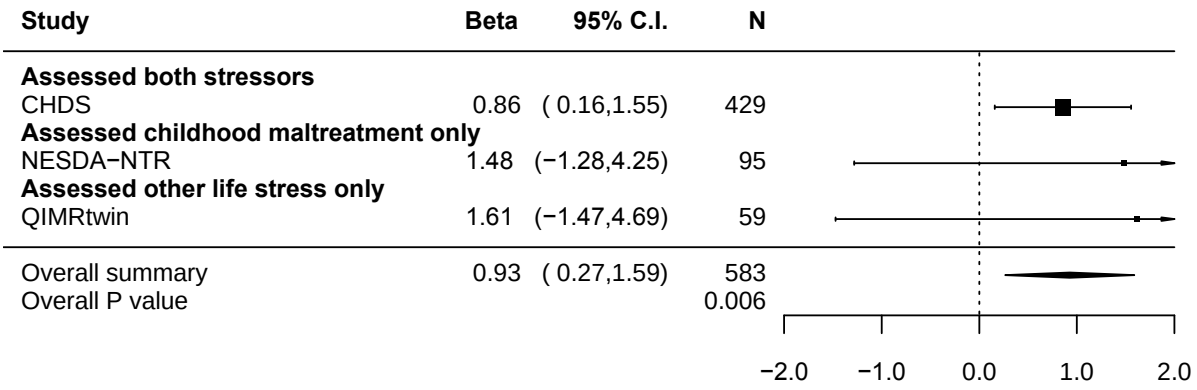
MODEL: $depression = \beta_0 + \beta_1(age) + \beta_2(sex) + \beta_3(stress) + \beta_4(gene) + \beta_5(gene \times stress)$

Sex (female = 0; male = 1)
Gene (additive coding in number of S alleles for 5-HTTLPR (LL = 0; LS=1; SS=2))
Hypothesized direction of effect is OR > 1

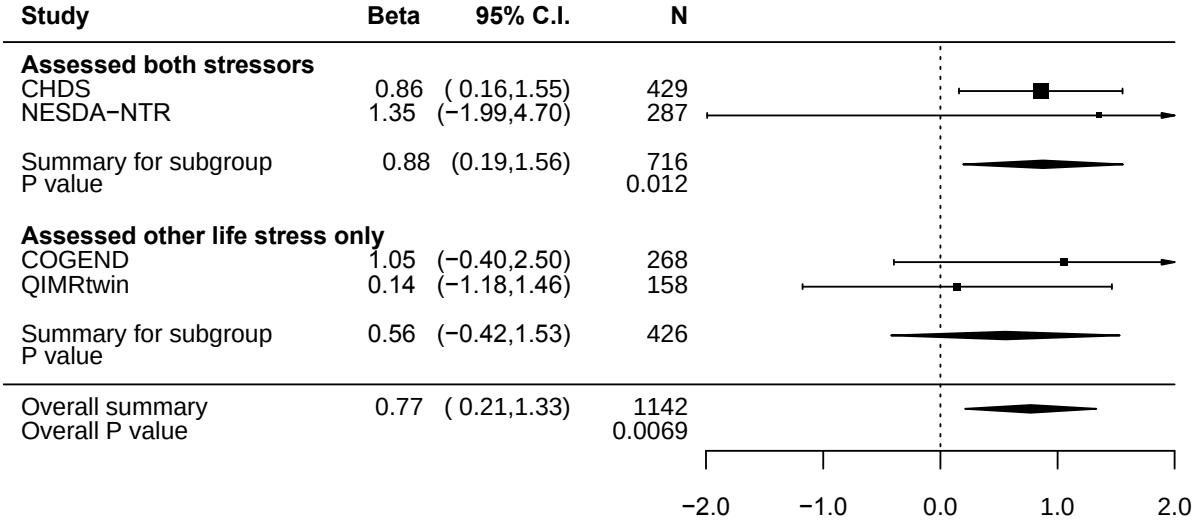
Figure S8: Forest plots for the gene x stress terms from the models based on DSM-IV symptom count, exposure to stress, and young adult subjects (ages 21 to 30). (Corresponds to the analyses in Supplemental Table S10b)



S8a. **GxE Interaction term**
Lifetime DSM-IV depression symptom count; childhood maltreatment



S8b. **GxE Interaction term**
Lifetime DSM-IV depression symptom count;
Broad stress (other life stress < 5 years prior or childhood maltreatment)



S8c. **GxE Interaction term**
Lifetime DSM-IV depression symptom count;
Broad stress (childhood maltreatment or life stress at any time)

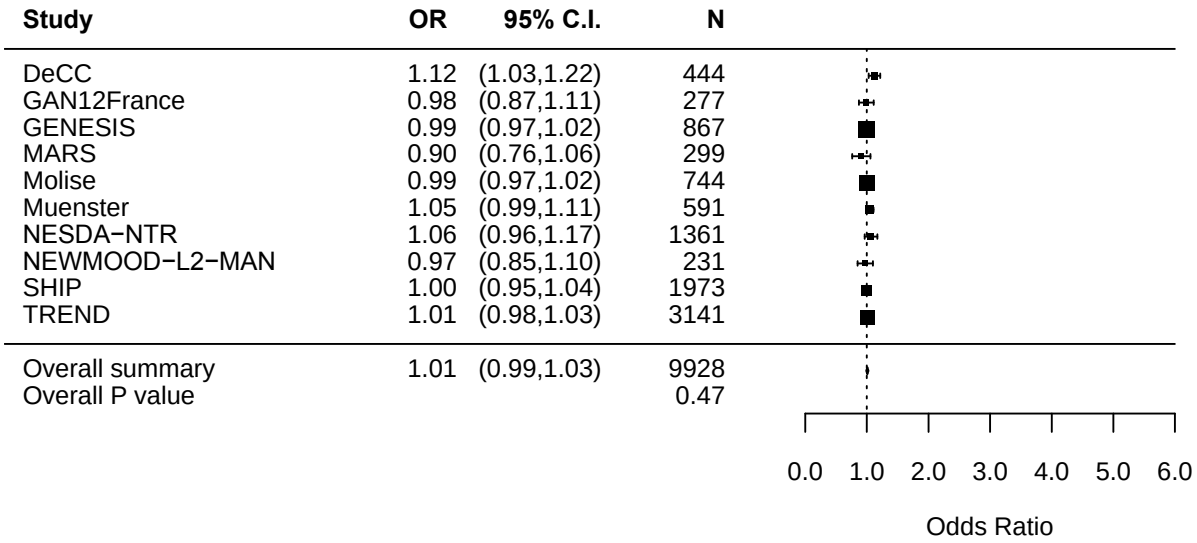
Figure S8: Forest plots for the **interaction term** from meta-analyses of Young Adults (ages 21 and 30 at assessment) based on quantitative depression (DSM-IV symptom count) and stress exposure (Primary analysis models 1Aii and 1Bii with results listed in Supplemental Table S10b)

MODEL: $depression = \beta_0 + \beta_1(age) + \beta_2(sex) + \beta_3(stress) + \beta_4(gene) + \beta_5(gene \times stress)$

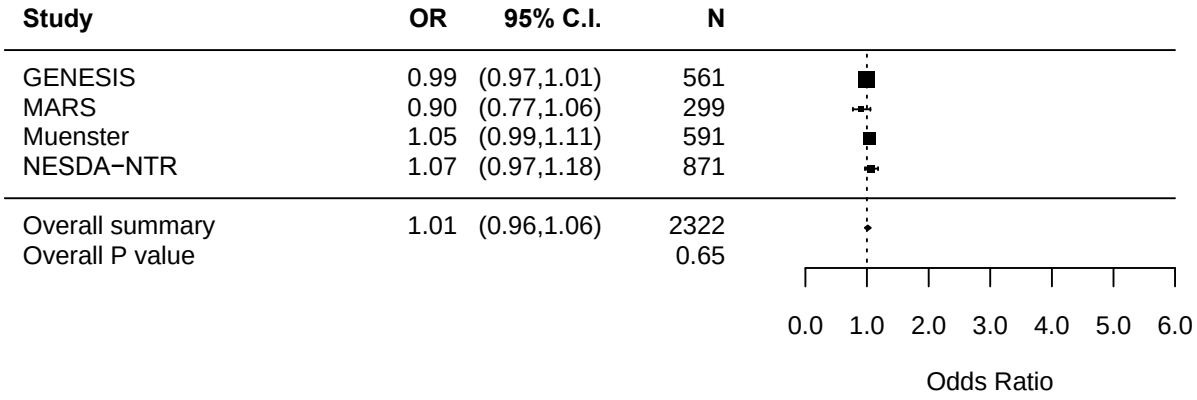
Gene (additive coding in number of S alleles for 5-HTTLPR (LL = 0; LS=1; SS=2))

Hypothesized direction of effect is $\beta > 0$

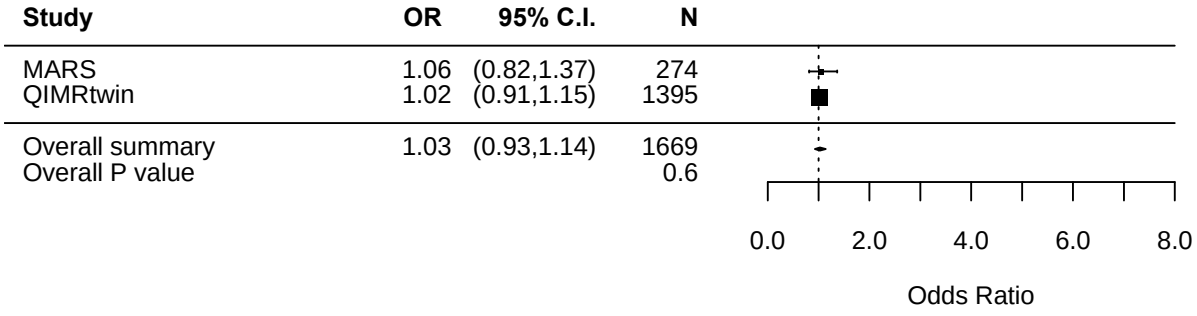
Figure S9: Forest plots for the gene x stress terms from the models based on depression diagnosis, quantitative assessments of stress, and subjects of all ages (Corresponds to the analyses in Supplemental Table S11a)



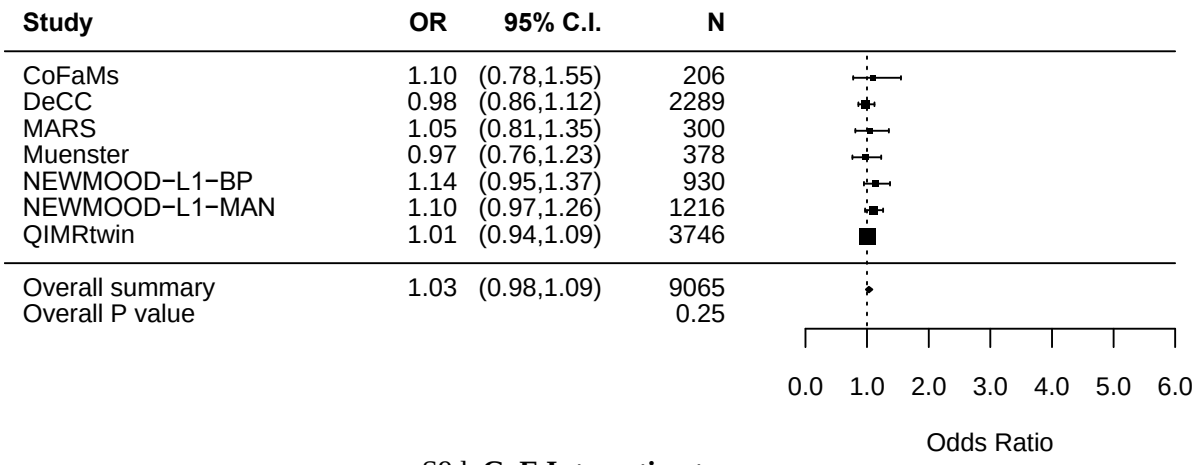
S9a. **GxE Interaction term**
Lifetime depression diagnosis; Quantitative childhood maltreatment (CTQ score)



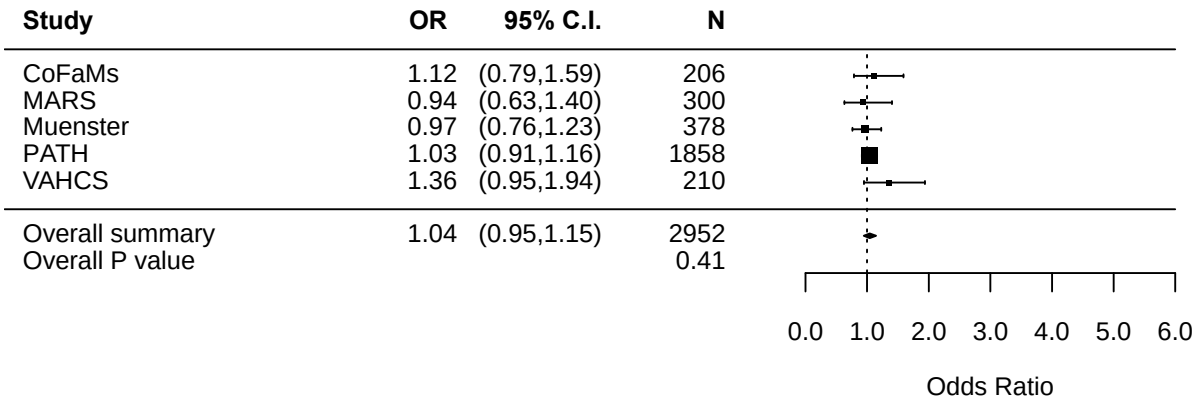
S9b. **GxE Interaction term**
Current depression diagnosis; Quantitative childhood maltreatment (CTQ score)



S9c. **GxE Interaction term**
Lifetime depression diagnosis; Quantitative other life stress (LTE-Q score) < 5 years prior



S9d. **GxE Interaction term**
Lifetime depression diagnosis; Quantitative other life stress (LTE-Q score) any time



S9e. **GxE Interaction term**
Current depression diagnosis; Quantitative other life stress (LTE-Q score) any time

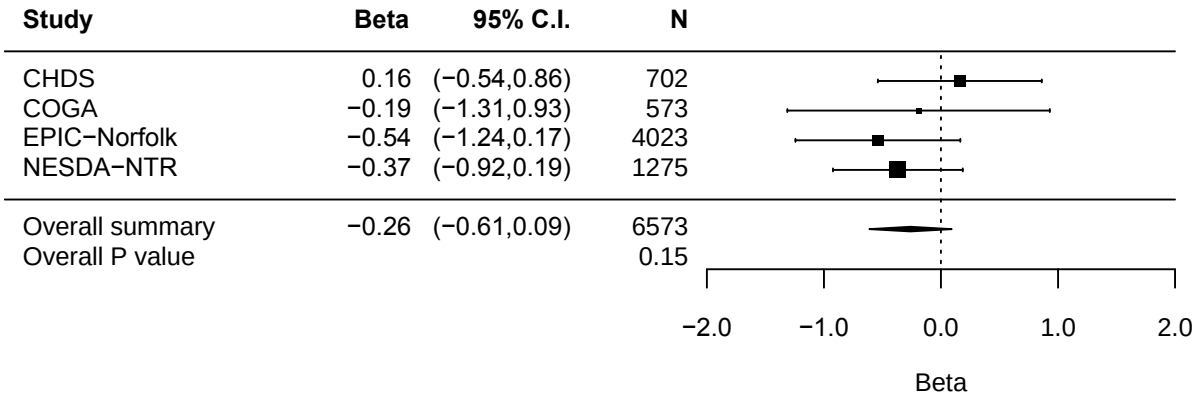
Figure S9: Forest plots for the **interaction term** from meta-analyses of subjects of all ages based on depression diagnosis and quantitative stress
(Primary analysis models 1Aii and 1Bii with results listed in Supplemental Table S11a)

MODEL: $depression = \beta_0 + \beta_1(age) + \beta_2(sex) + \beta_3(stress) + \beta_4(gene) + \beta_5(gene \times stress)$

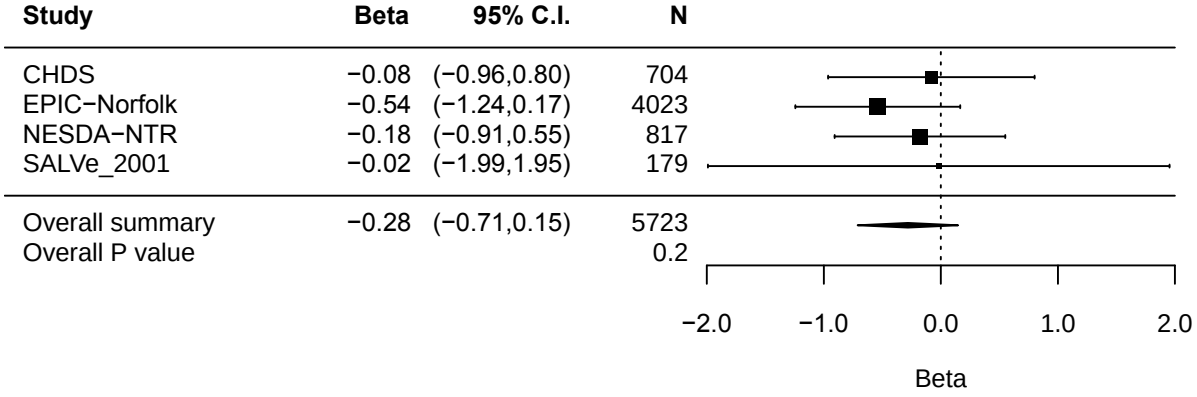
Sex (female = 0; male = 1)
Gene (additive coding in number of S alleles for 5-HTTLPR (LL = 0; LS=1; SS=2))

Hypothesized direction of effect is OR > 1

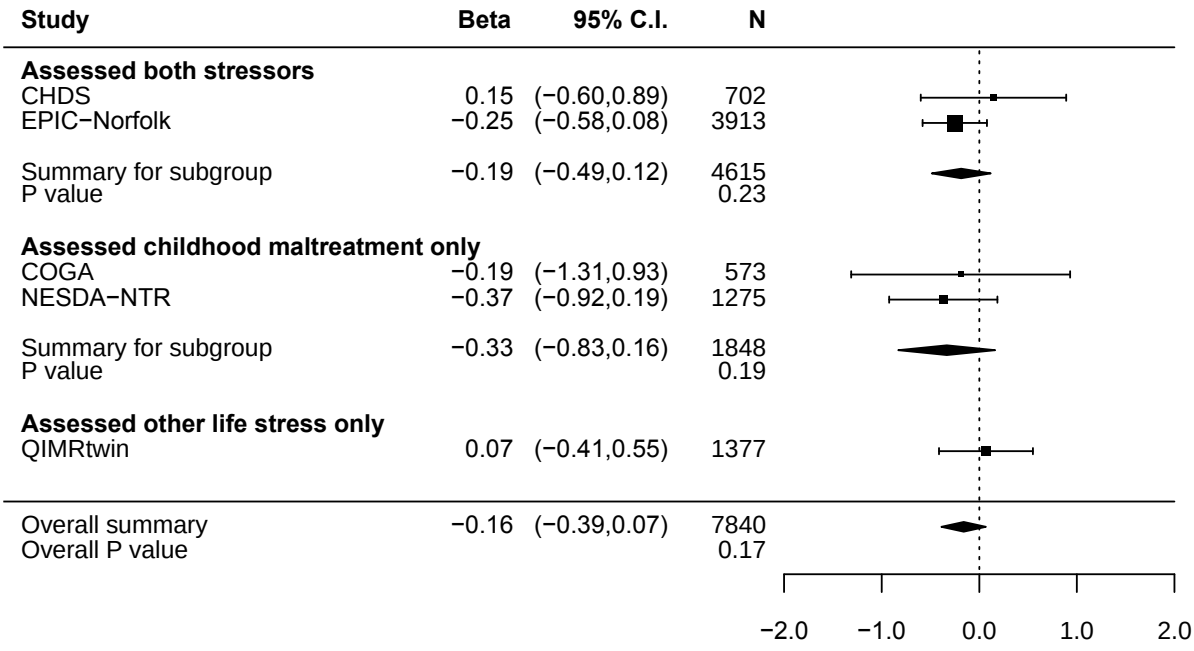
Figure S10: Forest plots for the gene x stress terms from the models based on DSM-IV symptom counts, exposure to stress, and subjects of all ages (Corresponds to the analyses in Supplemental Table S11b)



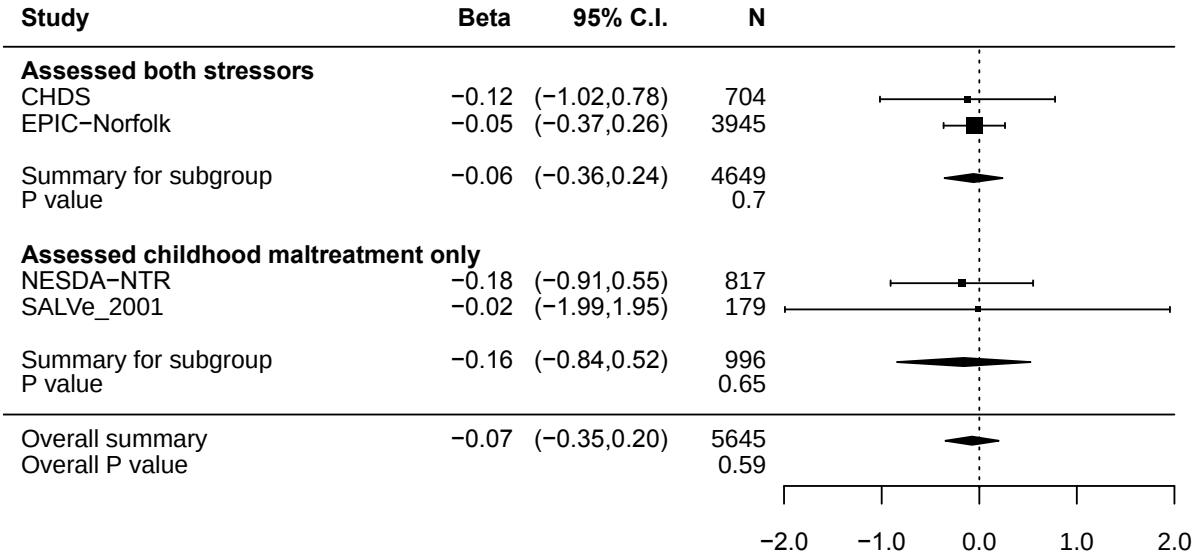
S10a. **GxE Interaction term**
Lifetime DSM-IV depression symptom count; childhood maltreatment



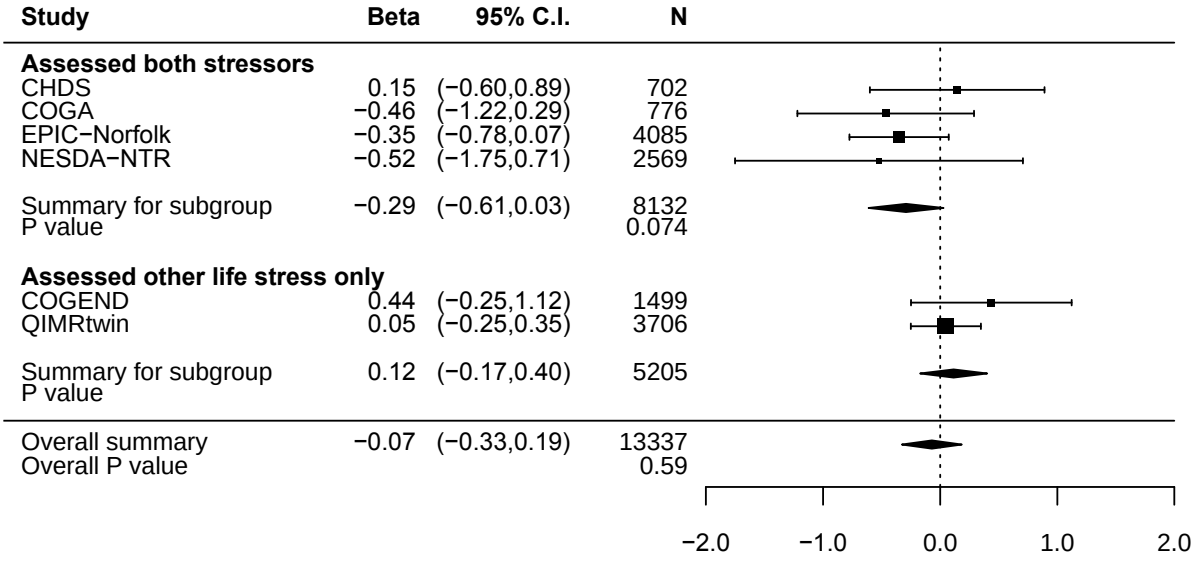
S10b. **GxE Interaction term**
Current DSM-IV depression symptom count; childhood maltreatment



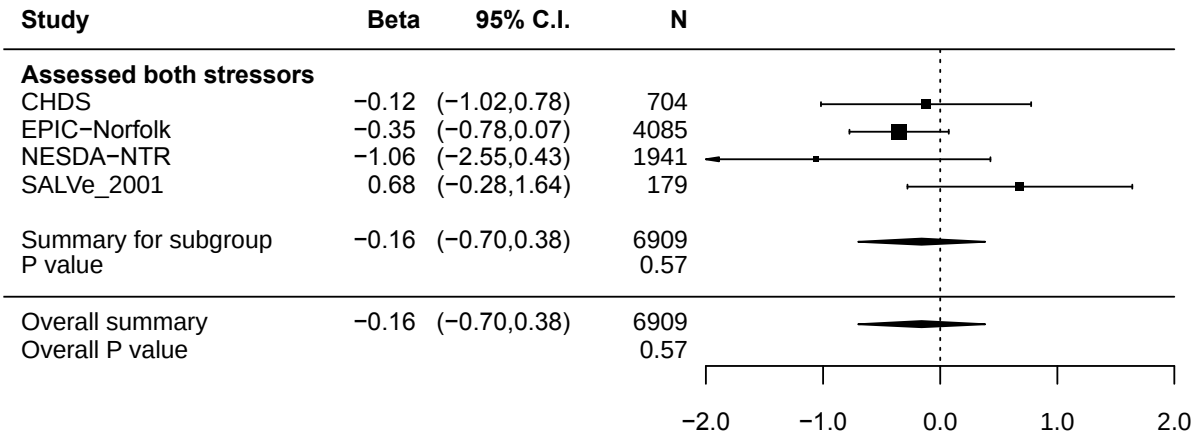
S10c. **GxE Interaction term**
Lifetime DSM-IV depression symptom count;
Broad stress (other life stress < 5 years prior or childhood maltreatment)



S10d. **GxE Interaction term**
Current DSM-IV depression symptom count;
Broad stress (other life stress < 5 years prior or childhood maltreatment)



S10e. **GxE Interaction term**
Lifetime DSM-IV depression symptom count;
Broad stress (childhood maltreatment or life stress at any time)



S10f. **GxE Interaction term**
Current DSM-IV depression symptom count;
Broad stress (childhood maltreatment or life stress at any time)

Figure S10: Forest plots for the **interaction term** from meta-analyses of subjects of all ages based on quantitative depression (DSM-IV symptom count) and stress exposure
(Primary analysis models 1Aii and 1Bii with results listed in Supplemental Table S11b)

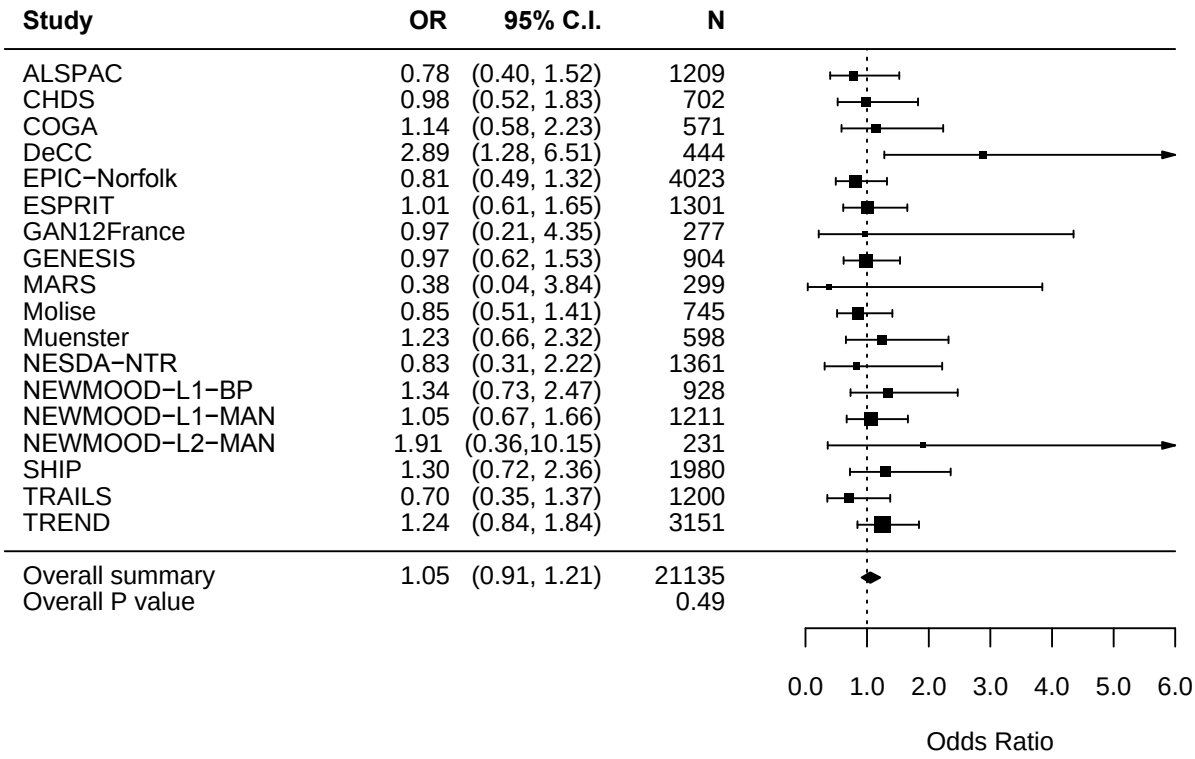
MODEL: $depression = \beta_0 + \beta_1(age) + \beta_2(sex) + \beta_3(stress) + \beta_4(gene) + \beta_5(gene \times stress)$

Sex (female = 0; male = 1)
Gene (additive coding in number of S alleles for 5-HTTLPR (LL = 0; LS=1; SS=2))

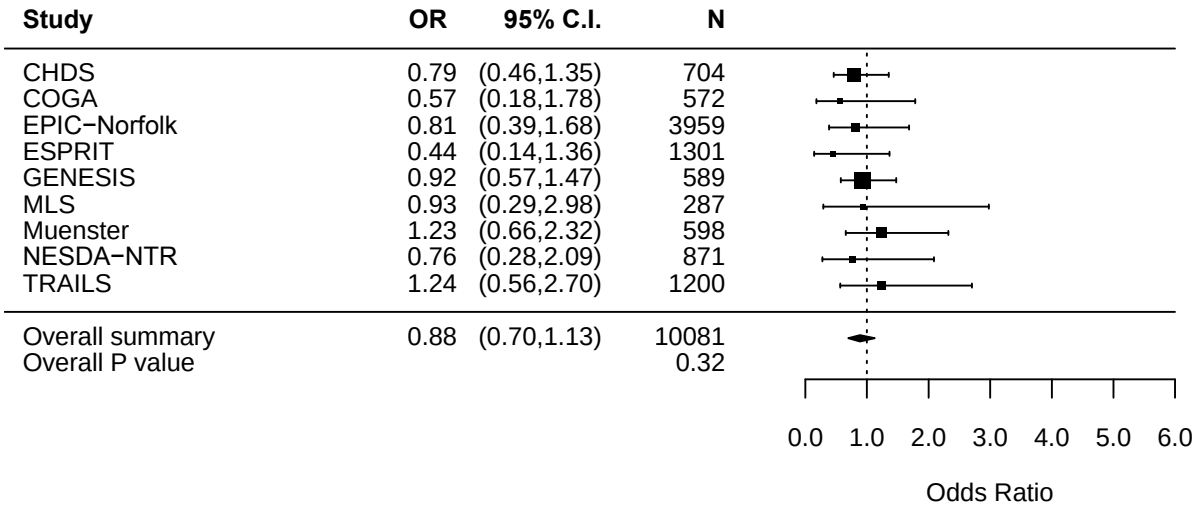
Hypothesized direction of effect is $\beta > 0$

Forest plots for interaction terms from the secondary analyses with results listed in Supplemental Tables S13 through S16

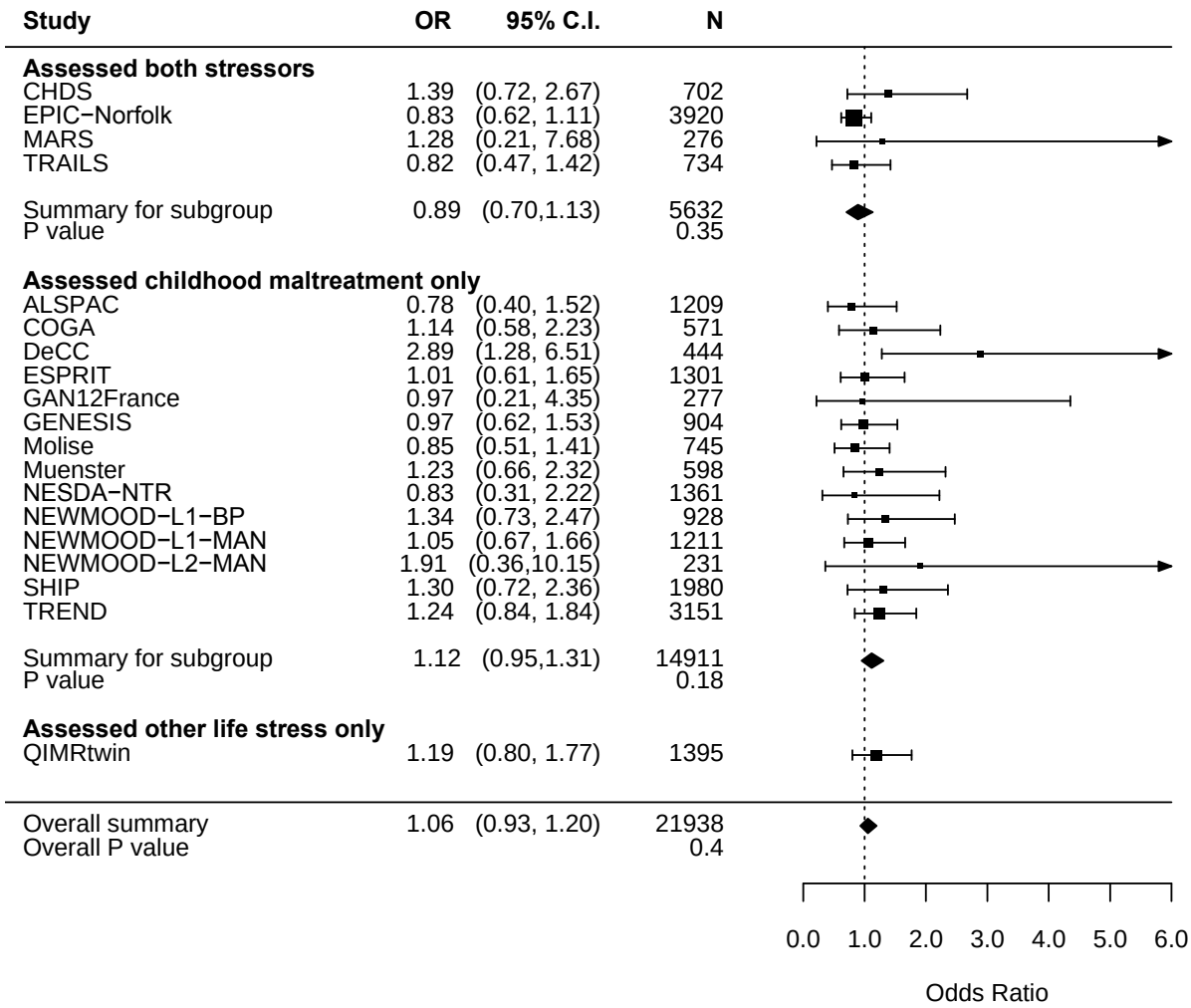
Figure S11: Forest plots for the gene x stress terms from the models based on depression diagnoses limited to DSM-IV or ICD-10 criteria, stress exposure, and subjects of all ages (Corresponds to the analyses in Supplemental Table S13)



S11a. **GxE interaction term**
Lifetime depression diagnosis; Childhood maltreatment

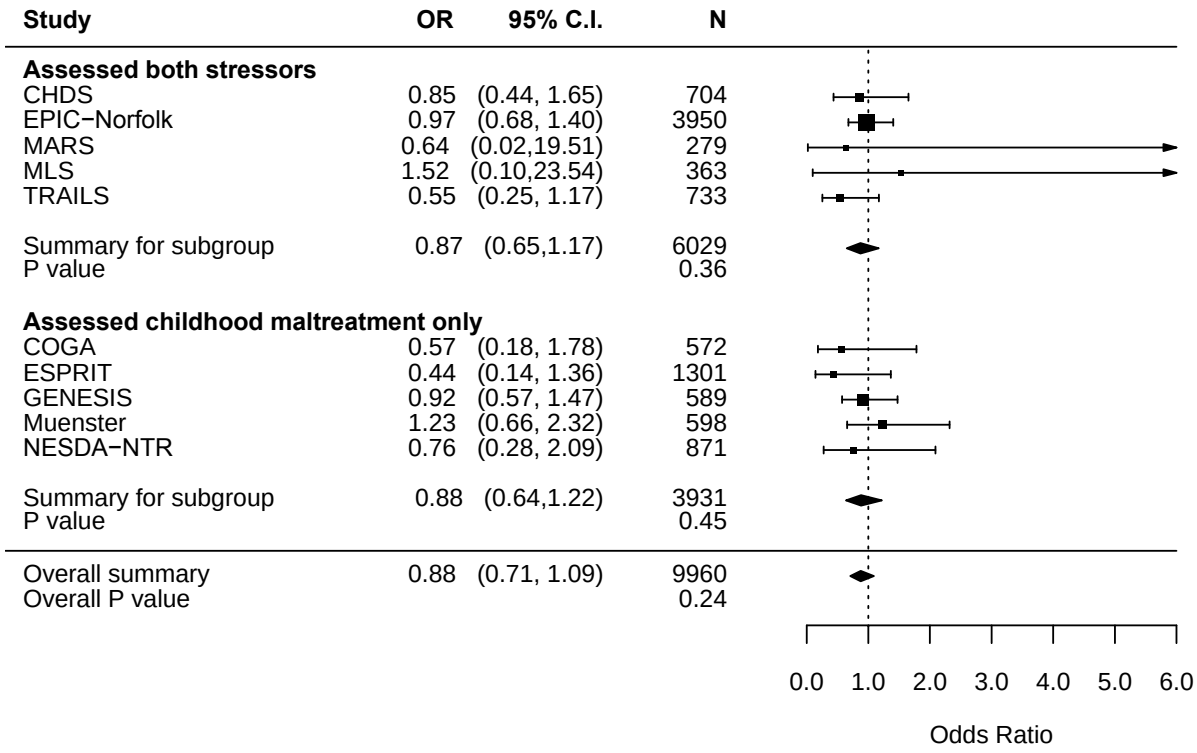


S11b. **GxE interaction term**
Current depression diagnosis; Childhood maltreatment



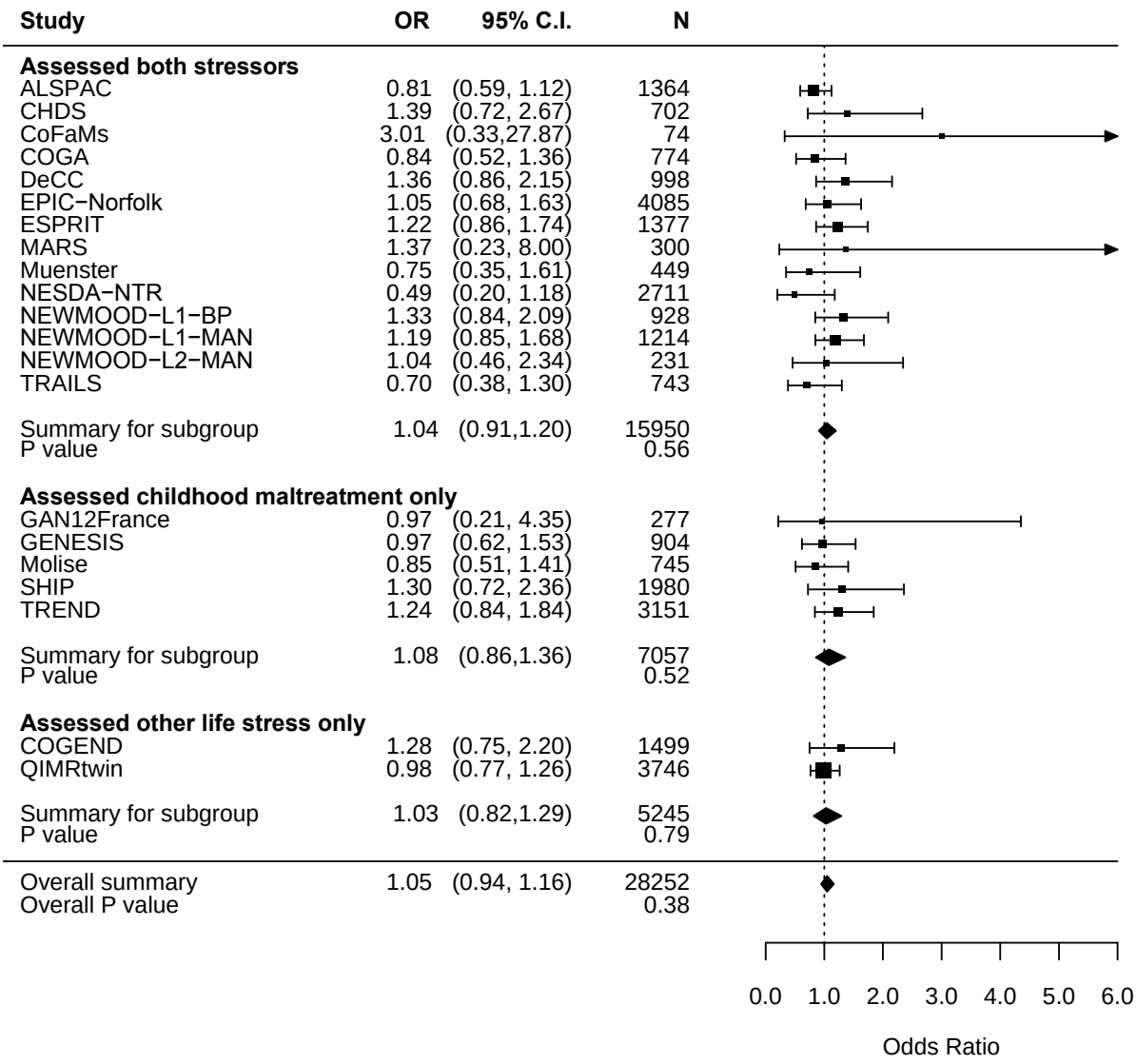
S11c. **GxE interaction term**

Lifetime depression diagnosis; Broad stress (other life stress < 5 years prior or childhood maltreatment)



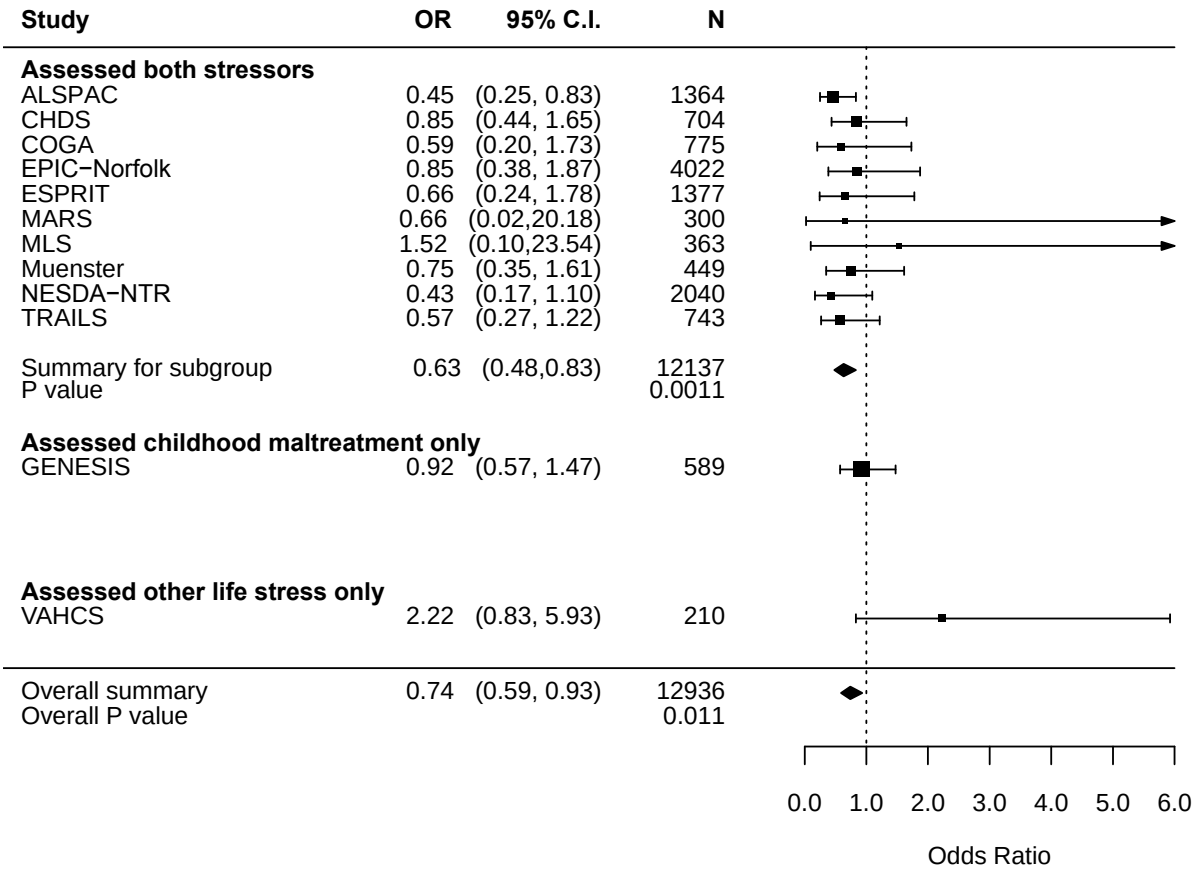
S11d. **GxE interaction term**

Current depression diagnosis; Broad stress (other life stress < 5 years prior or childhood maltreatment)



S11e. **GxE interaction term**

Lifetime depression diagnosis; Broad Stress (childhood maltreatment or other life stress at any time)



S11f. **GxE interaction term**

Current depression diagnosis; Broad Stress (childhood maltreatment or other life stress at any time)

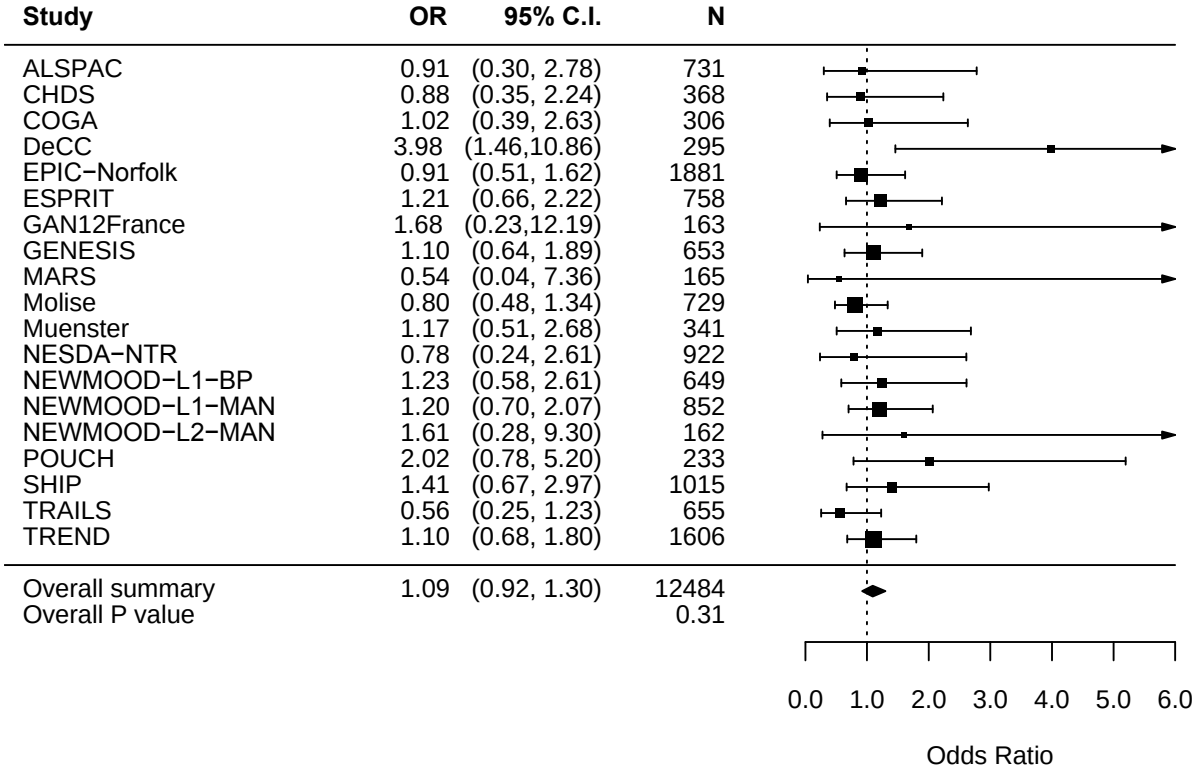
Figure S11: Forest plots for the **interaction term** from meta-analyses of subjects of all ages based on depression diagnosis limited to DSM-IV or ICD-10 criteria and stress exposure
(Corresponds to results listed in Supplemental Table S13)

MODEL: $depression = \beta_0 + \beta_1(age) + \beta_2(sex) + \beta_3(stress) + \beta_4(gene) + \beta_5(gene \times stress)$

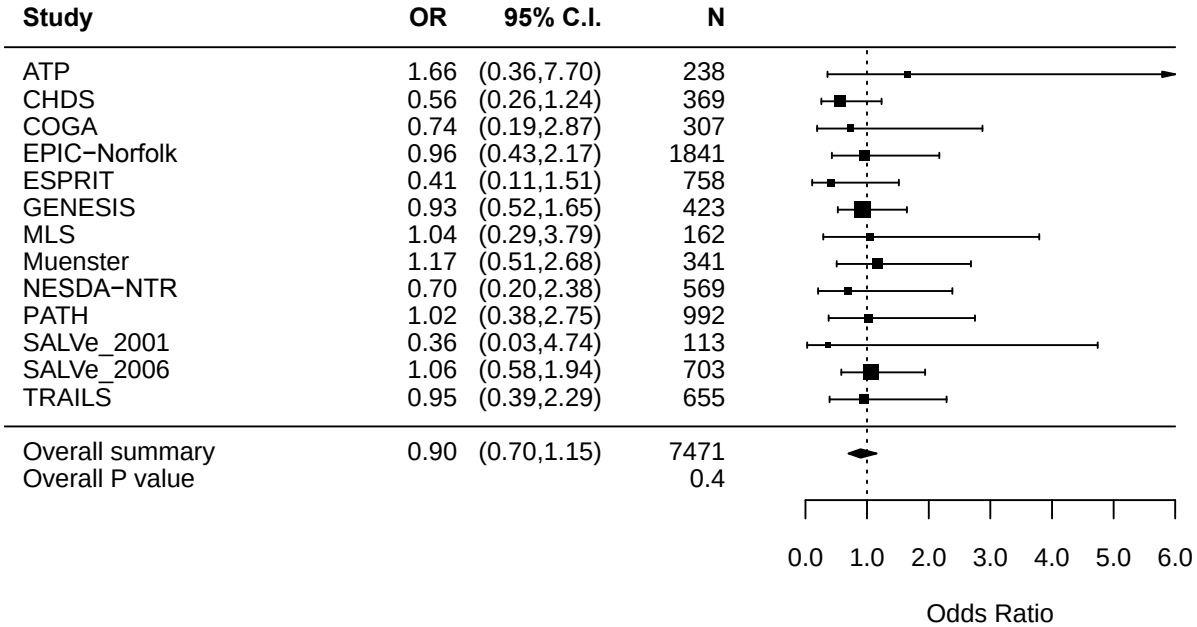
Sex (female = 0; male = 1)
Gene (additive coding in number of S alleles for 5-HTTLPR (LL = 0; LS=1; SS=2))

Hypothesized direction of effect is OR > 1

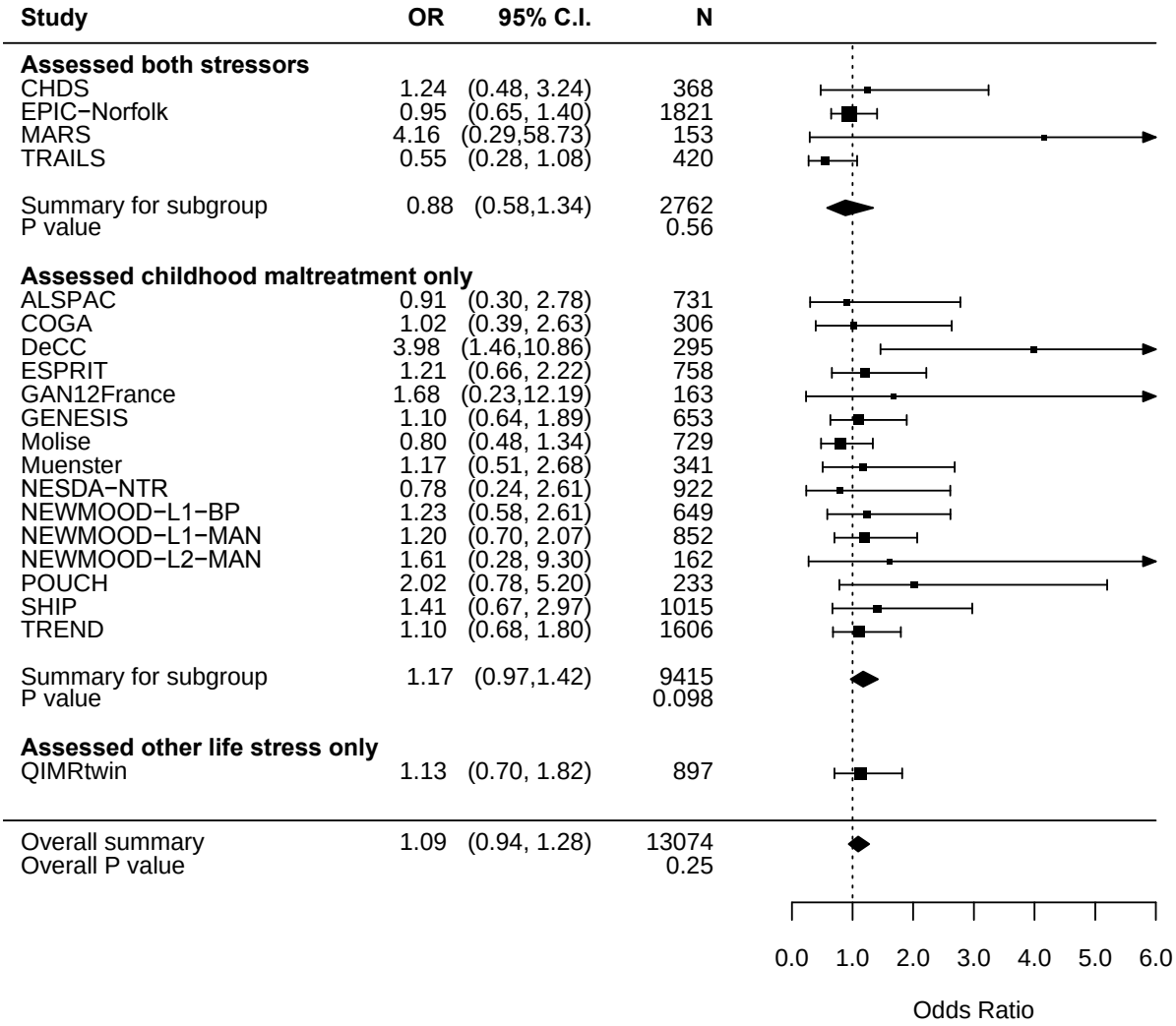
Figure S12: Forest plots for the gene x stress terms from the models evaluated using subjects of a single sex and based on depression diagnoses, stress exposure, and subjects of all ages (Corresponds to the analyses in Supplemental Table S14)



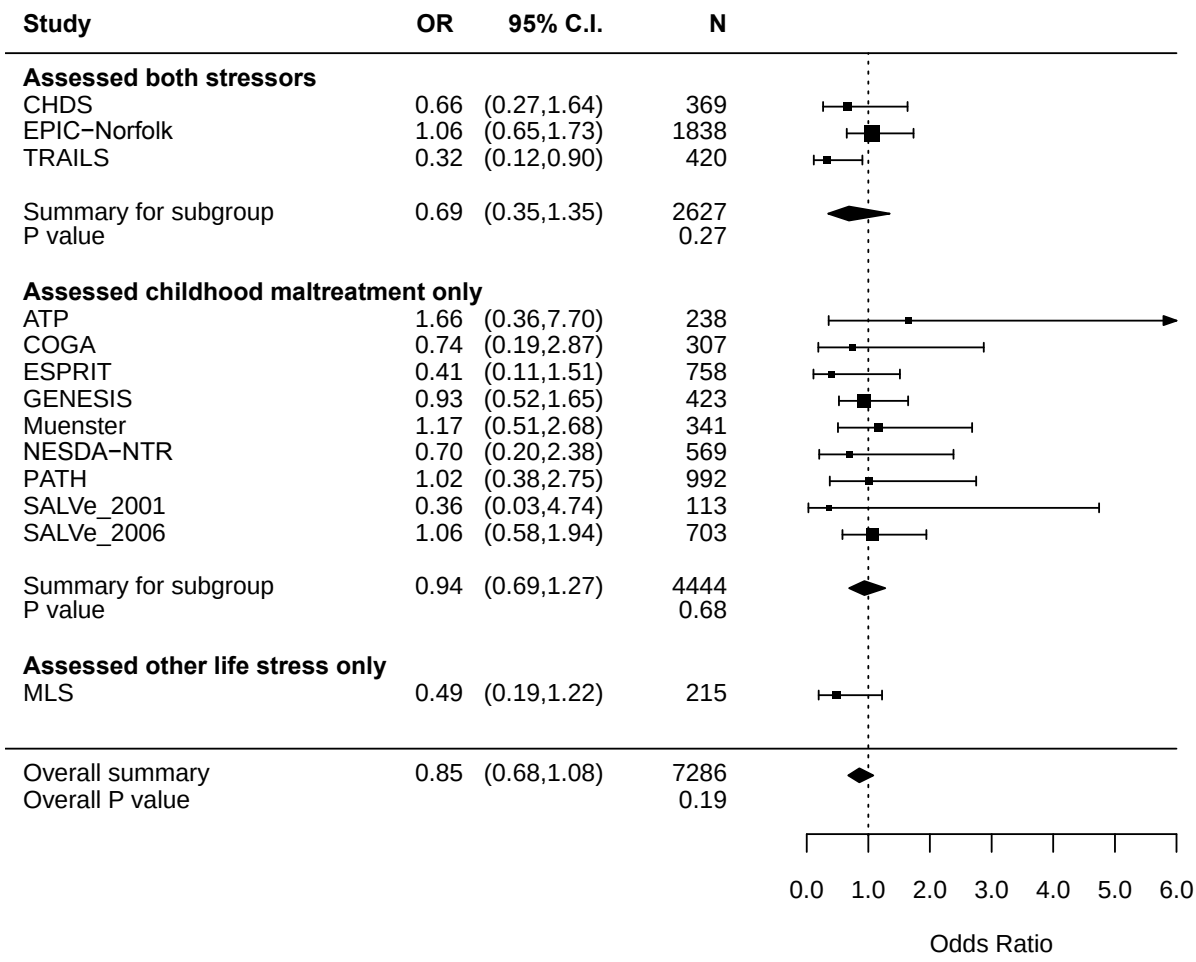
S12a. **GxE interaction term** (females only)
Lifetime depression diagnosis; Childhood maltreatment



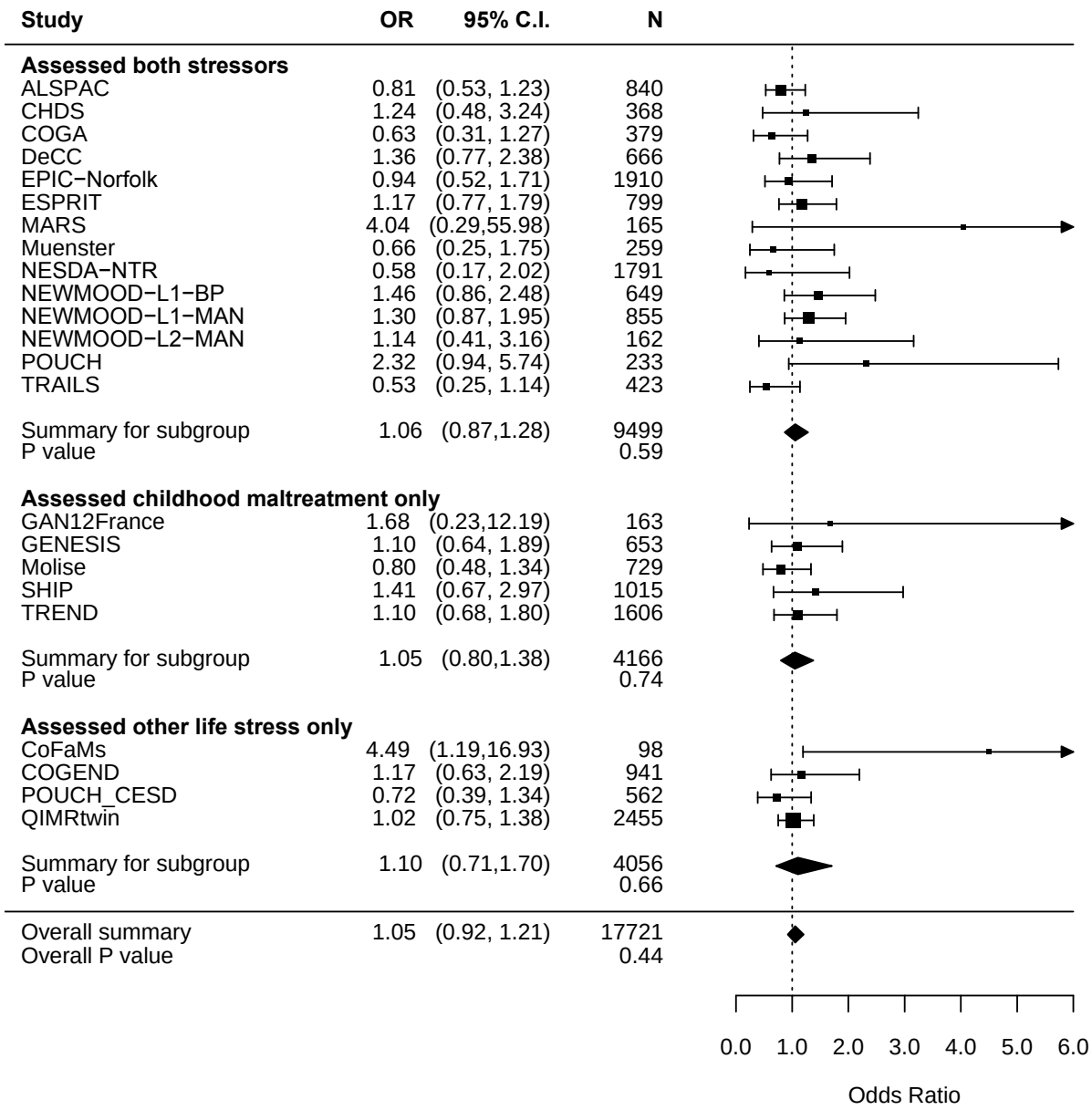
S12b. **GxE interaction term** (females only)
Current depression diagnosis; Childhood maltreatment



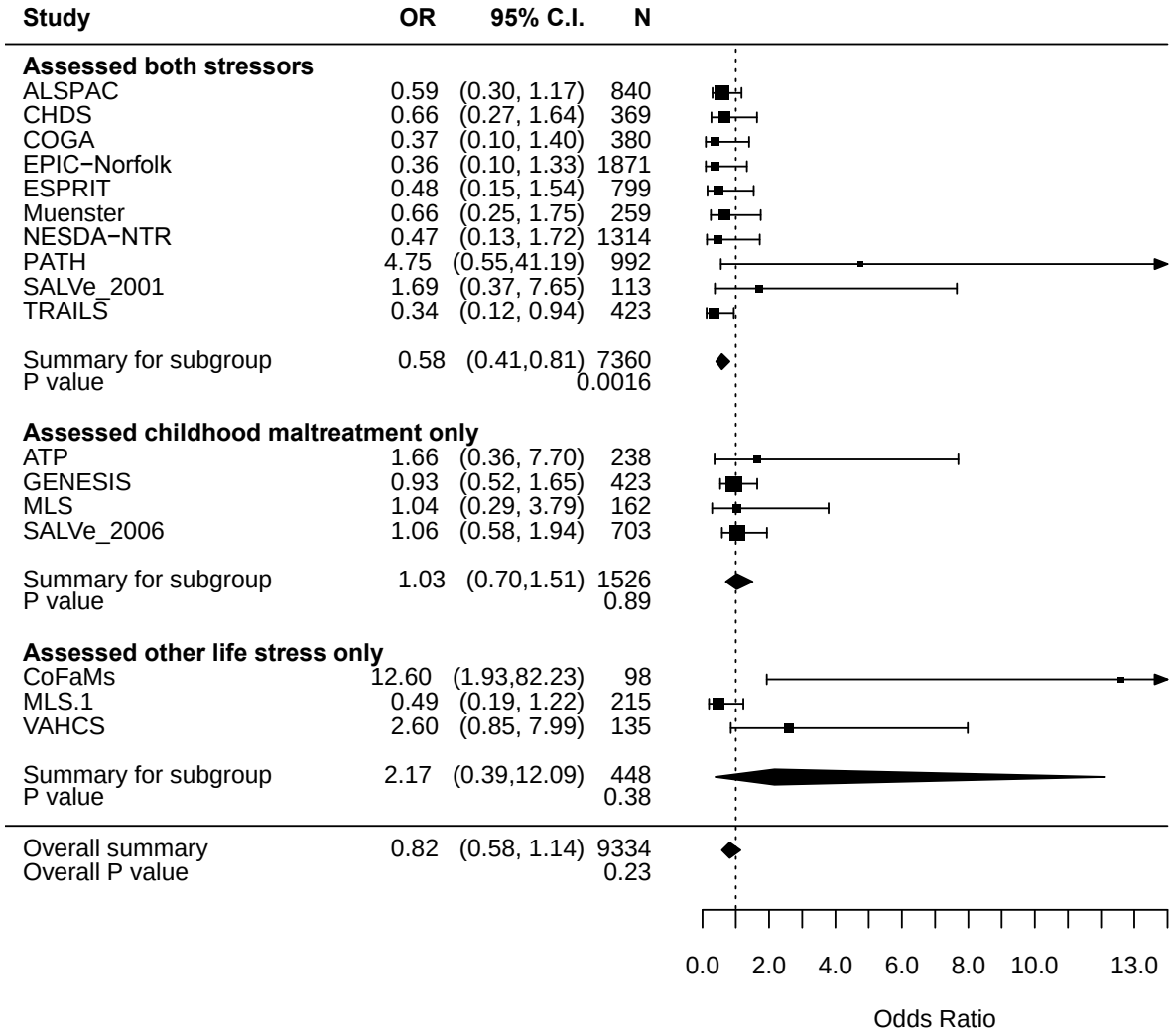
S12c. **GxE interaction term** (females only)
Lifetime depression diagnosis; Broad stress (other life stress < 5 years prior or childhood maltreatment)



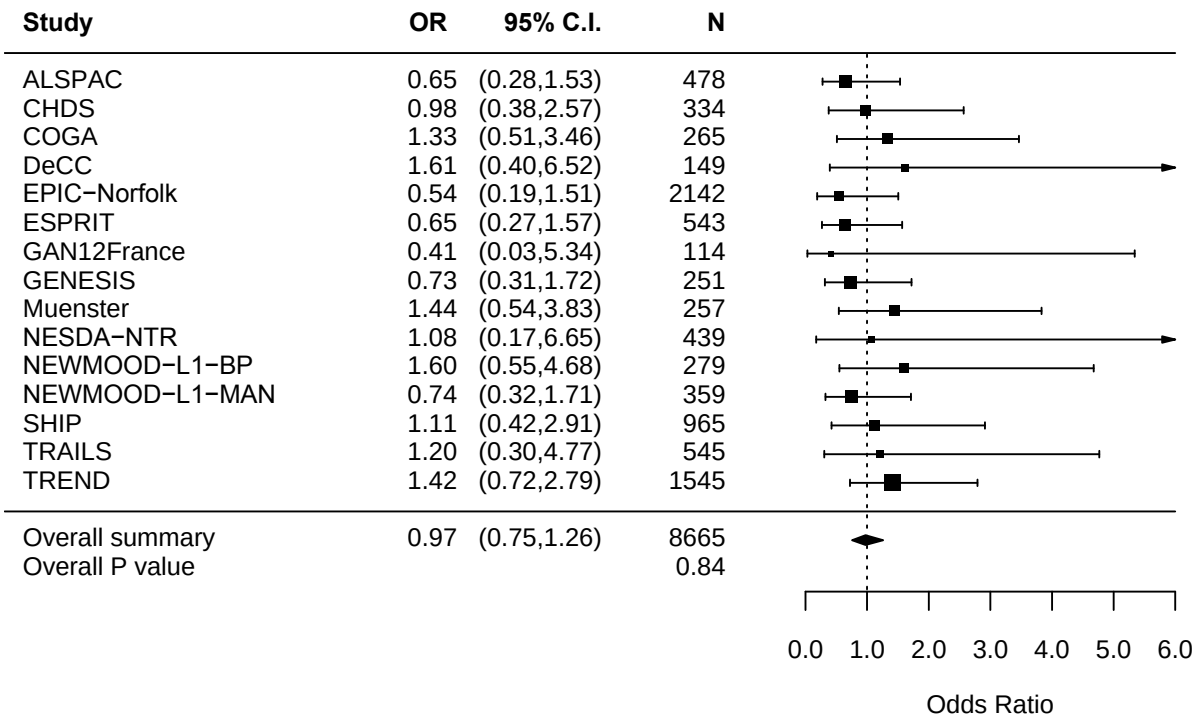
S12d. **GxE interaction term** (females only)
Current depression diagnosis; Broad stress (other life stress < 5 years prior or childhood maltreatment)



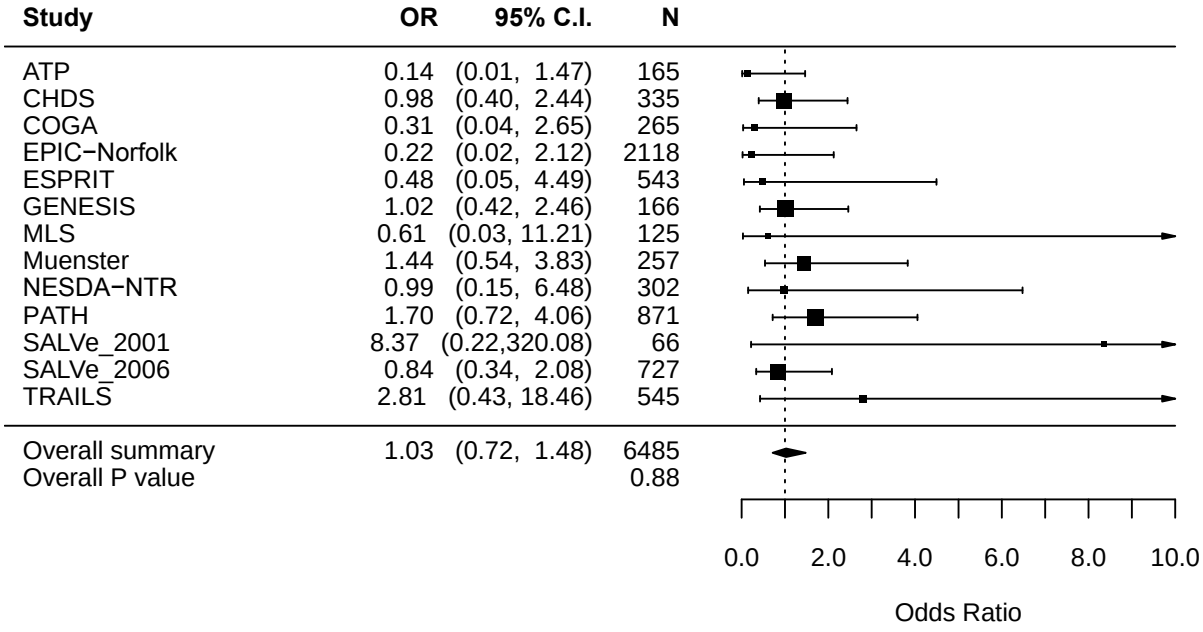
S12e. **GxE interaction term** (females only)
Lifetime depression diagnosis; Broad Stress (childhood maltreatment or other life stress at any time)



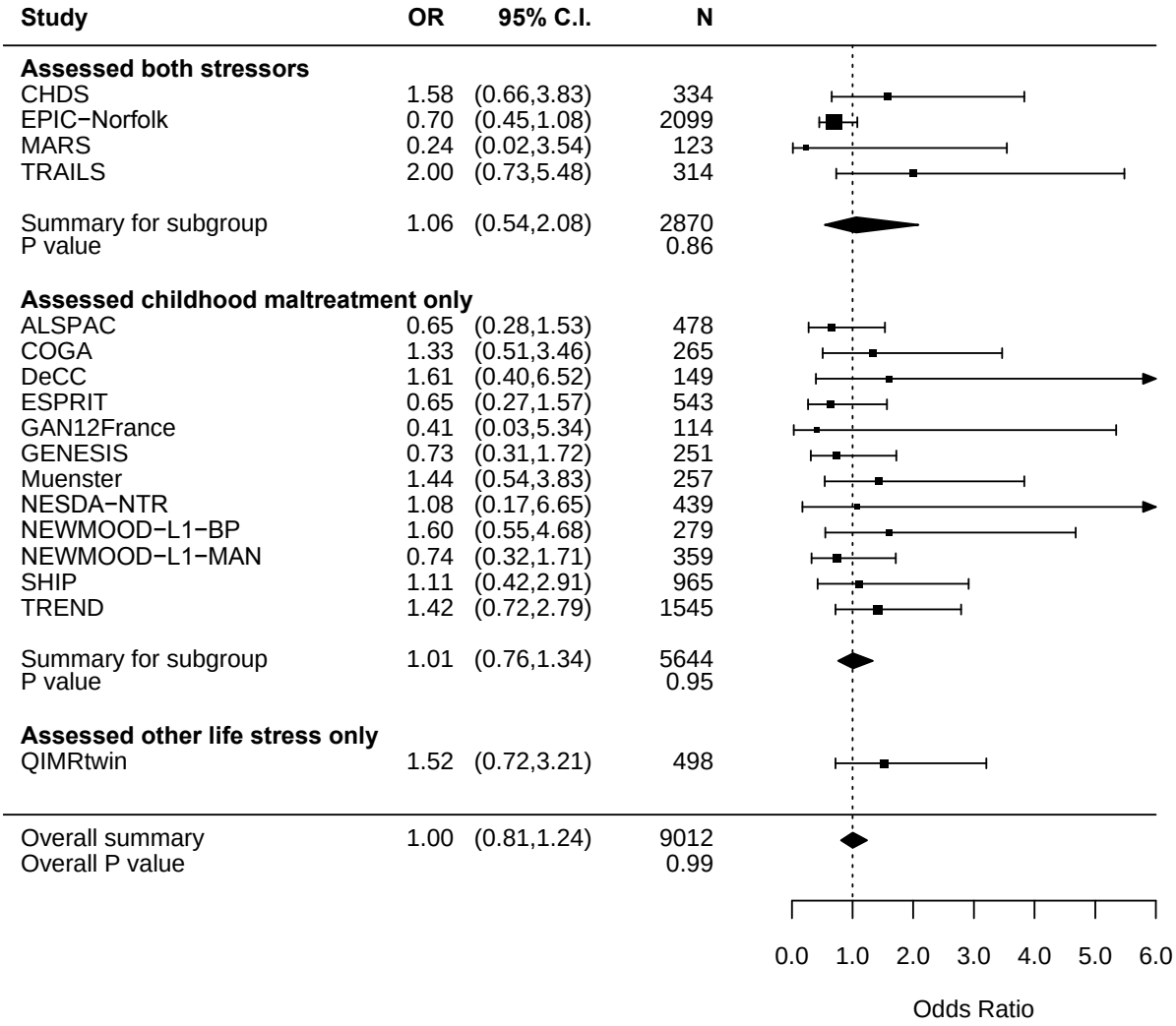
S12f. **GxE interaction term** (females only)
Current depression diagnosis; Broad Stress (childhood maltreatment or other life stress at any time)



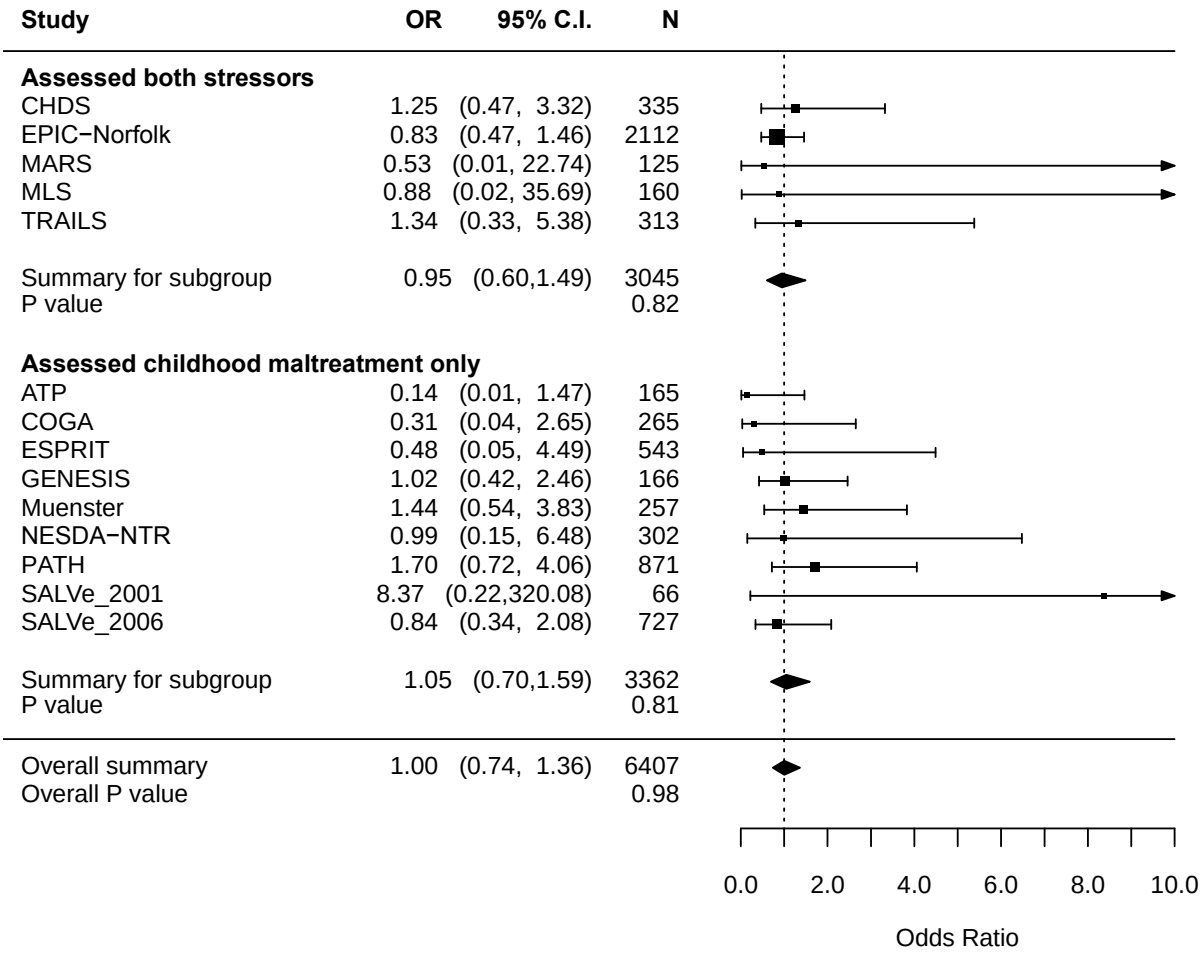
S12g. **GxE interaction term** (males only)
Lifetime depression diagnosis; Childhood maltreatment



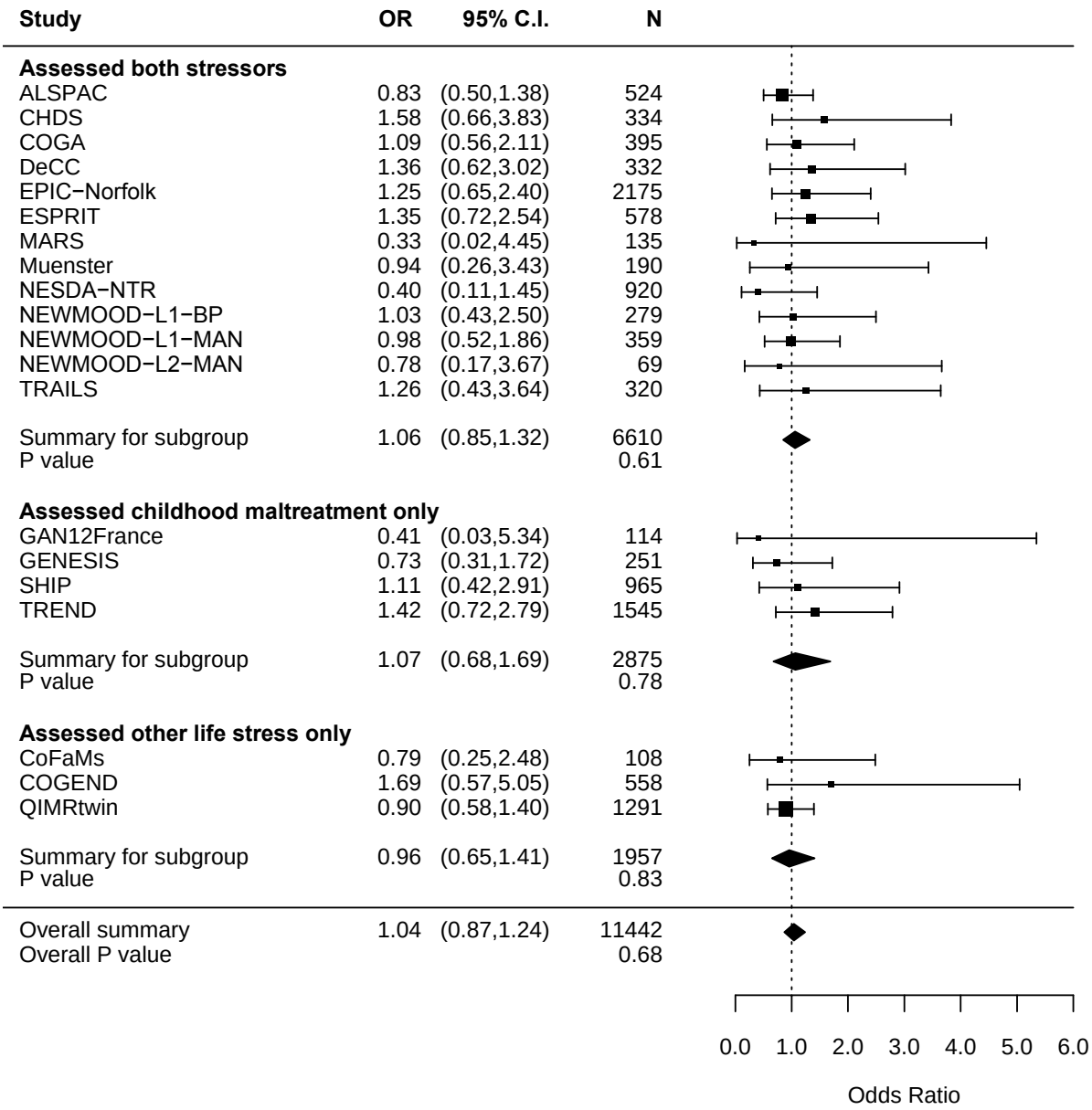
S12h. **GxE interaction term** (males only)
Current depression diagnosis; Childhood maltreatment



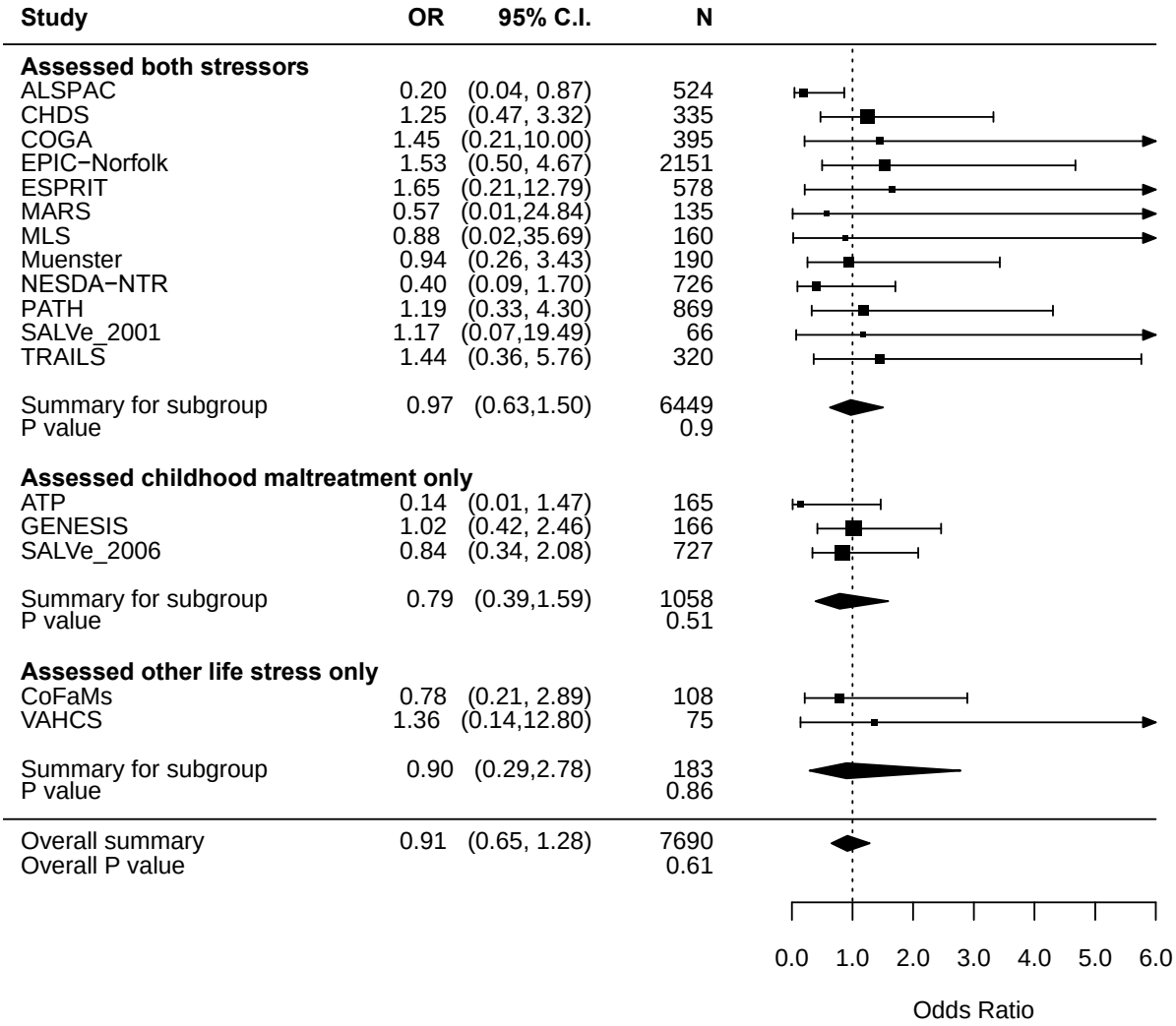
S12i. **GxE interaction term** (males only)
Lifetime depression diagnosis; Broad stress (other life stress < 5 years prior or childhood maltreatment)



S12j. **GxE interaction term** (males only)
Current depression diagnosis; Broad stress (other life stress < 5 years prior or childhood maltreatment)



S12k. **GxE interaction term** (males only)
Lifetime depression diagnosis; Broad Stress (childhood maltreatment or other life stress at any time)



S12l. **GxE interaction term** (males only)
Current depression diagnosis; Broad Stress (childhood maltreatment or other life stress at any time)

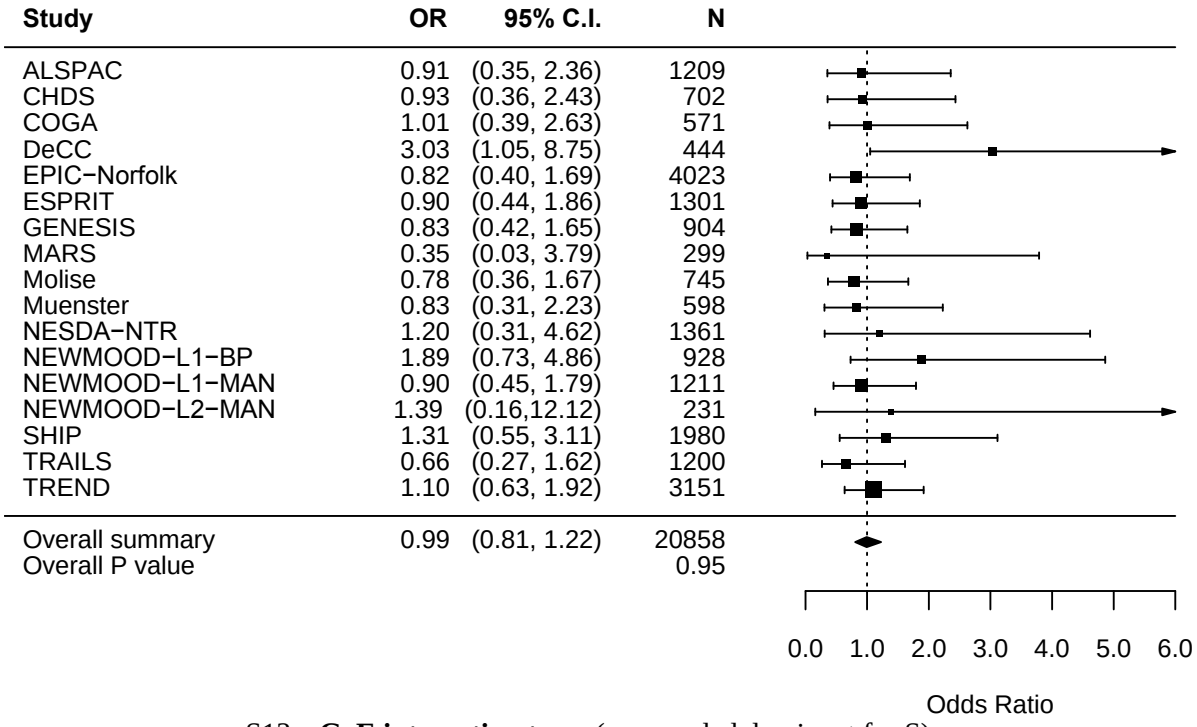
Figure S12: Forest plots for the **interaction term** from meta-analyses of subjects of all ages based on depression diagnosis and stress exposure stratified by sex
(Corresponds to results listed in Supplemental Table S14)

MODEL: $depression = \beta_0 + \beta_1(age) + \beta_2(sex) + \beta_3(stress) + \beta_4(gene) + \beta_5(gene \times stress)$

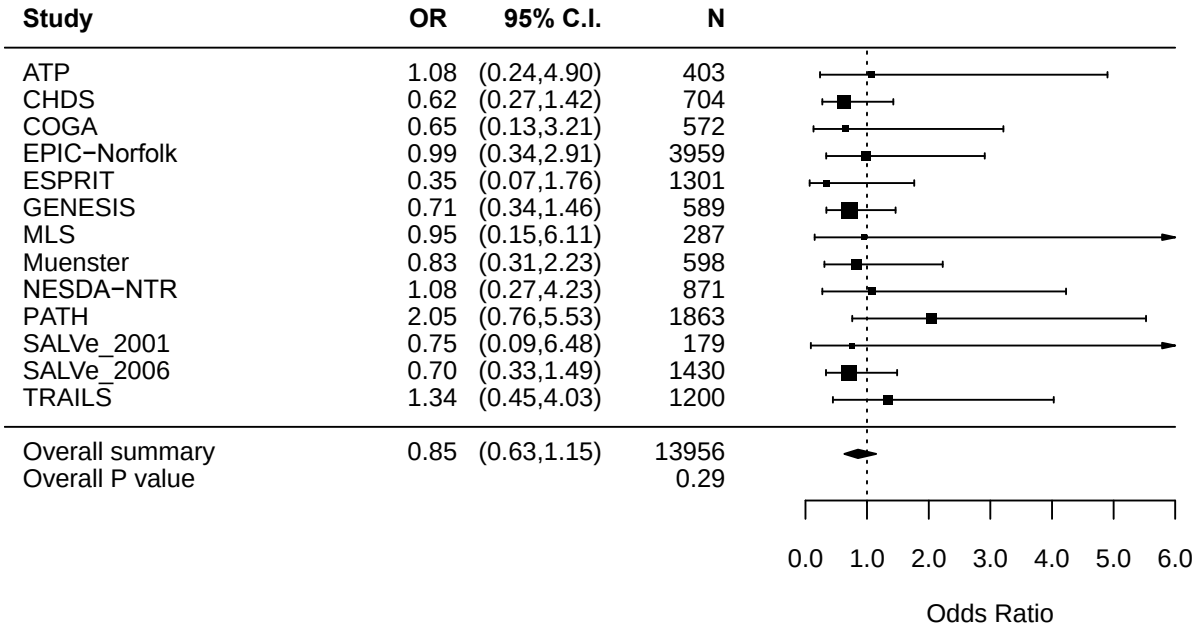
Gene (additive coding in number of S alleles for 5-HTTLPR (LL = 0; LS=1; SS=2))

Hypothesized direction of effect is OR > 1

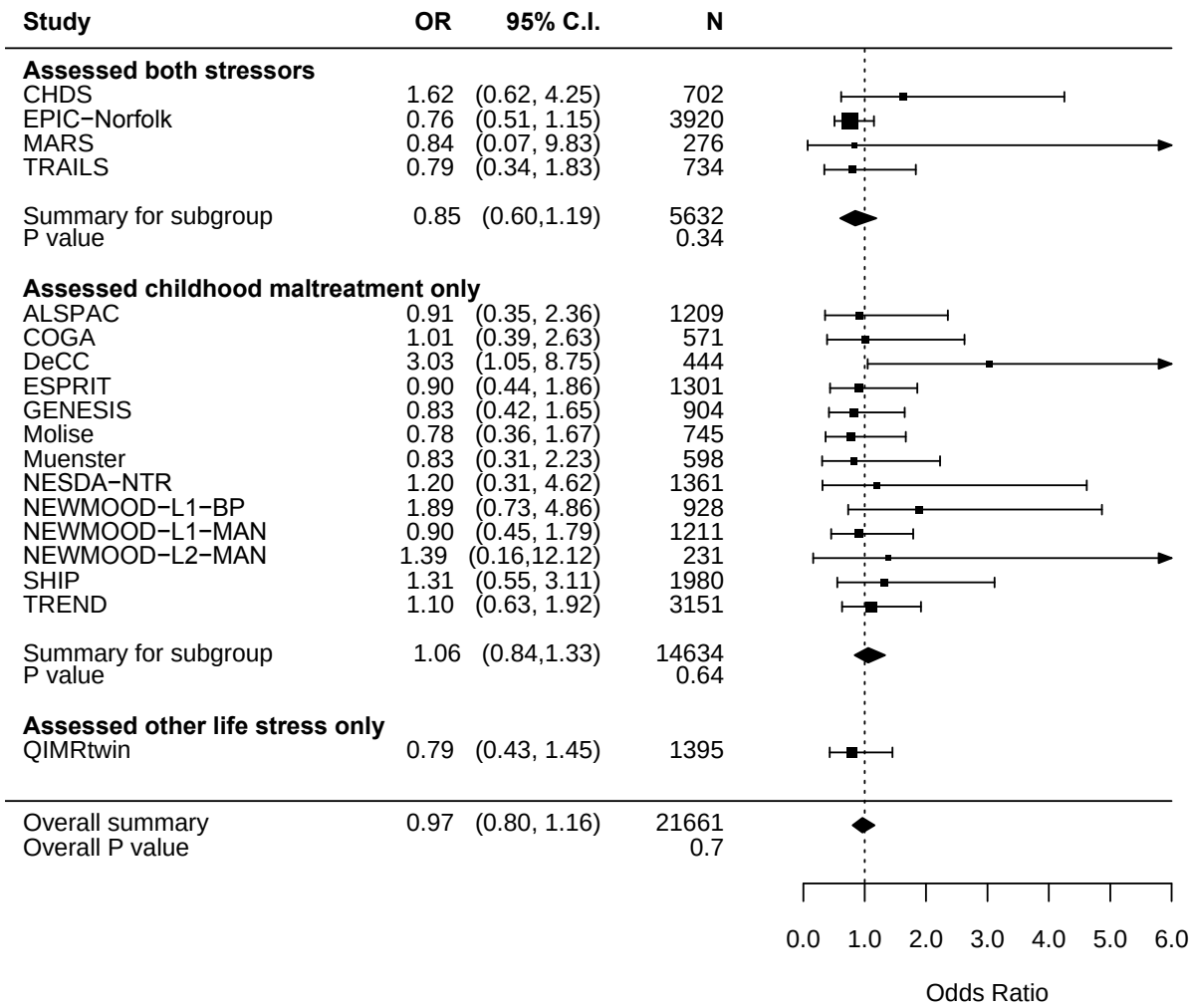
Figure S13: Forest plots for the gene x stress terms from models using alternate coding for the genetic term (dominant in the S allele, recessive in the S allele, and additive for the haplotypes other than L_A). These models were based on depression diagnosis stress exposure, and subjects of all ages. (Corresponds to the analyses in Supplemental Table S15)



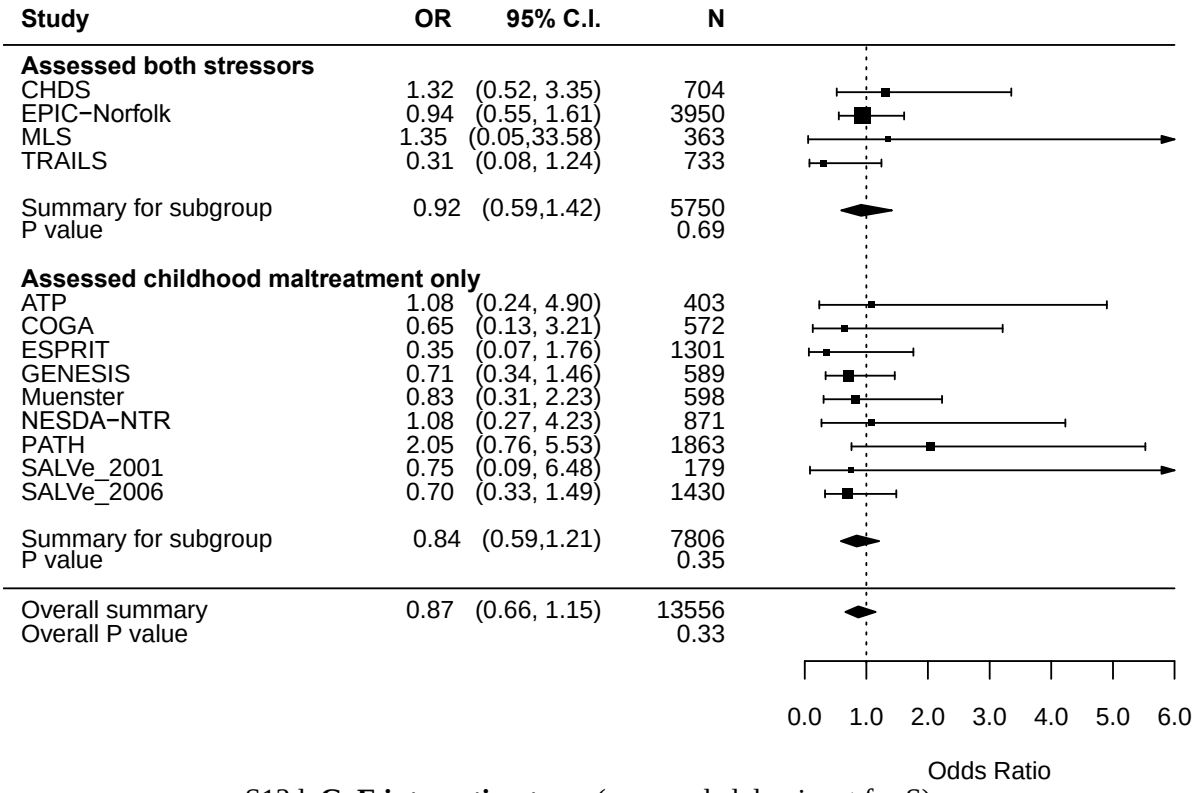
S13a. **GxE interaction term** (gene coded dominant for S)
Lifetime depression diagnosis; Childhood maltreatment



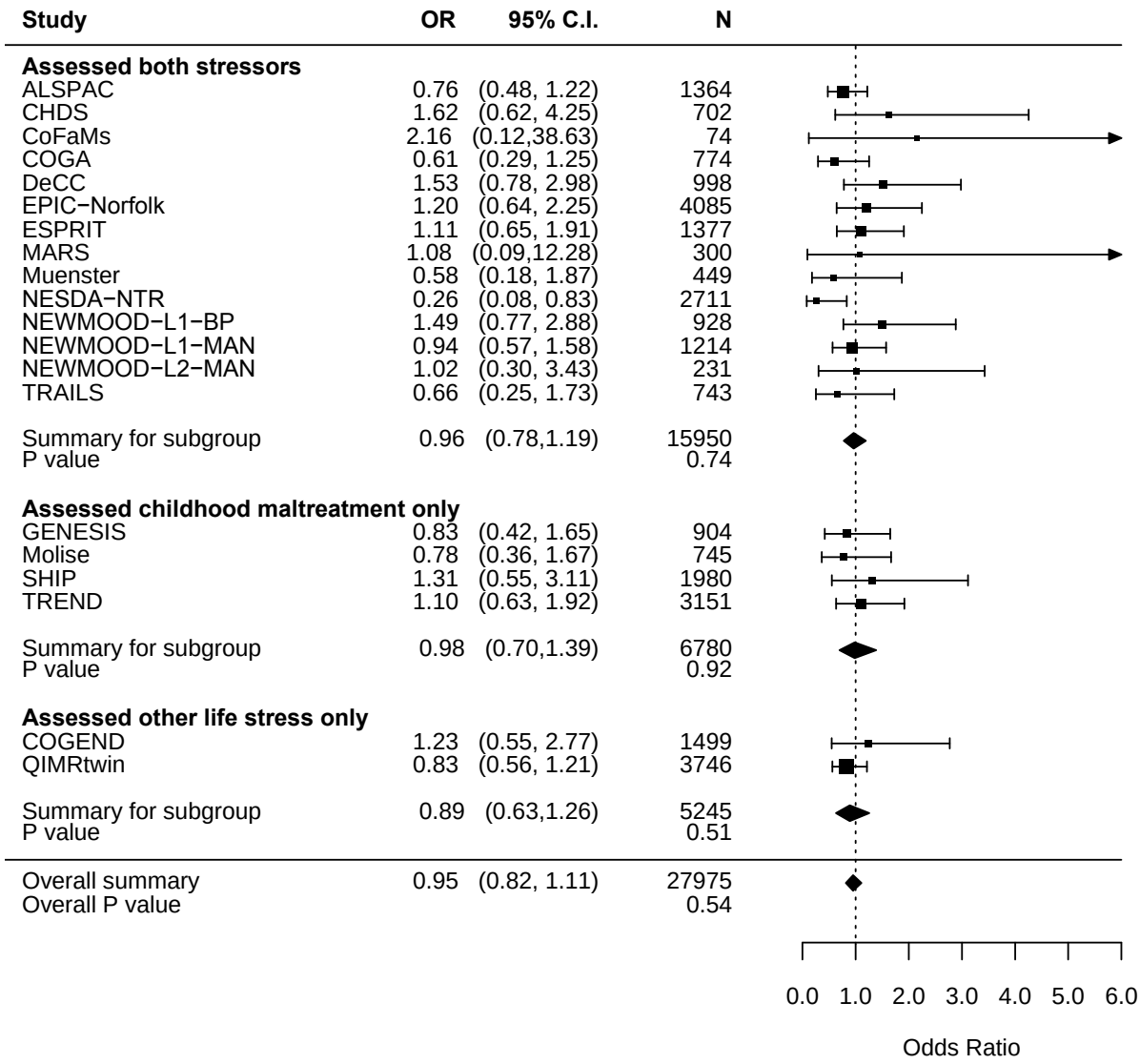
S13b. **GxE interaction term** (gene coded dominant for S)
Current depression diagnosis; Childhood maltreatment



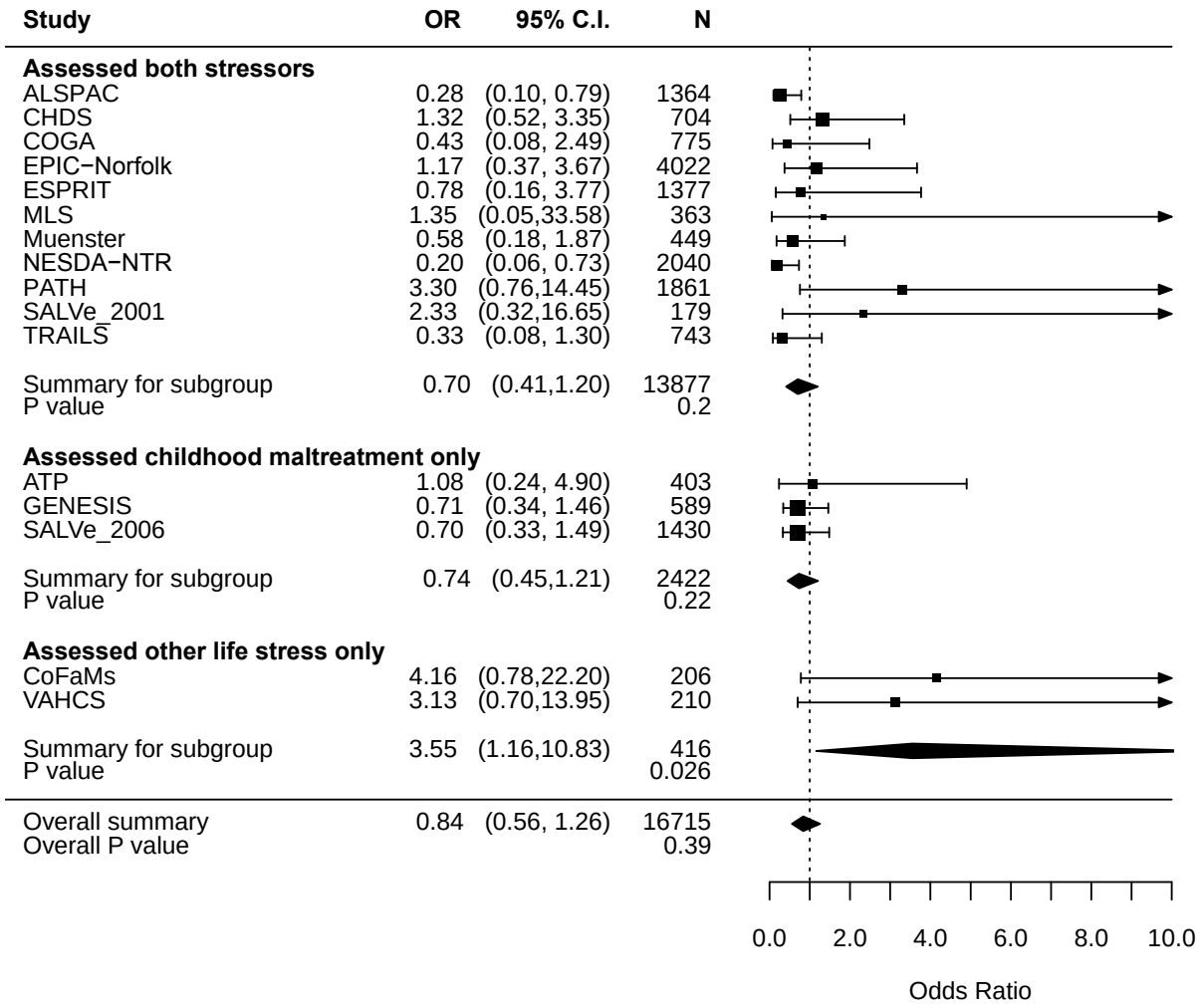
S13c. **GxE interaction term** (gene coded dominant for S)
Lifetime depression diagnosis; Broad stress (other life stress < 5 years prior or childhood maltreatment)



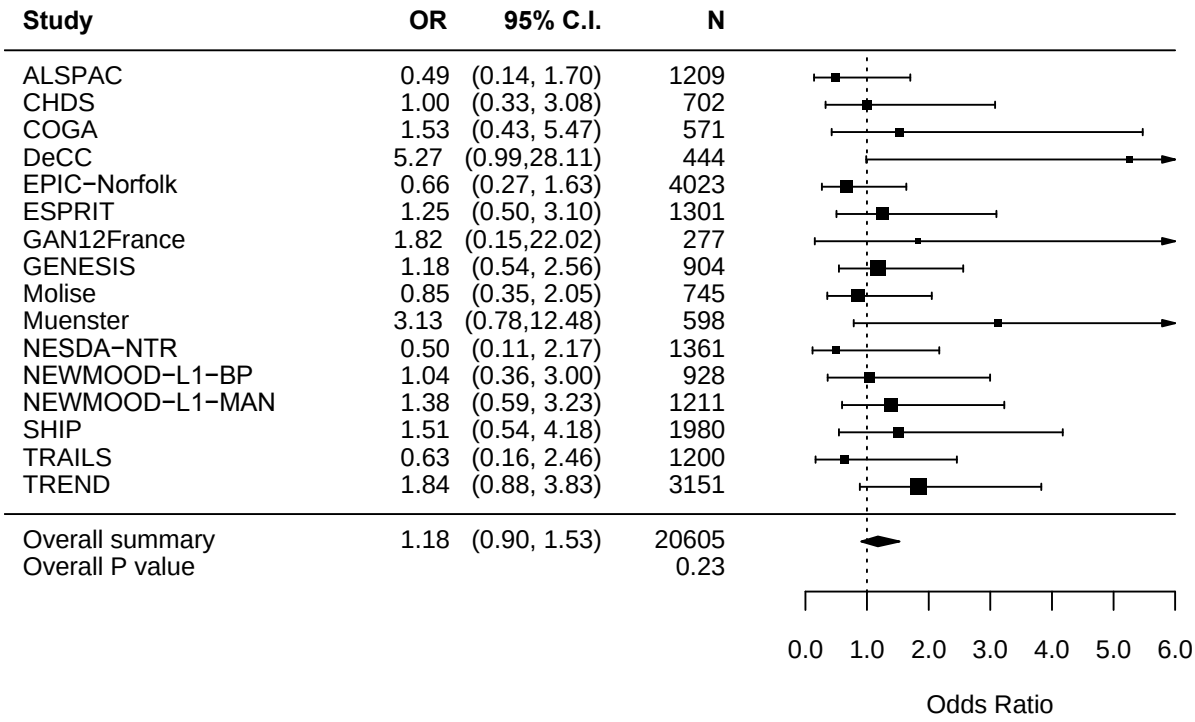
S13d. **GxE interaction term** (gene coded dominant for S)
Current depression diagnosis; Broad stress (other life stress < 5 years prior or childhood maltreatment)



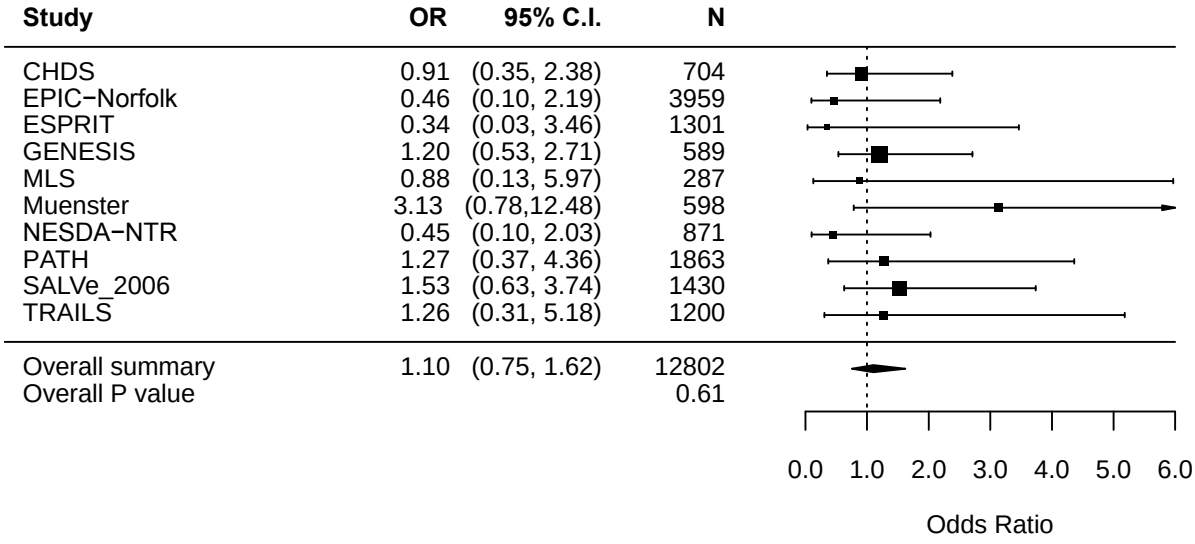
S13e. **GxE interaction term** (gene coded dominant for S)
Lifetime depression diagnosis; Broad Stress (childhood maltreatment or other life stress at any time)



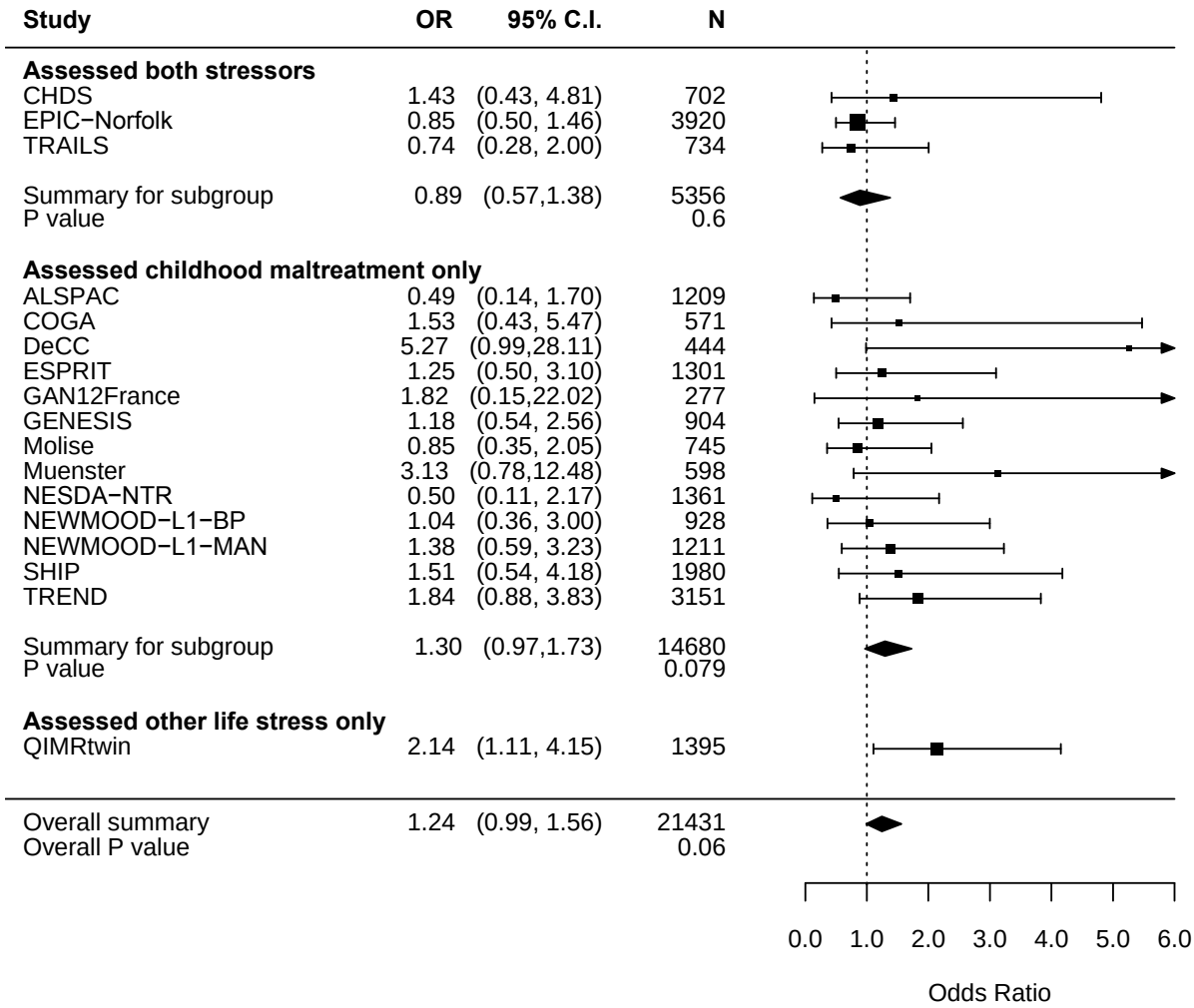
S13f. **GxE interaction term** (gene coded dominant for S)
Current depression diagnosis; Broad Stress (childhood maltreatment or other life stress at any time)



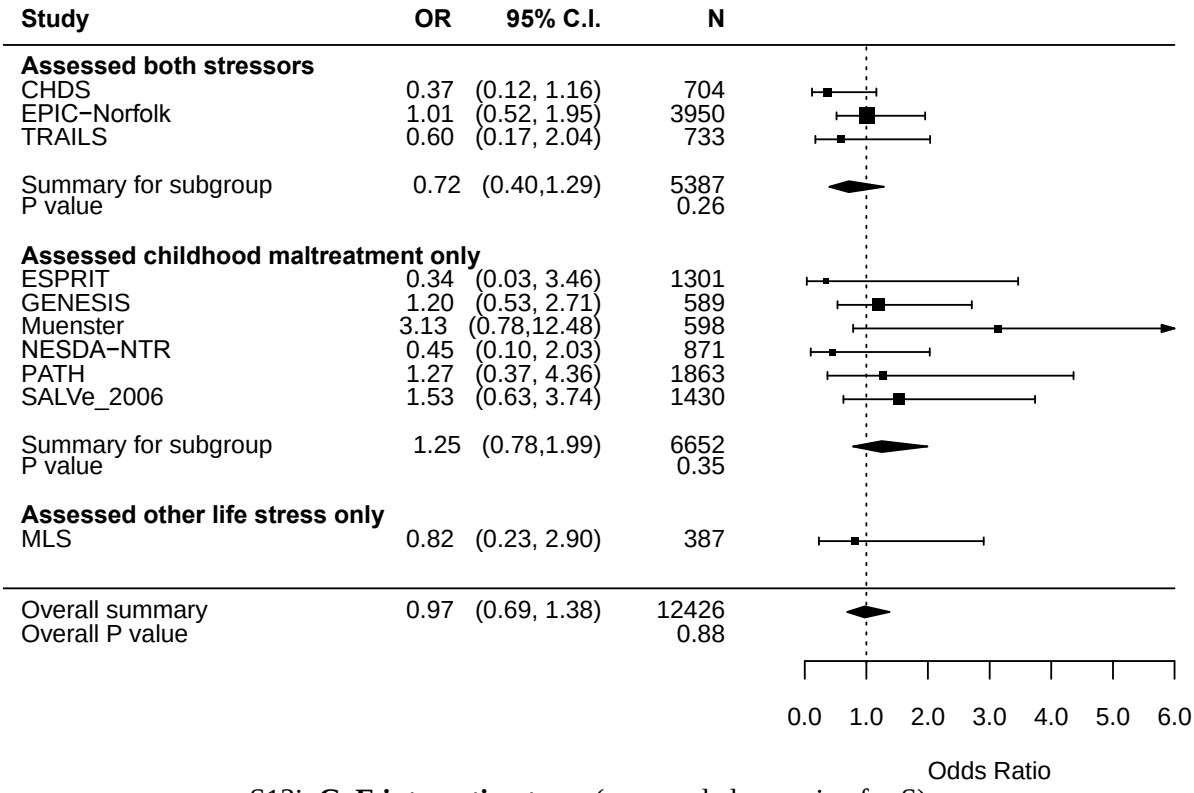
S13g. **GxE interaction term** (gene coded recessive for S)
Lifetime depression diagnosis; Childhood maltreatment



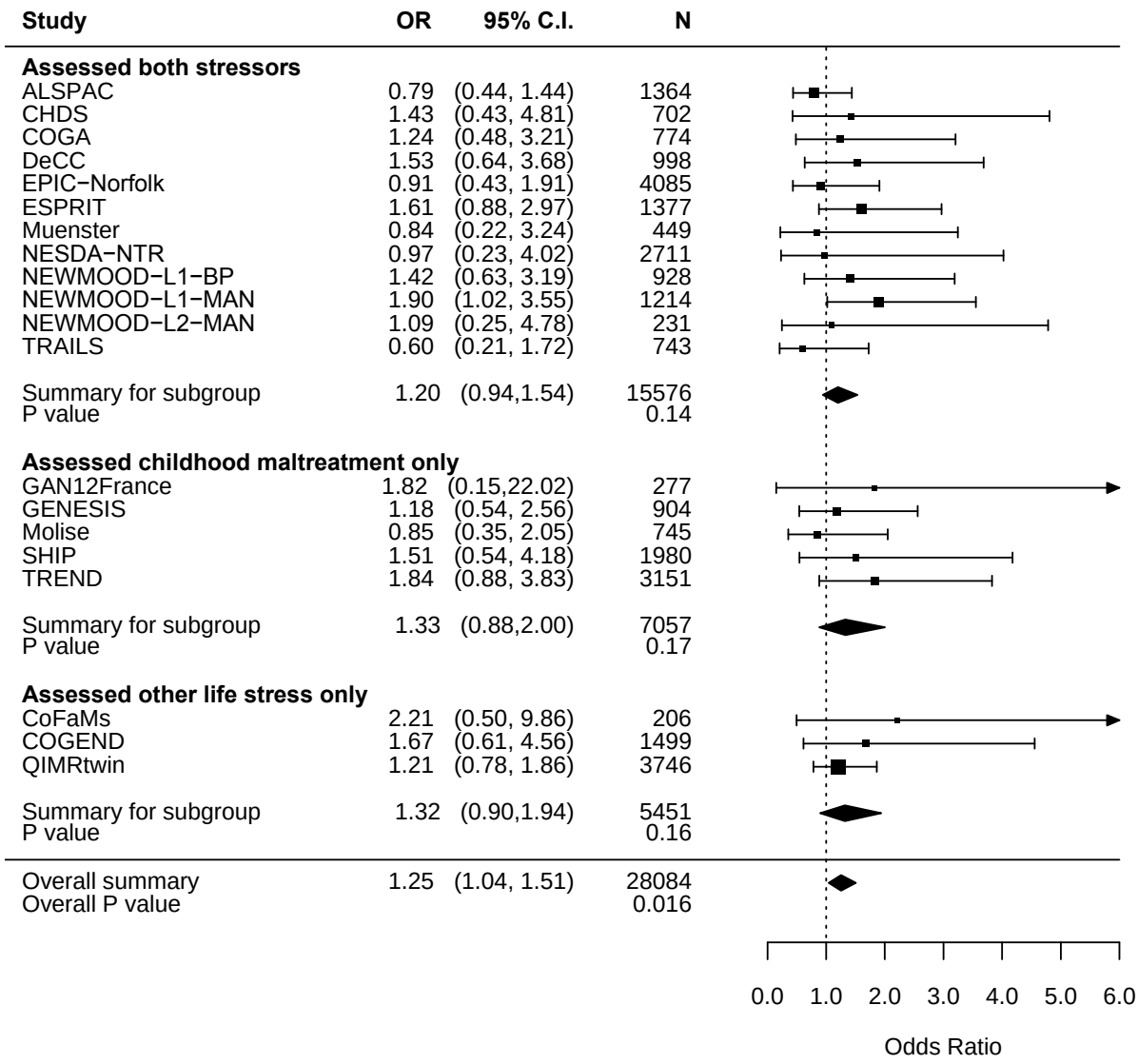
S13h. **GxE interaction term** (gene coded recessive for S)
Current depression diagnosis; Childhood maltreatment



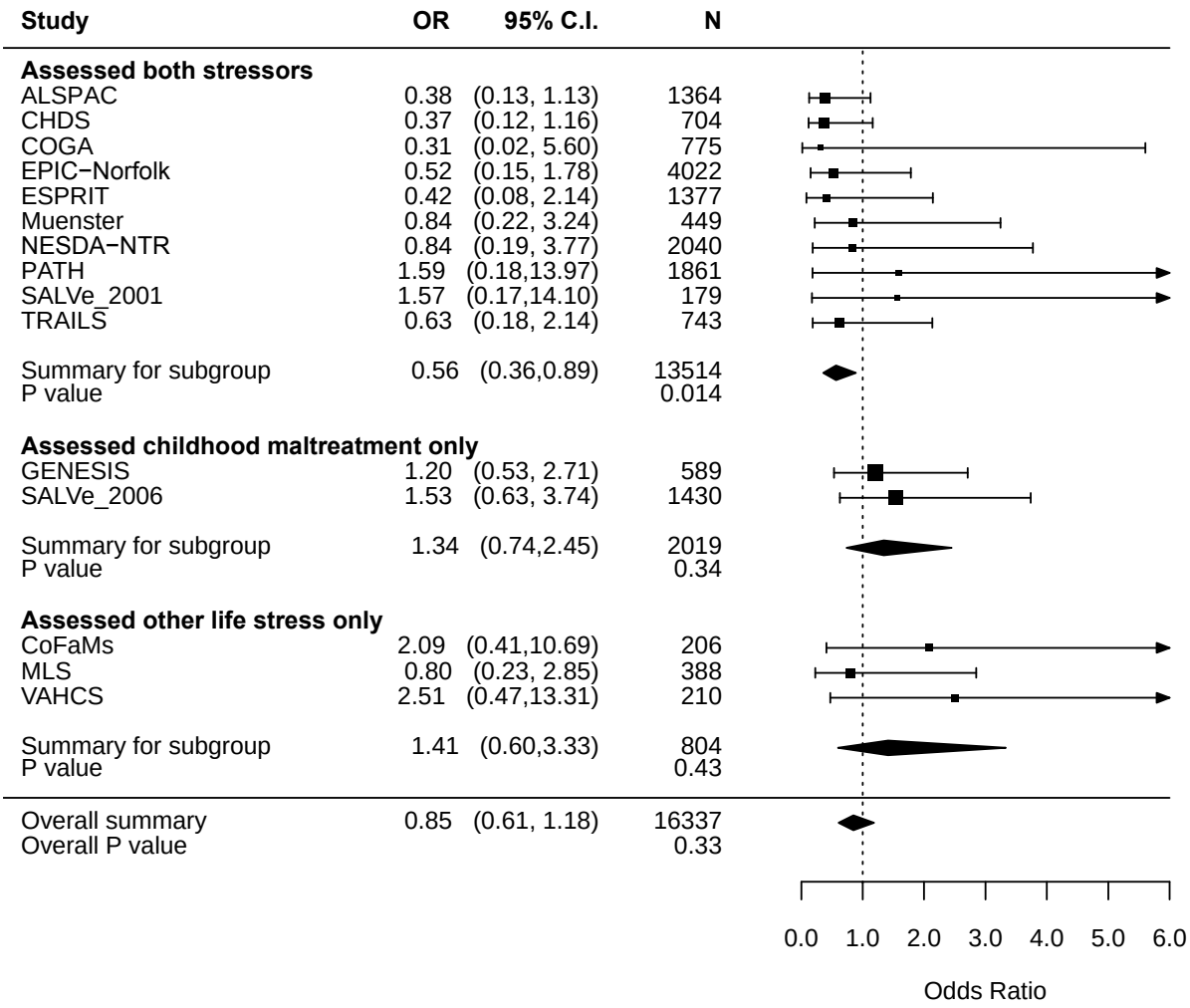
S13i. **GxE interaction term** (gene coded recessive for S)
Lifetime depression diagnosis; Broad stress (other life stress < 5 years prior or childhood maltreatment)



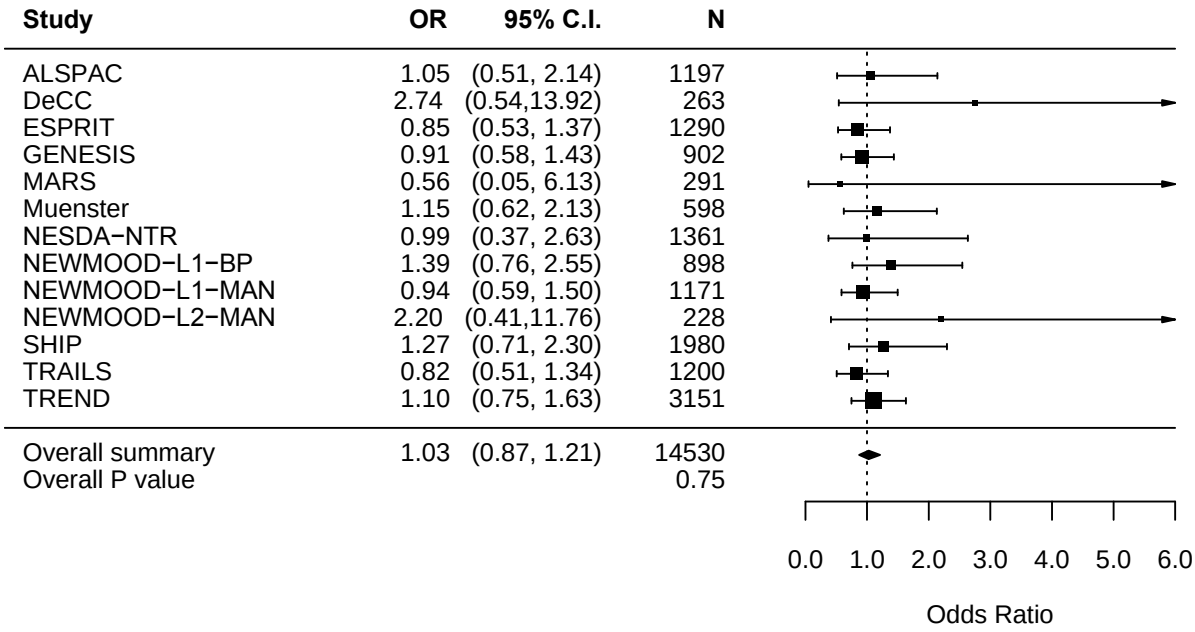
S13j. **GxE interaction term** (gene coded recessive for S)
Current depression diagnosis; Broad stress (other life stress < 5 years prior or childhood maltreatment)



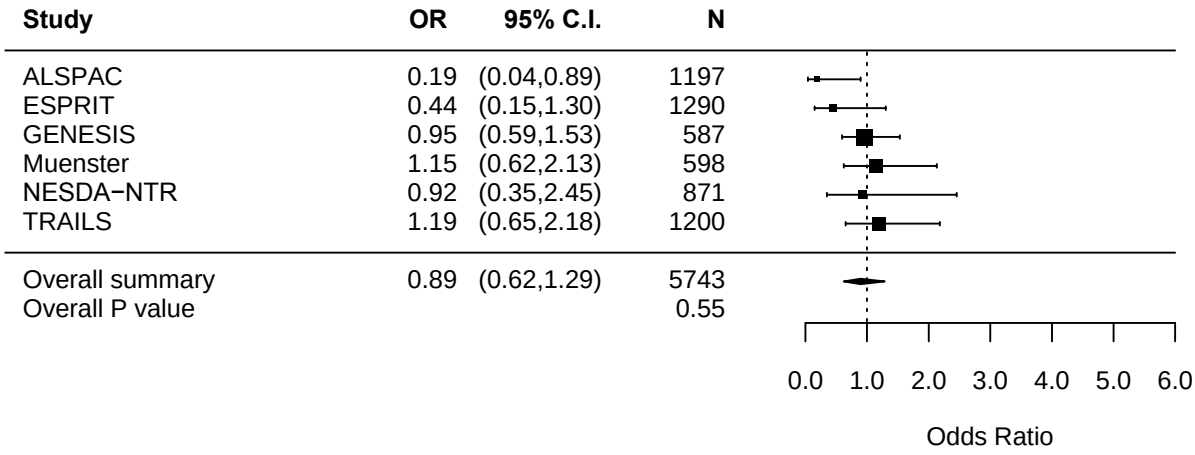
S13k. **GxE interaction term** (gene coded recessive for S)
Lifetime depression diagnosis; Broad Stress (childhood maltreatment or other life stress at any time)



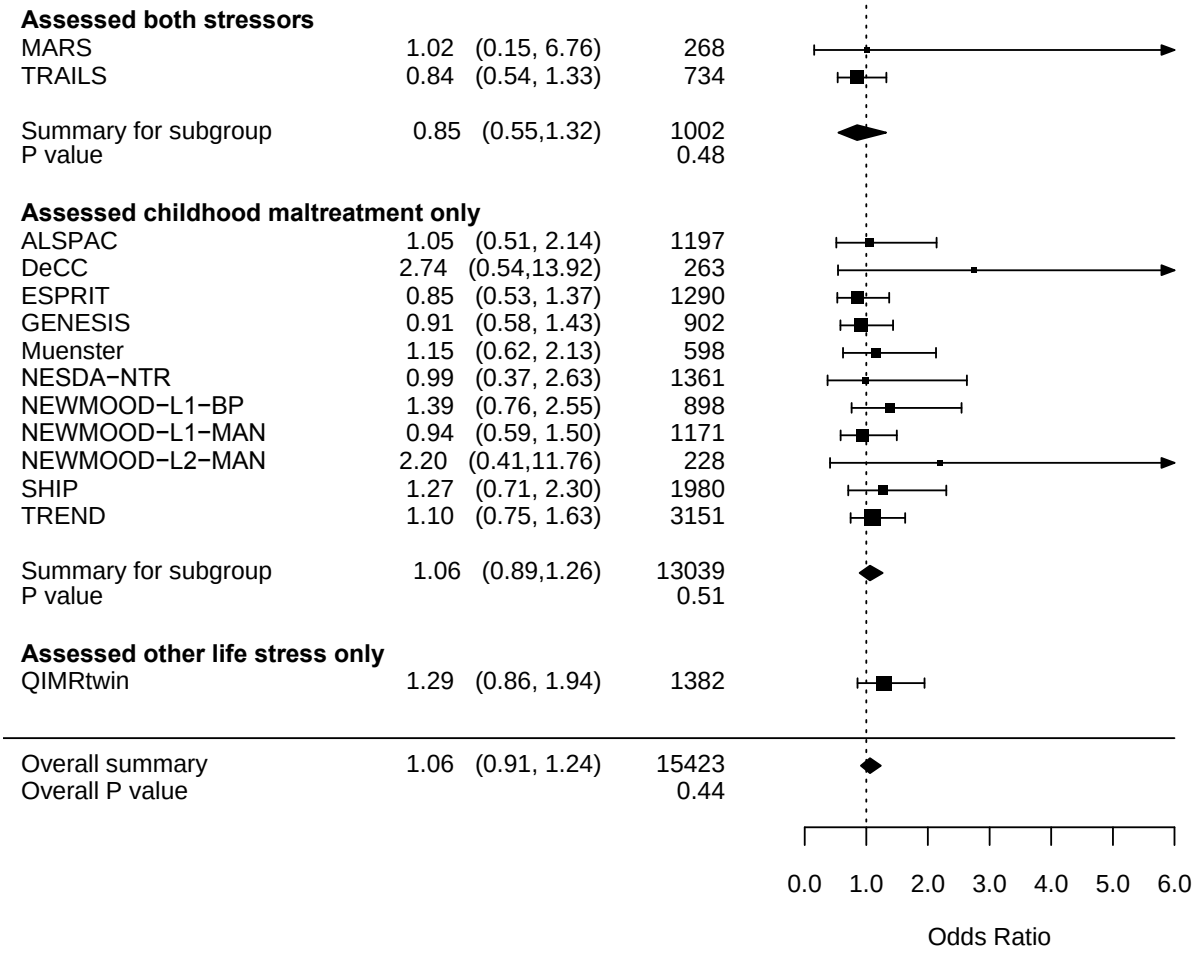
S13l. **GxE interaction term** (gene coded recessive for S)
Current depression diagnosis; Broad Stress (childhood maltreatment or other life stress at any time)



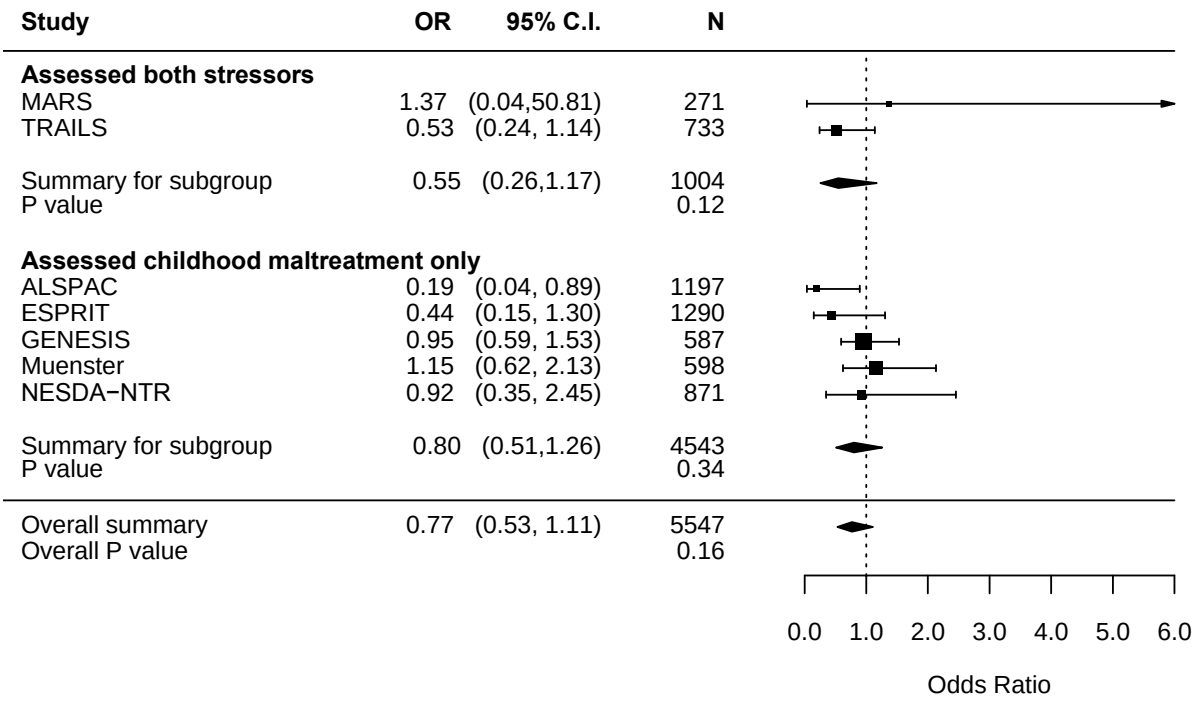
S13m. **GxE interaction term** (gene coded additive for the number of non-L_A haplotypes)
Lifetime depression diagnosis; Childhood maltreatment



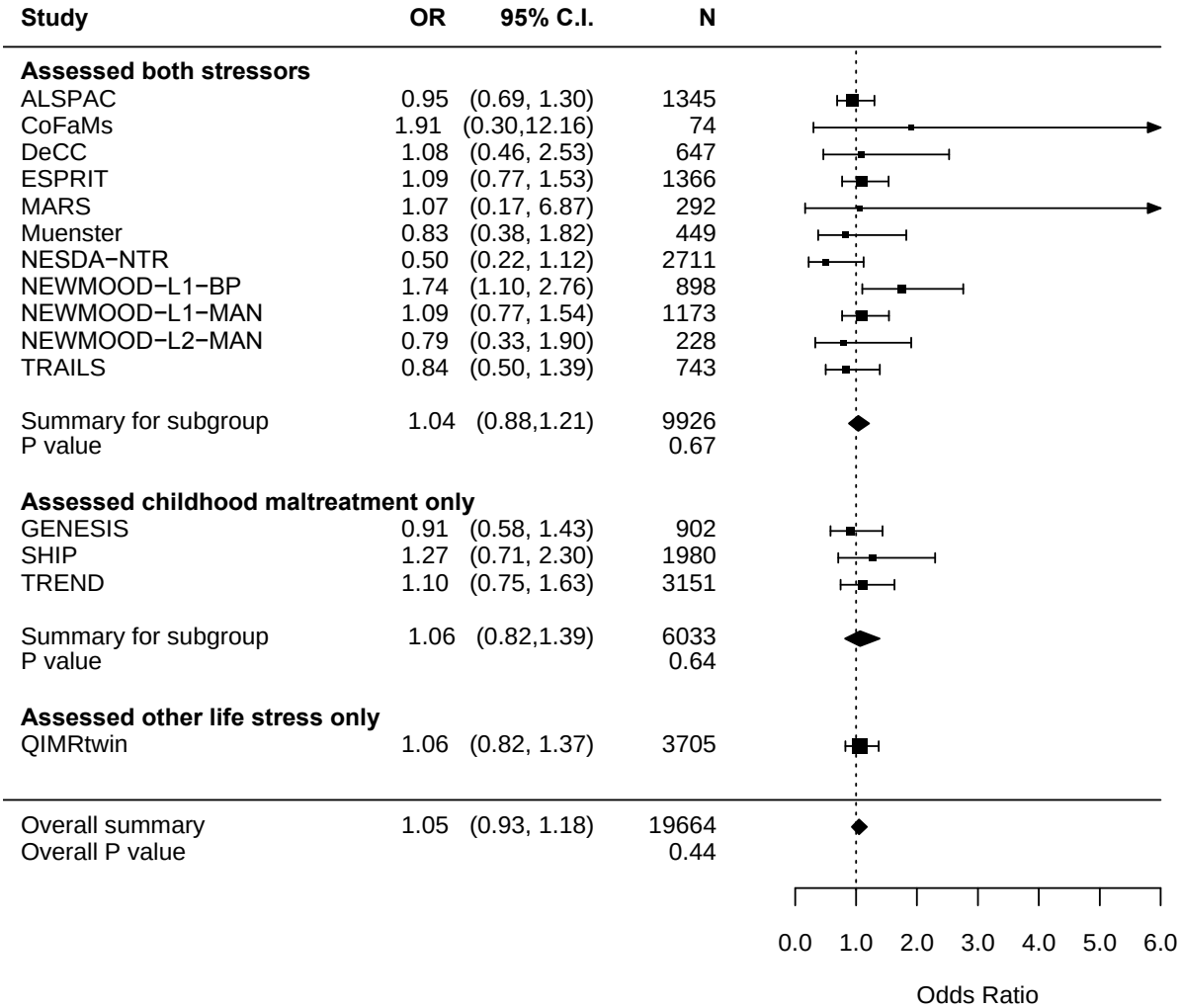
S13n. **GxE interaction term** (gene coded additive for the number of non-L_A haplotypes) Current depression diagnosis; Childhood maltreatment



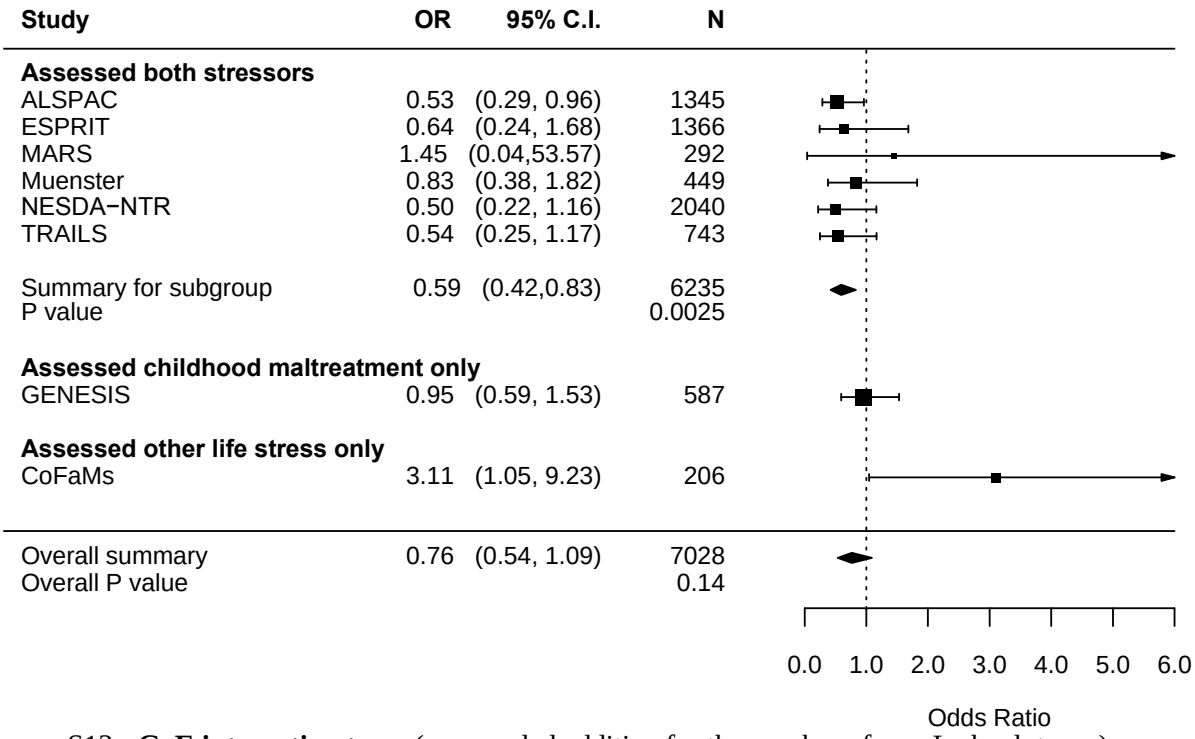
S13o. **GxE interaction term** (gene coded additive for the number of non-L_A haplotypes) Lifetime depression diagnosis; Broad stress (other life stress < 5 years prior or childhood maltreatment)



S13p. **GxE interaction term** (gene coded additive for the number of non-L_A haplotypes) Current depression diagnosis; Broad stress (other life stress < 5 years prior or childhood maltreatment)



S13q. **GxE interaction term** (gene coded additive for the number of non-L_A haplotypes) Lifetime depression diagnosis; Broad Stress (childhood maltreatment or other life stress at any time)



S13r. **GxE interaction term** (gene coded additive for the number of non-L_A haplotypes) Current depression diagnosis; Broad Stress (childhood maltreatment or other life stress at any time)

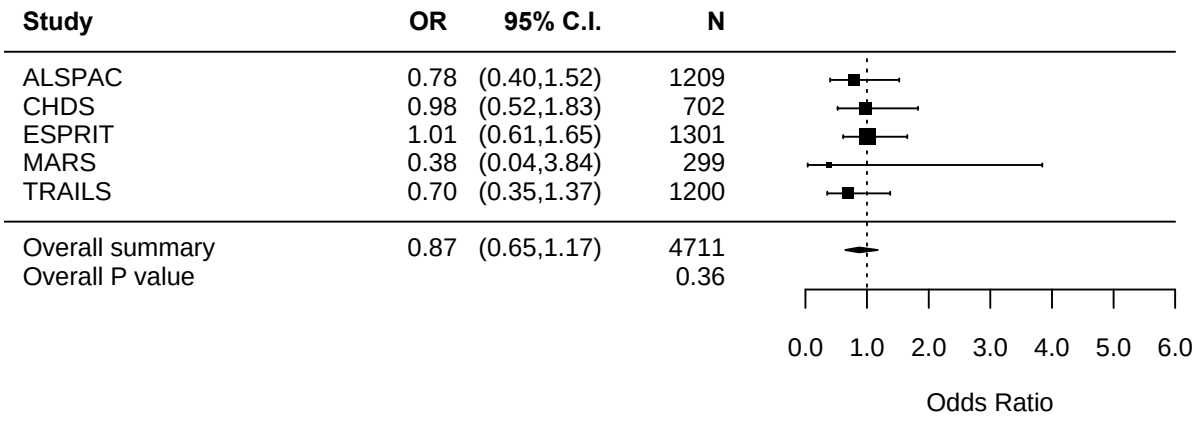
Figure S13: Forest plots for the **interaction term** from meta-analyses of subjects of all ages based on depression diagnosis and stress exposure using alternate coding for the genetic term (Corresponds to results listed in Supplemental Table S15)

MODEL: $depression = \beta_0 + \beta_1(age) + \beta_2(sex) + \beta_3(stress) + \beta_4(gene) + \beta_5(gene \times stress)$

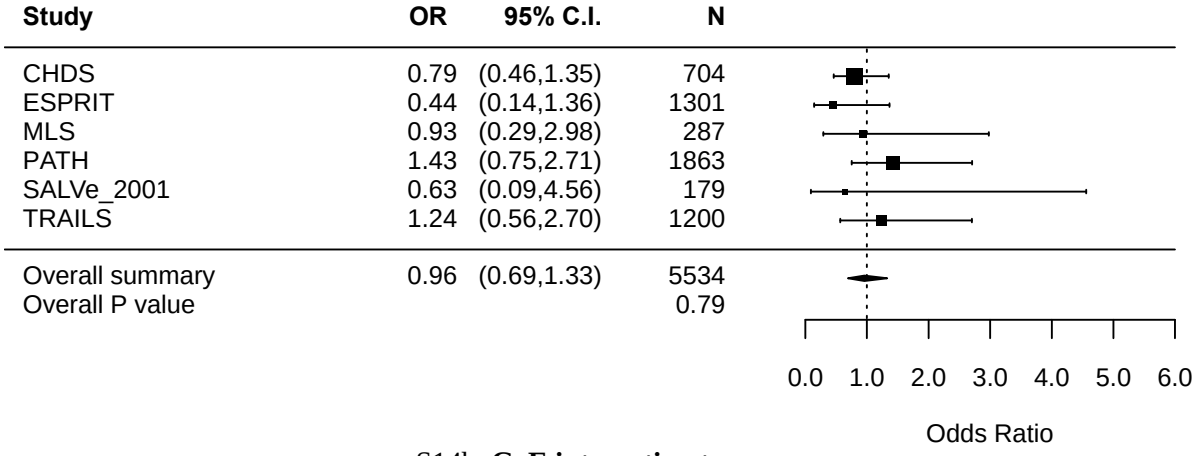
Gene (Dominant for S, Recessive for S, or additive for the number of non-L_A haplotypes)

Hypothesized direction of effect is OR > 1

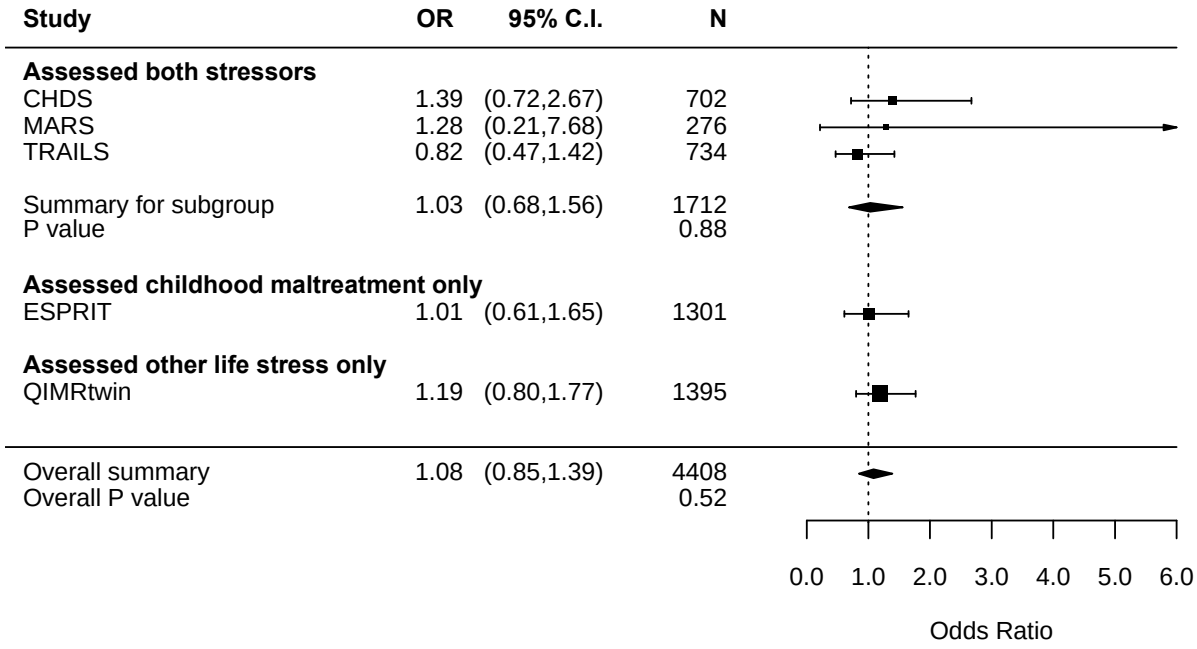
Figure S14: Forest plots for the gene x stress terms from the models based on depression diagnoses, stress exposure, and subjects of all ages, but limited to subjects from longitudinal studies (Corresponds to the analyses in Supplemental Table S16)



S14a. **GxE interaction term**
Lifetime depression diagnosis; Childhood maltreatment

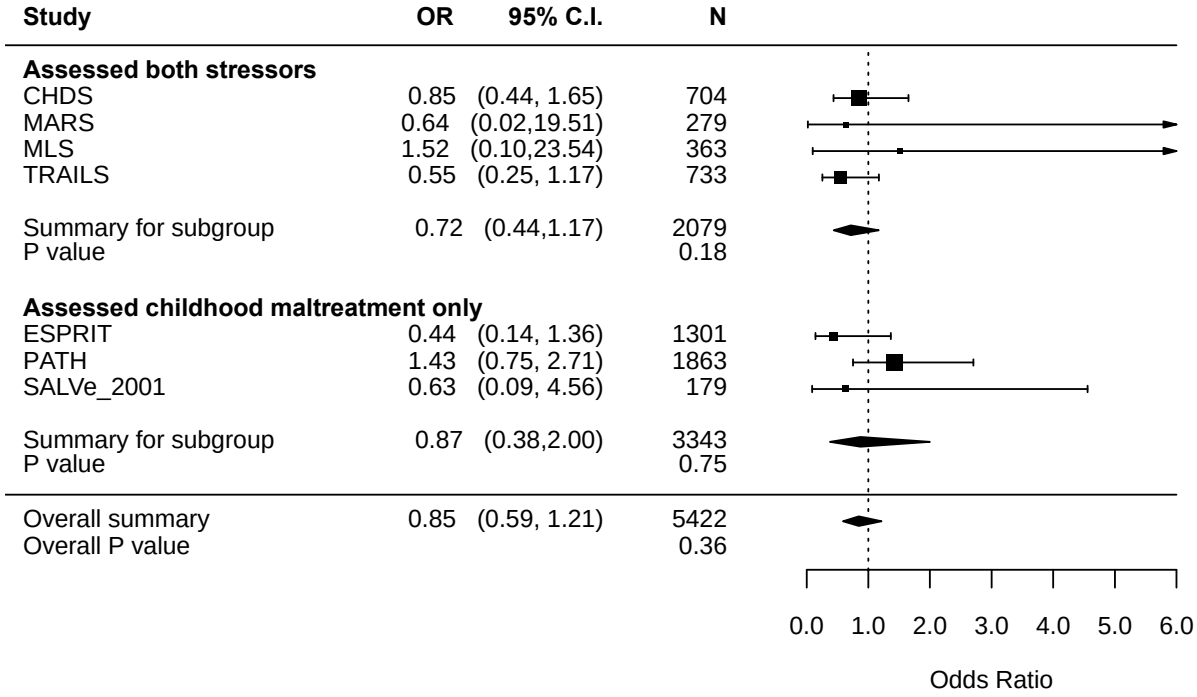


S14b. **GxE interaction term**
Current depression diagnosis; Childhood maltreatment



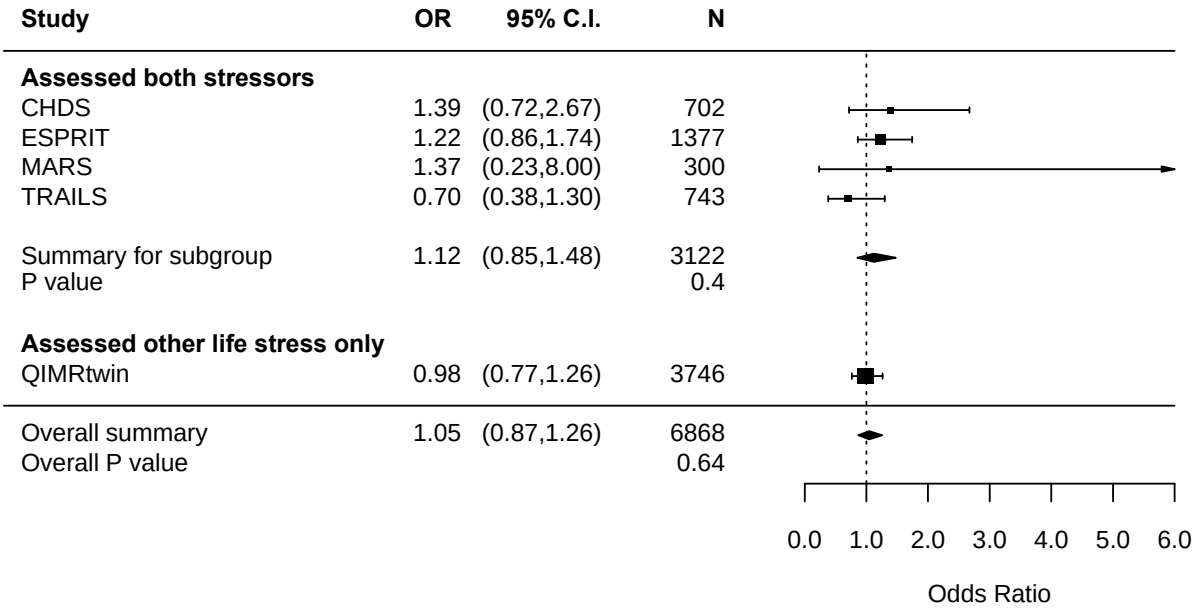
S14c. **GxE interaction term**

Lifetime depression diagnosis; Broad stress (other life stress < 5 years prior or childhood maltreatment)

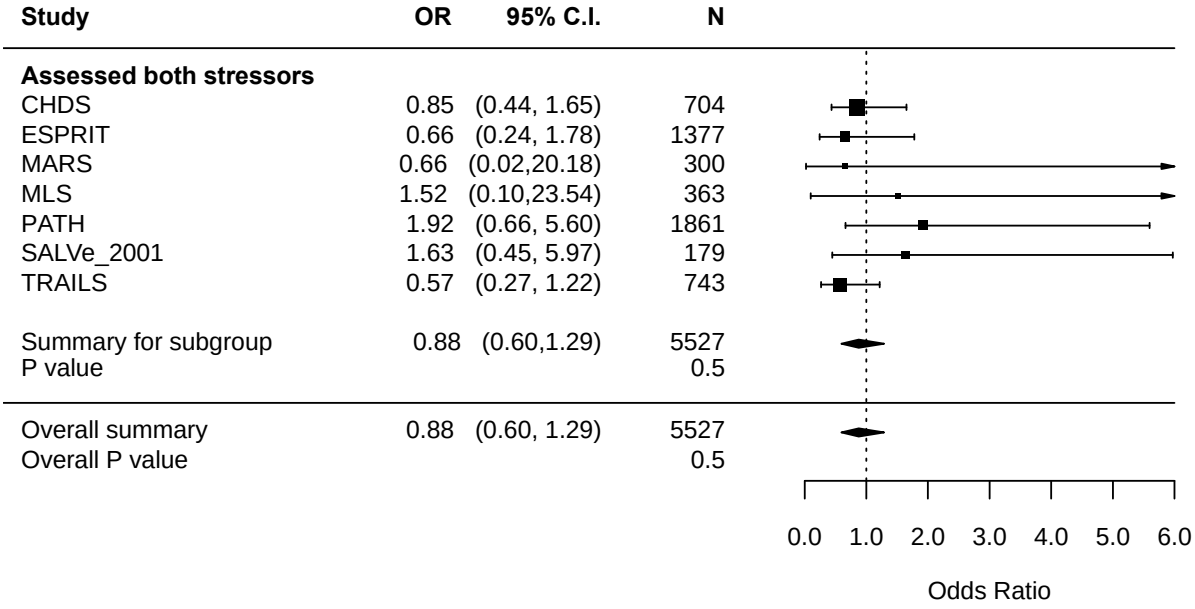


S14d. **GxE interaction term**

Current depression diagnosis; Broad stress (other life stress < 5 years prior or childhood maltreatment)



S14e. **GxE interaction term**
Lifetime depression diagnosis; Broad Stress (childhood maltreatment or other life stress at any time)



S14f. **GxE interaction term**
Current depression diagnosis; Broad Stress (childhood maltreatment or other life stress at any time)

Figure S14: Forest plots for the **interaction term** from meta-analyses of subjects of all ages based on depression diagnosis and stress exposure using only studies that followed their subjects longitudinally (Corresponds to results listed in Supplemental Table S16)

MODEL: $depression = \beta_0 + \beta_1(age) + \beta_2(sex) + \beta_3(stress) + \beta_4(gene) + \beta_5(gene \times stress)$

Gene (additive coding in number of S alleles for 5-HTTLPR (LL = 0; LS=1; SS=2))

Hypothesized direction of effect is OR > 1

REFERENCES for the Supplement

1 Culverhouse, R. C. *et al.* Protocol for a collaborative meta-analysis of 5-HTTLPR, stress, and depression. *BMC psychiatry* **13**, 304, doi:10.1186/1471-244X-13-304 (2013).

2 Caspi, A. *et al.* Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* **301**, 386-389, doi:10.1126/science.1083968301/5631/386 [pii] (2003).

3 R Development Core Team. *R: A language and environment for statistical computing.*, (R Foundation for Statistical Computing, 2008).

4 Huedo-Medina, T. B., Sanchez-Meca, J., Marin-Martinez, F. & Botella, J. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? *Psychol Methods* **11**, 193-206, doi:10.1037/1082-989X.11.2.193 (2006).

5 Cochran, W. G. The Combination of Estimates from Different Experiments. *Biometrics* **10**, 101-129, doi:Doi 10.2307/3001666 (1954).