

MAOA-uVNTR, childhood adversity and differential susceptibility

Paper V of the Peace Papers, six papers on one framework; each stands alone. Protocol for a systematic review and meta-analysis. Website version, working draft v9, 30 October 2026. Devon Summerhayes, London. Not yet registered or peer reviewed.

Abstract

Background. Variation in the monoamine oxidase A gene (MAOA), especially the promoter repeat MAOA-uVNTR, has been linked to antisocial and related outcomes in people who experienced childhood adversity. A meta-analysis of 27 papers supported the interaction in males only, by combining p values rather than effect sizes, while several large replications were mixed, and few reviews test whether carriers of the low-activity allele also do better in supportive environments.

Objectives. To estimate the pooled MAOA-uVNTR by environment interaction as an effect size, by sex and outcome; to test diathesis-stress against differential susceptibility where studies report the full range of environments; and to assess bias and heterogeneity. **Methods.** A systematic review and random-effects meta-analysis of observational studies, to be registered before data extraction, with one pre-specified primary analysis (males, primary outcomes), outcome-specific secondary analyses, an exploratory female analysis, a pre-specified conversion for interaction coefficients, a smallest effect of interest for interpreting a null, a named risk-of-bias tool, a multilevel model for dependent effects, and publication-bias tests. **Context.** Modern environments may interact with MAO variation (an evolutionary-mismatch idea); this is background (Supplement A) and is not tested here.

In the series. This protocol tests the worked example of paper IV (section 4), whether MAOA-uVNTR modifies the effect of childhood adversity, which paper IV uses to show how genetic variation may modify sensitivity to the environment and treats as its weakest evidence. The evolutionary-mismatch idea in the background (Supplement A) is the one paper II (section 4) uses for the humanity paradox.

1. Rationale

MAOA variation is a plausible modifier of how people respond to stress, but the idea that it moderates the effect of maltreatment began with one birth cohort (Caspi et al. 2002), and the literature is built largely on candidate-gene studies, a design criticised for small samples and non-replication (Duncan and Keller 2011; Border et al. 2019). A meta-analysis of 27 studies published to August 2012 (Byrd and Manuck 2014; 20 male and 11 female cohorts) supported a gene-by-maltreatment interaction in males, with weak and inconsistent findings in females. An earlier meta-analysis also found it in males (Kim-Cohen et al. 2006). Large cohort replications have since been mixed (for example Ruisch et al. 2019 in ALSPAC). In this protocol the gene is treated as a marker of sensitivity to environment, not as a defect or a cause of behaviour. The review asks whether the reported interaction holds up, and it may find that it does not.

Two gaps motivate a new review. First, the most recent pooled test of the interaction the author found (Byrd and Manuck 2014) covers studies to August 2012, and it combined p values by the Liptak-Stouffer weighted Z method and reported no pooled effect size; later work is narrative (Nilsson et al. 2018) or a systematic review of candidate genes with no pooled estimate (Weeland et al. 2015; 53 studies, several genes), and main-effect meta-analyses (Vassos et al. 2014; Ficks and Waldman 2014) do not test the interaction. As far as the author's searches show, no pooled effect size for the interaction has been published for the literature since the five-study meta-analysis of Kim-Cohen et al. (2006), and no sex-stratified, outcome-specific pooling with bias adjustment exists; this review would supply both. The 13 October 2026 PubMed search (204 records) turned up no later pooled test, and a further web search on 25 October 2026 found none either; the final search string (section 4) is wider and will return many more records. This will be re-checked in the other

databases and in PROSPERO before registration. Second, the usual reading is diathesis-stress (the risk allele matters only under adversity), but a rival model, differential susceptibility, predicts that allele carriers also do better under supportive conditions (Belsky et al. 2009; Belsky and Pluess 2009). Most studies dichotomise “maltreated or not”, which hides the supportive side. A review can test it only in studies that report the whole range of environments, so a scoping search comes first (section 9).

The review tests one narrow piece, whether variation in one gene changes responses to adversity, and makes no claim that any variant alone causes any condition, and no claim about differences between populations. The evolutionary-mismatch context that motivates the author’s interest is set out in Supplement A; it is background, not a question this review tests. Paper IV of the series uses this interaction as its worked example (section 4); this review is the test of it.

2. Objectives and questions

- Q1 (primary question). What is the pooled MAOA-uVNTR by childhood-adversity interaction on antisocial and aggressive outcomes in males? And, as an exploratory question, in females?
- Q2. Does the interaction hold for the secondary outcomes (callous-unemotional traits, depression, alcohol and substance use)?
- Q3. In studies reporting the full range of environments, does the pattern fit diathesis-stress or differential susceptibility?
- Q4. How large is heterogeneity within each sex, and how much of it is explained by the moderators of section 6 (ancestry, outcome type, adversity type, retrospective or prospective measurement, allele coding, age and the risk-of-bias items)?
- Q5. What is the risk of bias and of publication bias?

3. Eligibility criteria

Element	Include	Exclude
Population	Humans of any age. Studies that report results by sex, or whose authors supply them, enter the sex-stratified analyses; mixed-sex studies without sex-specific results are included as a mixed-sex stratum for exploratory analysis and are not pooled with the stratified estimates	Animal-only studies (reviewed separately), clinical samples selected for the outcome without a comparison group
Genotype	MAOA-uVNTR classified by expression (extract each study’s coding)	Studies of other MAOA variants only
Environment	Childhood adversity (maltreatment, abuse, neglect, harsh parenting, adverse childhood experiences) and/or positive environment (supportive parenting, warmth)	Adult-only exposures with no childhood measure
Outcome	Primary: antisocial behaviour, aggression, conduct problems (including delinquency, violence and conduct disorder), and externalising scales where an antisocial or conduct subscale is reported, measured by validated scale, diagnostic interview or official records of offending. Secondary: callous-unemotional traits, depression, alcohol and substance use	Outcomes without a validated measure or official record
Design	Cohort, case-control or cross-sectional studies that test or allow a genotype by environment interaction; published or unpublished	Case reports, editorials without data

Element	Include	Exclude
Other	English language; 1993 to the search date. 1993 is the year of the first report linking MAOA variation to behaviour (Brunner et al. 1993), and the uVNTR itself was described in 1998 (Sabol et al. 1998), so no eligible study can predate it	Duplicate reports of the same outcome on the same sample (the larger report is kept; overlapping samples otherwise share a sample identifier, section 6)

4. Search strategy

- **Databases:** PubMed and Europe PMC (searched), plus the free sources OpenAlex, Lens.org, Semantic Scholar, BASE and CORE, and Google Scholar (first 200 results of short queries). PsycINFO will be searched in the British Library reading rooms, or by the second screener through an institutional subscription, before screening is complete, since psychology journals carry a large share of this literature. Embase, Web of Science and Scopus could not be accessed by the author (a university library confirmed on 13 October 2026 that alumni cannot use them off site) and are not searched; this is a limitation. If access is later obtained, they will be searched and the protocol amended. Grey literature: PsyArXiv and bioRxiv preprints, theses, conference abstracts. Citation chasing: backward (reference lists) and forward (cited-by, in OpenAlex and Semantic Scholar) from every included study and from both prior meta-analyses (Kim-Cohen et al. 2006; Byrd and Manuck 2014), repeated until no new eligible study is found.
- **Author contact:** ask authors of included studies for stratified effects or raw interaction data where papers report only a significance test.
- **Record:** database, date searched, exact string, and number of hits, for every source. Searches so far: PubMed on 13 October 2026 with the v4 string, 204 records exported; Europe PMC on 13 October 2026, restricted to titles and abstracts and excluding PubMed-indexed records, 2 records (both conference supplements, excluded at title level). The final PubMed string below will be run, and its record count reported, before registration; it is wider than the v4 string and will return well over 204 records. OpenAlex, Lens.org, Semantic Scholar, BASE, CORE and Google Scholar are to be searched with adapted strings before screening is complete, each string recorded in the registry as a dated amendment (section 9) before it is run. The omission of the subscription databases is stated as a limitation.

PubMed string, final (to adapt for each database; the v4 string lacked the externalising, trauma, stress, victimisation, discipline, callous, drug, offending, crime, hostility, impulsivity and oppositional terms):

("Monoamine Oxidase"[Mesh] OR MAOA[tiab] OR "MAO-A"[tiab] OR "monoamine oxidase A"[tiab]) AND (VNTR[tiab] OR uVNTR[tiab] OR "variable number tandem repeat"[tiab] OR polymorphi*[tiab] OR genotyp*[tiab] OR promoter[tiab] OR allele*[tiab]) AND (maltreat*[tiab] OR abuse*[tiab] OR neglect*[tiab] OR adversit*[tiab] OR "adverse childhood"[tiab] OR trauma*[tiab] OR stress*[tiab] OR victimi*[tiab] OR parent*[tiab] OR harsh[tiab] OR discipline[tiab] OR punish*[tiab] OR "family environment"[tiab] OR "gene-environment"[tiab] OR "gene by environment"[tiab] OR interaction[tiab]) AND (aggress*[tiab] OR antisocial[tiab] OR "conduct disorder"[tiab] OR "conduct problems"[tiab] OR externali*[tiab] OR delinquen*[tiab] OR violen*[tiab] OR offend*[tiab] OR crim*[tiab] OR hostil*[tiab] OR impulsiv*[tiab] OR oppositional[tiab] OR callous*[tiab] OR psychopath*[tiab] OR "behavior problems"[tiab] OR "behaviour problems"[tiab] OR depress*[tiab] OR alcohol*[tiab] OR substance*[tiab] OR drug*[tiab])

The studies found in the quick web scoping of 13 and 25 October 2026 are listed, with their verification status, in Supplement B.

5. Selection, extraction and bias

- **Screening:** the author screens every record at title and abstract and at full text, against a one-page rule sheet (Include, Maybe or Exclude, each with a reason code), in a spreadsheet

or Rayyan. An independent second screener screens a random sample of at least 40 records at the title-and-abstract stage against the same rule sheet, and all records at the full-text stage where a screener is available; agreement is reported as Cohen's kappa and disagreements are resolved by discussion. The second screener is being recruited and has not yet been named. If none is found, this is stated as a limitation, the rule sheet and a fixed extraction form are applied identically to every record, and the author re-screens a random 10 per cent of records after a week to report self-agreement. Screening has started: before registration, PubMed records were given a first-pass title-and-abstract screen by one screener (section 9), and this is declared at registration.

- **Extraction:** a fixed extraction form, piloted on five studies. The second screener extracts a random 20 per cent of included studies in duplicate and agreement is reported; if no second screener is found, single extraction is named as a limitation. Fields: sample size and sex split; ancestry; age; country; allele coding and genotyping method; adversity measure and whether retrospective or prospective; outcome measure and type (scale, interview or official record); effect sizes by genotype group, or the interaction coefficient with its standard error, t or p value and degrees of freedom; full-range or dichotomised environment; covariates; handling of heterozygous females; pre-specification of the interaction; funding and conflicts.
- **Risk of bias:** the Q-Genie tool for genetic association studies (Sohani et al. 2015), with its published scoring, which classifies each study as good, moderate or poor quality, plus five gene-by-environment items adapted from Duncan and Keller (2011) and one item on exposure, each coded yes or no: sample size justified, interaction hypothesis pre-specified, ancestry adjusted, allele classification stated and standard, the interaction tested with both main effects in the model, and adversity measured prospectively or with a validated retrospective instrument. Q-Genie was built for association studies and does not rate the measurement of the environment, which is why the exposure item is added. The ratings are duplicated by the second screener on the same random 20 per cent as extraction, with disagreements resolved by discussion. Ratings enter the analysis in two ways: a sensitivity analysis excludes poor-quality studies (section 6), and the Duncan-Keller items (pre-specification and both-main-effects in particular) are pre-specified moderators in the meta-regression. The tool is fixed here and will not change at registration.

6. Synthesis plan

- **Effect size:** within each genotype group, the correlation between adversity and outcome, with adversity coded so that higher means more adversity and the outcome so that higher means more antisocial behaviour, converted to Fisher z. The interaction effect is $\Delta z = z(\text{low}) - z(\text{high})$, the low-activity group's z minus the high-activity group's, so that H1 predicts $\Delta z > 0$, with variance $1/(n(\text{low}) - 3) + 1/(n(\text{high}) - 3)$. A difference in standardised slopes can differ from the unstandardised interaction when the variance of the exposure or the outcome differs by genotype; the partial-correlation analyses below are the check. Regression coefficients and odds ratios are converted where needed.
- **Conversions and incomplete reports:** convert odds ratios and main-effect regression coefficients to correlations with standard formulae (Borenstein et al. 2009); code adversity so higher means more; convert "maltreated or not" comparisons to point-biserial correlations. Interaction coefficients are converted by a pre-specified rule: the interaction term's t statistic (or its coefficient divided by its standard error) and the model's residual degrees of freedom give a partial correlation, $r(p) = t / \sqrt{t^2 + df}$, with variance $(1 - r(p)^2)^2 / df$ (Aloe and Thompson 2013), which is the second effect-size scale of this review. Where a study reports only a p value for the interaction, t is recovered from the p value and the degrees of freedom; where only a bound is reported (for example "p < .05"), the bound is used, which gives a conservative estimate, and the study is flagged. Studies that report only "not significant", with no statistic, go to author contact; if unanswered they are excluded from the pooled analyses, counted, and entered at t = 0 in a sensitivity analysis, since leaving them out would select toward significant reports. The primary pool uses stratified estimates (Δz), obtained from the paper or from the authors; studies with interaction-only reports go to author

contact first. The partial-correlation scale is then analysed in two sensitivity analyses: all studies that report an interaction coefficient or test, on that scale, the stratified (Δz) studies entering through their own reported interaction test and leaving this analysis, with their number given, if they report none; and the primary pool with the interaction-only studies added on that scale, so that leaving them out of the primary pool, which would select against non-significant reports, can be seen to matter or not. Both estimates are reported beside the primary one.

- **Dependent effects:** where a study reports several outcomes, samples or time points, all eligible effects are extracted and the dependence is modelled, with a multilevel model (effects within samples within studies), tested with t distributions and robust variance estimation with the CR2 small-sample correction (Hedges, Tipton and Johnson 2010; Tipton 2015; Pustejovsky and Tipton 2018), as implemented in the clubSandwich package; no averaging within studies. The primary outcome hierarchy, used where one effect per study is needed (for the funnel plot and for descriptive tables), is: (1) a diagnostic or composite antisocial measure (conduct disorder, antisocial personality symptoms), first because it is the outcome of the discovery study (Caspi et al. 2002) and depends least on a single informant's scale; (2) violent or aggressive behaviour, including official records of offending, violent offending first; (3) conduct problems, or externalising scales where the antisocial or conduct subscale is reported. Official records of offending count as primary outcomes and are coded as a measurement type in the moderator analyses. Overlapping samples across papers are clustered by a sample identifier; where two papers report the same outcome on the same sample, the larger report is kept.
- **Primary analysis (pre-specified):** males, primary outcomes, low-activity versus high-activity genotype, random-effects (REML) in the multilevel form above, with t-distribution tests and the CR2 correction; report the variance components, level-specific I^2 (Cheung 2014) and a prediction interval. Hartung-Knapp adjustment is used for any two-level sensitivity model.
- **Three classes of analysis:** each analysis belongs to one class and is labelled so in the report. Primary: H1, in males, on the primary outcomes. Pre-specified secondary: the secondary outcomes of Q2, H2, H3, H4 and the moderators named below. Exploratory: the female analysis, the mixed-sex stratum, and anything added after registration.
- **Smallest effect of interest:** an interaction of $\Delta z = 0.10$, about 0.25 per cent of outcome variance when the genotype groups are equal (the first row of the power table in section 8), and about 0.23 per cent at the low-activity frequency of roughly 0.35 in males of European ancestry. The threshold is practical, not clinical: it is the smallest interaction that one large cohort of about 3,000 males could detect with 80 per cent power at $\alpha = 0.05$, so an effect below it is one that no single study in this literature could have found or could be expected to replicate, and a pooled interaction smaller than that would not support the use any study has made of the finding: below $\Delta z = 0.10$ the interaction would not change any individual-level prediction or policy that has been drawn from it. A null pooled estimate is reported as evidence of absence only when the upper bound of its 95 per cent confidence interval is below $\Delta z = 0.10$; otherwise it is reported as inconclusive.
- **Model:** random-effects (REML), multilevel, as above. Analyse males and females separately; the female analysis is exploratory (section 7). A pooled estimate is reported when at least three studies contribute; with fewer, the studies are reported in a narrative table.
- **Subgroups and meta-regression (pre-specified):** ancestry, outcome type, adversity type, retrospective versus prospective measurement, allele coding, age, and the Duncan-Keller items. Only when at least 10 studies are available per analysis; the variance explained (R^2) is reported with its interval and is not tested. Ancestry enters as a heterogeneity moderator and as a control for allele-frequency differences between samples; it is not a test of differences between populations, and the review makes none (section 11).
- **Publication bias:** funnel plots, with Egger's test (asymmetry at $p < 0.10$; Egger et al. 1997) and PET-PEESE (Stanley and Doucouliagos 2014) when 10 or more studies are available, and

a comparison of small and large studies, on one effect per study chosen by the outcome hierarchy.

- **Sensitivity:** leave-one-out; excluding the original discovery sample; excluding poor-quality studies on Q-Genie; alternative allele codings; excluding heterozygous females where they are reported separately; the two partial-correlation analyses above; the “not significant” reports entered at $t = 0$.
- **Differential susceptibility:** for studies with a continuous or full-range environment, estimate regions of significance and the proportion of interaction (Roisman et al. 2012), and report whether lines cross. The proportion of interaction has no standard error, so it is summarised as the median across qualifying studies, with a bootstrap interval. If fewer than five studies qualify, H4 is untested and the studies are reported descriptively.
- **Certainty of evidence:** rate each main result with GRADE, noting that observational candidate-gene studies start at low certainty.
- **Software:** R with the metafor (Viechtbauer 2010) and clubSandwich packages. Code and data to be shared, with the power simulation of section 8.

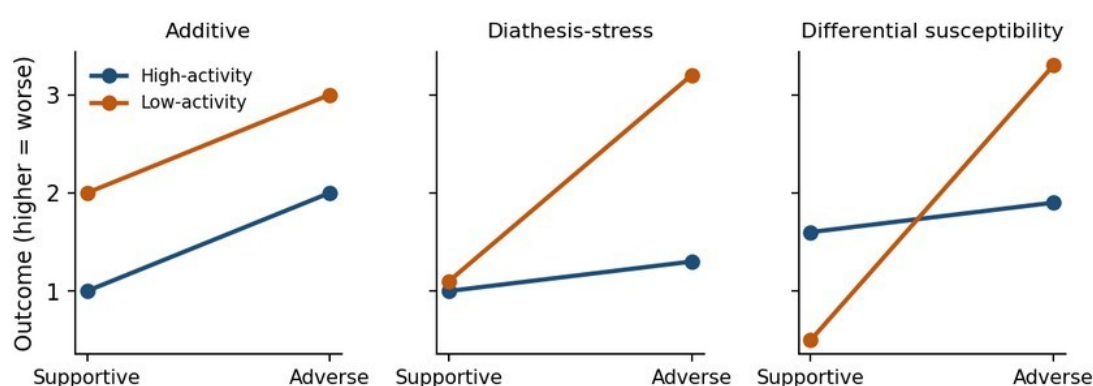


Figure 1. Illustrative patterns for three models (schematic, not data): additive, with no interaction; diathesis-stress, in which the low-activity allele matters only under adversity; and differential susceptibility, in which allele carriers do worse under adversity and better under support, so that the lines cross. The supportive-environment side is where the last two differ.

Evidence for the differential-susceptibility pattern on the supportive side (the plasticity pattern) is limited. One Swedish adolescent cohort reported it in females, but it was not significant after full adjustment and was absent in males (Bendre et al. 2024). A Spanish preschool cohort found low-activity girls more responsive to both punitive and positive parenting, but positive parenting went with more callous-unemotional traits, not fewer (Pueyo et al. 2021).

7. Pre-specified hypotheses

Hypothesis	Diathesis-stress expects	Differential susceptibility expects	Counts against
H1. In males, pooled interaction is positive (low-activity carriers show a stronger adversity effect)	Positive	Positive	Pooled interaction with the upper bound of its 95 per cent confidence interval below $\Delta z = 0.10$
H2. Heterogeneity is substantial (level-specific I^2 of 50 per cent or more at either level, or a prediction interval that includes zero), and the measurement and ancestry moderators account for part of it (R^2 reported with its interval, not tested)	Yes	Yes	Level-specific I^2 below 50 per cent at both levels, with a prediction interval that excludes zero

Hypothesis	Diathesis-stress expects	Differential susceptibility expects	Counts against
H3. Small studies show larger effects	Yes (bias)	Yes (bias)	No funnel asymmetry on Egger's test at $p < 0.10$ (10 or more studies)
H4. In full-range studies (five or more), allele carriers do better under support: the median proportion of interaction across qualifying studies, with a bootstrap interval, lies in the 0.40 to 0.60 band, and the lines cross within the observed range of the environment	No: no difference under support (proportion of interaction near zero)	Yes: lines cross	A reversed crossover, carriers doing worse than non-carriers at the supportive end and better at the adverse end, rules out both; a uniform difference across the range is a main effect, not an interaction; with fewer than five studies H4 is untested, not supported

Exploratory, not a hypothesis. The female interaction is estimated and reported with its interval. The reported estimate uses each study's own classification of females, extracted as such; two recodings, low/low and low/high against high/high, and heterozygotes analysed separately where reported, are sensitivity analyses (heterozygous females were the susceptible group in Ruisch et al. 2019). No prediction is made, because female data are sparse and the X-inactivation question is open (Supplement A); the estimate is reported for the next review to build on.

8. Why pool: single studies are underpowered

Sample size for one pre-specified interaction term (80% power, continuous outcome, ΔR^2 the extra variance explained by the interaction beyond the main effects):

ΔR^2 of the interaction	N needed, $\alpha = 0.05$	N needed, $\alpha = 0.005$
0.25%	3,132	5,312
0.5%	1,562	2,650
1%	778	1,318
2%	385	653

The table uses $N = \lambda / f^2$, with $f^2 = \Delta R^2 / (1 - \Delta R^2)$ and $\lambda = 7.85$ at $\alpha = 0.05$ and 13.3 at $\alpha = 0.005$ (80 per cent power, one degree of freedom), which assumes the main effects explain no variance; with main effects explaining 10 per cent, the first row falls to about 2,820. The $\alpha = 0.005$ column follows the proposal to require that threshold for claims of new discoveries (Benjamin et al. 2018). Early studies used a few hundred males, enough only for large effects. If true effects are around 0.5% of variance or smaller, a single study needs 1,500 or more participants, which most MAOA studies lack. Pooling is therefore the practical route. A simulation of the same models (3,000 runs each) gave power of 0.78 to 0.80 at every row, matching the table; its code will be shared with the analysis code, and a statistician should still confirm the assumptions.

9. Feasibility, registration and timeline

- **Scoping search (first):** count studies that report a continuous or supportive-end environment, and studies since 2014. If fewer than about 10 qualify for the main analysis, narrow the questions (for example drop H4 or meta-regression).
- **Register the protocol before data extraction begins.** PubMed records were given a first-pass title and abstract screen by one screener before registration, with 56 records provisionally marked include and 13 for full-text checking; this is disclosed, and the registration will state that screening has started and extraction has not. PROSPERO requires a health-related outcome: the primary outcomes include conduct disorder (ICD-11 6C91), and the secondary outcomes add depression and alcohol and substance use; it accepts registration until data extraction has begun, and asks for the stage the review has reached; it does not accept narrative or scoping reviews. If PROSPERO declines the review, register on

OSF instead. Follow PRISMA-P for the protocol (Moher et al. 2015; Shamseer et al. 2015) and PRISMA 2020 (Page et al. 2021) and MOOSE (Stroup et al. 2000) for reporting.

- **Amendments:** any change after registration, including each free-source search string and any database later searched, is recorded in the registry with its date and reason.
- **Team:** find a statistician and a second screener; ask a genetics or psychiatry researcher to review the protocol.
- **Timeline:** November 2026, scoping search, final search string, the remaining free-source searches and PsycINFO, PROSPERO check and registration. December 2026 to January 2027, title and abstract screening with the second screener's sample, full-text screening, author contact. February to March 2027, extraction, risk-of-bias rating and analysis. April 2027, preprint (PsyArXiv or bioRxiv), then journal submission.
- **Run and report:** target journals with a free subscription route, such as Development and Psychopathology or Behavior Genetics, which published earlier work in this area (Roisman et al. 2012; Ficks and Waldman 2014); Evolution, Medicine, and Public Health is fully open access with a publication charge. Other exposures that a mismatch view suggests (sleep and light, diet, tobacco, urban stress) are untested for MAO variants and are not part of this review; if the main analysis finds a robust interaction, they define a later new-data study.
- **Registration details.** Title: as above. Keywords: MAOA; MAOA-uVNTR; gene-environment interaction; childhood maltreatment; antisocial behaviour; differential susceptibility; meta-analysis. Anticipated start: November 2026; anticipated completion: April 2027. Named contact: Devon Summerhayes, devon.summerhayes@gmail.com. Stage at registration: searches and a first-pass title-and-abstract screen of the PubMed records done; extraction not started.

10. Limitations

- A review inherits the limits of its studies: candidate-gene designs, small samples, and inconsistent allele coding.
- Full screening is by one author, with a second screener on a sample at the title-and-abstract stage, on all records at the full-text stage where one is available, and on a fifth of the extraction and the risk-of-bias ratings; if no second screener is found, single-author screening and extraction raise the risk of selection and transcription error.
- Female data are sparse, so female results are exploratory.
- Full-range environment data may be too rare to test differential susceptibility; H4 is then untested.
- Embase, Web of Science and Scopus are not searched, and PsycINFO only through a reading room or a second screener, so some eligible studies may be missed. The free sources, the expanded search string and citation chasing from every included study and both prior meta-analyses reduce but do not remove this risk, so the review cannot claim to have found all available data. The English-language limit and partial grey-literature coverage add to it.
- Converted interaction effects (the partial-correlation scale) are not on the same scale as the stratified estimates, which is why they are analysed separately and reported beside the primary estimate rather than pooled with it.
- Screening decisions made before registration are provisional and were made by one screener; agreement with the second screener will be reported.

11. Ethics

- Findings are population-level and must not be used to predict individuals or in legal, clinical or employment decisions.
- Allele frequencies differ by ancestry. The review makes no claims about differences between populations; ancestry enters the analysis only as a heterogeneity moderator and an allele-frequency control (section 6). The review rejects the "warrior gene" framing, which has been misused (Lea and Chambers 2007).

- Gene editing to alter behaviour is out of scope and not proposed.
- The review uses published or shared aggregate data. Any author-contact data must follow the original consent terms.

PRISMA-P 2015 checklist: where each item is addressed

Item	Where
1a Title: identification	Title page
1b Title: update	Not applicable (new review)
2 Registration	Section 9 (to be registered; stage declared)
3a Authors: contact	Title page (name, independent researcher, email)
3b Authors: contributions	Declarations (contributions; guarantor: DS)
4 Amendments	Section 9 (any later change recorded in the registry with its date and reason)
5a Support: sources	Declarations (unfunded)
5b Support: sponsor	Not applicable
5c Support: role of sponsor or funder	Not applicable
6 Rationale	Section 1
7 Objectives	Section 2
8 Eligibility criteria	Section 3
9 Information sources	Section 4
10 Search strategy	Section 4 (PubMed string)
11a Study records: data management	Section 5 (spreadsheet or Rayyan)
11b Study records: selection process	Section 5
11c Study records: data collection process	Section 5 (extraction form, duplicate extraction on a sample)
12 Data items	Section 5 (extraction fields)
13 Outcomes and prioritisation	Sections 2, 3 and 6 (outcome hierarchy)
14 Risk of bias in individual studies	Section 5 (Q-Genie plus Duncan-Keller items)
15a Data synthesis: criteria for quantitative synthesis	Section 6 (a pooled estimate when at least three studies contribute)
15b Data synthesis: summary measures and methods	Section 6 (effect sizes, conversions, multilevel model)
15c Data synthesis: additional analyses	Section 6 (subgroups, meta-regression, sensitivity)
15d Data synthesis: narrative synthesis where pooling is not possible	Section 6 (analyses with fewer than three studies, and H4 with fewer than five, reported in a narrative table)
16 Meta-bias(es)	Section 6 (publication-bias tests)
17 Confidence in cumulative evidence	Section 6 (GRADE)

Declarations

Competing interests. The author founded Centricity, a community project about neighbours sharing tools, skills and help. It pays the author no salary or other income, and it is not connected to the question, methods or planned analyses in this protocol.

Contributions. DS conceived the review, wrote the protocol and is its guarantor.

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Use of AI. Generative AI (Claude, from Anthropic; Sonnet 5.5 for the first drafts, Opus 5.5 for v4 and v8, and Fable 5.1 for v5 to v7) was used to help draft and edit the text, build the figures, review the draft and check references. The author directed the work, reviewed all content and takes full responsibility for it.

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Supplement A: background (not part of the protocol's methods)

The material here is background to the question. Nothing in the eligibility criteria, search, extraction or synthesis depends on it.

A1. Background biology.

- **Genes.** MAOA and MAOB sit side by side on Xp11.3; the enzymes sit on the outer mitochondrial membrane. MAO-A mainly breaks down serotonin and noradrenaline; MAO-B prefers phenylethylamine and benzylamine; both handle dopamine.
- **Variation.** Rare loss-of-function mutations (Brunner syndrome; Brunner et al. 1993); a common 30 base-pair promoter repeat (MAOA-uVNTR) that changes transcriptional activity in vitro (Sabol et al. 1998); and methylation variation. Classifying the rare repeat lengths (2R and 5R) as high or low activity is inconsistent (Sabol et al. 1998). Naming also varies: L means “long” in some papers and “low activity” in others, so each study’s definition must be extracted.
- **Sex.** Males carry one copy. Females carry two. MAOA is reported to partly escape X-inactivation, with promoter methylation ranging from about 2% to nearly complete in one brain study (Pinsonneault et al. 2006), so female effects are treated as exploratory.
- **Inhibition paradox.** Reversible MAO-A inhibitors (moclobemide) are antidepressants, yet low-activity genotypes are linked to worse outcomes under adversity. One hypothesis is

timing: lifelong differences act during brain development (as in knockout mice, Cases et al. 1995), while drugs act acutely in the mature brain. This is untested in humans.

A2. X-linkage and sex ratios.

- For a recessive X-linked allele at frequency q , affected males are about q of males and affected females about q squared, so the male to female ratio is about $1/q$. A 4:1 ratio needs q of about 0.25. The ratio is not a fixed property of X-linkage (Figure A1).
- The low-activity repeat is common (roughly a third or more of males in many samples, varying by ancestry). It is a risk modifier, not a disease status.

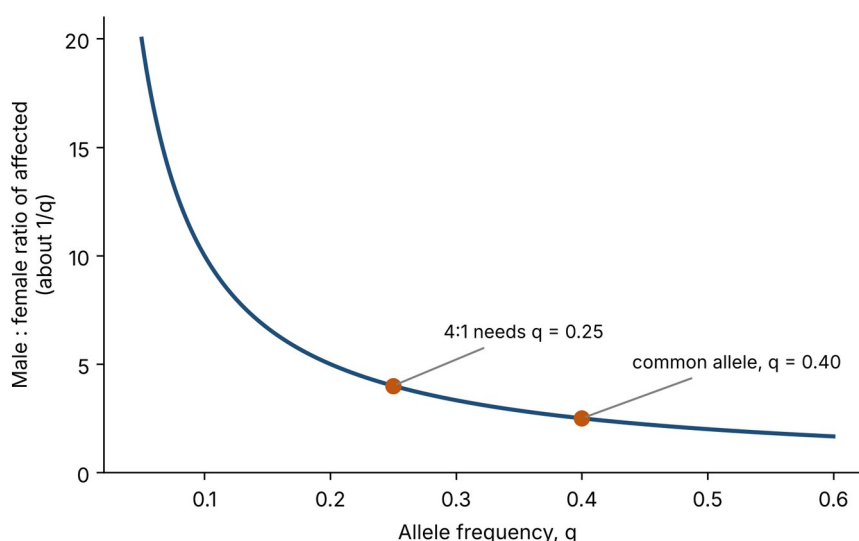


Figure A1. Expected male to female ratio of affected people for an X-linked recessive allele, as a function of allele frequency q .

A3. The mismatch context. Mismatch here means a gap between the environments in which human biology was shaped and the ones people now live in (Gluckman, Beedle and Hanson 2009; Nesse and Williams 1994); a mismatch view asks whether such gaps affect people differently by MAO genotype. That is the author's reason for interest in the question. The review tests none of it.

A4. How the narrative claims above are graded. The table below is used only for the background claims in this supplement; the review's own evidence is rated with GRADE (section 6).

Rating	Criteria used for narrative claims
Strong	Replicated in at least two independent samples or by meta-analysis, with a plausible mechanism.
Moderate	Supported by meta-analysis or replication, but effects are small or heterogeneous.
Weak	A single study, animal or cell work only, or inconsistent results.
Unsupported	Contradicted by evidence, or no source found.

Supplement B: quick web scoping (audit trail)

Quick web scoping of 13 October 2026, not a systematic search; one row updated 25 October 2026.

Study	Relevance	Status
Kim-Cohen et al. 2006, Molecular Psychiatry 11:903	Earlier meta-analysis plus 975 boys; males only	Verified online
Byrd and Manuck 2014, Biological Psychiatry 75:9	Meta-analysis to August 2012; 20 male and 11 female cohorts; p values combined by the Liptak-Stouffer method, no pooled effect size	Verified online (method re-checked 27 October 2026)

Study	Relevance	Status
Ruisch et al. 2019, European Archives of Psychiatry and Clinical Neuroscience 269:741	ALSPAC; mostly failed to replicate earlier MAOA findings	Verified online
Bendre et al. 2024, Frontiers in Psychiatry 15:1375363	Parent-child relationship; plasticity pattern in females	Verified online
Weder et al. 2009, Biological Psychiatry 65(5):417-424	Full-range trauma test for H4 (114 children)	Verified in PubMed record
Pueyo et al. 2021, The European Journal of Psychiatry 35(4):225-233	368 preschoolers; punitive and positive parenting each interacted with genotype on callous-unemotional traits only in low-activity girls at age 5 (15 girls); positive parenting went with more such traits, so no for-better pattern	Verified online (25 October 2026)