Appendix A – Amendments to PROSPERO protocol

Protocol Registration Number: CRD42021237510

Amended areas are in **bold**

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| --- | --- | --- |
| Item | Registered version | Updated version |
| Title | Factors determining change in pathways between childhood adversity and adult social, occupational and mental health outcomes: a systematic review and meta-analysis | **Protective factors following cumulative childhood adversity**: A systematic review |
| Review question | What social, psychological and environmental factors are responsible for positive change in the relationship between cumulative childhood adversity and social, occupational and mental health functioning in adulthood? | What social, psychological and environmental factors are responsible for positive change in the relationship between cumulative childhood adversity and social, occupational and mental health **and wellbeing** functioning in adulthood? |
| Condition or domain being studied | The social, occupational and mental health outcomes of cumulative childhood adversity | The social, occupational and mental health **and wellbeing** outcomes of cumulative childhood adversity |
| Participants/population | Inclusion: Human participants asked about childhood adversity occurring before they were 10 years of age, assessed using a validated measure of cumulative childhood adversity.  Exclusion: Animal population; participants asked about childhood adversity occurring after age 10; assessed using either a measure of a singular childhood adversity or a non-validated measure. | Inclusion: Human participants asked about **cumulative** childhood adversity occurring before they were 10 years of age, assessed using a validated measure of cumulative childhood adversity.  Exclusion: Animal population; participants asked about childhood adversity occurring **only** after age 10; assessed using either a measure of a singular childhood adversity or **a measure that is deemed by researchers to be not valid.** |
| Intervention(s), exposure(s) | The exposure of interest is an intervening factor (such as a mediator or moderator) that is social, environmental, or psychological. This factor must have conferred statistically significant change on the pathway from childhood adversity towards a more favourable adult outcome. In other words, factors could have a negative relationship with an unfavourable outcome, or a positive relationship with a favourable outcome. This factor must be a validated measure that is social, psychological or environmental in focus. The exposure must have occurred after the predictor occurred, and before the outcome is measured. | The exposure of interest is an intervening factor (such as a mediator or moderator) that is social, environmental, or psychological. This factor must have conferred statistically significant change on the pathway from **cumulative** childhood adversity towards a more favourable adult outcome. In other words, factors could have a negative relationship with an unfavourable outcome, or a positive relationship with a favourable outcome. This factor must be a validated measure that is social, psychological or environmental in focus. The exposure must have occurred after the predictor occurred, and before the outcome is measured. |
| Comparator(s)/control | Included studies will have compared a group that has experienced childhood adversity and who have been exposed to the intervening factor to a group that has experienced childhood adversity but has not been exposed to the intervening factor | Included studies will have compared a group that has experienced **cumulative** childhood adversity and who have been exposed to the intervening factor to a group that has experienced **cumulative** childhood adversity but has not been exposed to the intervening factor |
| Main outcome(s) | Validated measure (as described by the study’s authors) related to social or occupational functioning, or mental health measured after age 18. | **Valid measure (as deemed by researchers)** by the study’s authors) related to social or occupational functioning, or mental health **and wellbeing** measured after age 18. |
| Risk of bias assessment | We will use the Risk of Bias in Non-randomised Studies – of Interventions (ROBINS-I) to assess the methodological quality and risk of bias in individual studies. Two reviewers will independently answer the signalling questions for every paper included in the review, and compare answers. The quality of the review’s outcome will be measured using the GRADE checklist.  Two reviewers will independently apply the checklist criteria, and compare answers. If there are any discrepancies in reviewers’ decisions for the ROBINS-I or for the GRADE checklist, the reviewers will discuss their decision until an agreement can be made. If no decision can be agreed upon, a third reviewer will be available for consultation to make the final decision. The results of these assessments will be taken into account during the review process. | We will use the **Methodological Standards for Epidemiological Research (MASTER)** to assess the methodological quality and risk of bias in individual studies. Two reviewers will independently answer the signalling questions for every paper included in the review, and compare answers. The quality of the review’s outcome will be measured using the GRADE checklist.  Two reviewers will independently apply the checklist criteria, and compare answers. If there are any discrepancies in reviewers’ decisions for the **MASTER** or for the GRADE checklist, the reviewers will discuss their decision until an agreement can be made. If no decision can be agreed upon, a third reviewer will be available for consultation to make the final decision. The results of these assessments will be taken into account during the review process. |
| Strategy for data synthesis | Separate analyses will be conducted for each domain of mediator as long as each has at least three papers. Odds ratios (ORs) will be calculated for the results of each study, comparing the group who express the study’s target outcome depending on the exposure to the mediator. A pooled odds ratio will then be calculated as well as confidence intervals (CIs) at the 95 percent level to determine the likelihood that the observed effect is the true one. These will be summarised in a forest plot. Heterogeneity will be determined with a χ² test in order to assess the statistical validity of combining the included studies in the analysis. | **A narrative qualitative review will be conducted separately for each domain of mediator.** |
| Analysis of subgroups or subsets | Data will be synthesised based on four domains of intervening factor. These will be psychological factors, social factors, factors in the school environment and factors in the home environment. Separate analyses will be conducted for each domain. Sensitivity analyses will be performed for each domain. If a domain does not include results from three papers, or if the domains are no longer appropriate given the literature found, the domains will be reassessed. Any change will be declared in the results section of the review. | Data will be synthesised based on **domains of mediators, determined by similarity of papers to one another.** |
| Type and method of review | Meta-analysis, Narrative synthesis, Systematic review | Narrative synthesis, Systematic review |

Appendix B – search strategies

Ovid Medline: 824 results

((((((child abuse/ OR battered child syndrome/ OR adverse childhood experiences/ OR (child\* adj2 (abus\* or maltreat\* or victim\* or advers\* or stress\* or trauma\* or struggl\* or violen\* or assault\* or ((dysfunction\* or toxic\*) adj2 (famil\* or hous\* or upbringing or environment\*)))).tw,kw,kf.) AND adult\*.tw.) OR "adult survivors of child adverse events"/ OR "adult survivors of child abuse"/) AND (mechanism\* or mediat\* or process\* or "structural equation model\*" or path\* or intervening).tw,kw,kf.) AND limit to english language) AND (cohort studies/ or longitudinal studies/ or prospective studies/ or cohort.ti,ab. or longitudinal.ti,ab. or prospective.ti,ab.) OR Epidemiologic Studies/))

Ovid APA PsycINFO: 865 results

(((((child abuse/ OR battered child syndrome/ OR Childhood Adversity/ OR (child\* adj2 (abus\* or maltreat\* or victim\* or advers\* or stress\* or trauma\* or struggl\* or violen\* or assault\* or ((dysfunction\* or toxic\*) adj2 (famil\* or hous\* or upbringing or environment\*)))).ti,ab,id.) AND adult\*.tw.) AND (mechanism\* or mediat\* or process\* or "structural equation model\*" or path\* or intervening).ti,ab,id.) AND limit to english language) AND ((cohort\* or longitudinal or prospective\*).ti,ab,id. or longitudinal study.md. or prospective study.md.) not "Literature Review".md.)

Scopus: 1,191 results

( ( ( KEY ( "adult survivor\*" ) ) OR ( ( TITLE-ABS-KEY ( ( child\* W/2 ( abus\* OR maltreat\* OR battered OR victim\* OR advers\* OR stress\* OR trauma\* OR struggl\* OR violen\* OR assault\* OR ( ( dysfunction\* OR toxic\* ) W/2 ( famil\* OR hous\* OR upbringing OR environment\* ) ) ) ) ) ) AND ( ( TITLE ( adult\* ) OR ABS ( adult\* ) ) ) ) ) AND ( TITLE-ABS-KEY ( mechanism\* OR mediat\* OR process\* OR "structural equation model\*" OR path\* OR intervening ) ) ) AND ( ( TITLE-ABS-KEY ( cohort\* OR longitudinal OR prospective ) ) OR ( KEY ( "epidemiologic\* stud\*" ) ) ) AND ( LIMIT-TO ( LANGUAGE , "English" ) )

Web of Science Core Collection: 1,124 results with English Language filter applied

((((TS=(child\* NEAR/2 ( abus\* OR maltreat\* OR battered OR victim\* OR advers\* OR stress\* OR trauma\* OR struggl\* OR violen\* OR assault\* OR ( ( dysfunction\* OR toxic\* ) NEAR/2 ( famil\* OR hous\* OR upbringing OR environment\* )))) AND (TS=adult\*)) OR (KP="adult survivor\*" OR AK="adult survivor\*")) AND TS=(mechanism\* OR mediat\* OR process\* OR "structural equation model\*" OR path\* OR intervening ) ) AND (TS=(cohort\* OR longitudinal OR prospective OR "epidemiologic\* stud\*")))

Appendix C - MASTER scale and Interpretations

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| --- | --- | --- |
| **Safeguard item** | Interpretation in the current review | No. papers met /28 |
| **Format Recruitment** |  |  |
| **1. Data collected after the start of the study was not used to exclude participants or to select them into the analysis**  This safeguard applies to all analytic study designs and is considered present if there was no further selection (or exclusions) of participants after the start of the study (as defined by study authors) or if there was evidence that any selection that occurred after the start of the study was unrelated to the intervention and development of the outcome. For example, if BMI was recorded after the start of a study on GDM and women were excluded based on a BMI cut-off this safeguard would be considered absent. | This safeguard was unmet if there was unreasonable exclusion/inclusion which was unrelated to the mediator or outcome, unless this is part of the research question. It was also unmet if there was a protocol change or decision part way into the analysis to exclude certain groups. | 26 |
| **2. Participants in all comparison groups met the same eligibility requirements and were from the same population and timeframe**  This safeguard is considered present if participants across all groups were recruited from the same population and within the same timeframe and could meet the same eligibility requirements. If there were contrived comparison groups, this safeguard is absent. Case-control studies with a clear primary or secondary study base from which eligible participants are then recruited are deemed to have met this safeguard. A randomized controlled trial design automatically means this safeguard is present. | This safeguard was unmet if there were different criteria depending on the level of the mediator.  This safeguard was met for cohort studies with continuous variables as mediators (i.e. without ‘intervention’ groups). | 28 |
| **3. Determination of eligibility and assignment to treatment group/ exposure strategy were synchronized**  This safeguard is considered present if the start of follow-up coincides with both determination of eligibility criteria and with participant assignment to intervention / exposure and control groups. In addition, this process must have been similar for all participants. This safeguard may be considered absent in observational studies where determination of eligibility can be at the start of follow-up, but the treatment/ exposure could have been assigned a) before or b) after the start of follow-up. An example is a) participants on medication who continue using at the start of follow-up or b) participant not previously using medication that start using some time after the start of follow-up. Two other problems involve moving eligibility before assignment (in example a) or moving eligibility after assignment (in example b). All four problems mean that this safeguard is absent. This safeguard is considered present if the study design is a randomized controlled trial. | This safeguard was not applicable, and was always unmet. | 0 |
| **4. None of the eligibility criteria were common effects of exposure and outcome**  This safeguard is considered absent if both the exposure and the outcome are a cause of any of the variables considered in the eligibility of participants. For example, if the exposure and outcome can both modulate the eligibility criterion then this should not have been an inclusion or an exclusion variable (such as demographics like education or a medical condition or even a medical status such as hospitalization). A specific example of this may be selecting on case status,  such as diabetes, which will induce an association between exposure (family history) and outcome (obesity). Only one of exposure or outcome being a modulator of the criterion means that the safeguard is still present | This safeguard was met unless they excluded based on a factor that is an effect of both the predictor and outcome. | 25 |
| Equal Retention |  |  |
| **5. Any attrition (or exclusions after entry) was less than 20% of total participant numbers**  This safeguard is considered present if a study reports loss to follow-up of less than 20% and this is verified through examination of the text, flow-charts, tables and figures. Note that equality of treatment rates is not enough to safeguard against attrition (the attritors might still be selected differently in the two groups), nor differential response rates more likely to cause bias (attrition may still be unrelated to the outcome of interest) and therefore this safeguard refers to total attrition only being less than 20% of total participant numbers. | This safeguard was met if the attritted sample was less than 20% (i.e. retained sample at least 80%). If the rate of attrition was not explicitly stated, this safeguard was unmet. | 5 |
| **6. Missing data was less than 20%**  This safeguard is considered present if missing data is less than 20% and this is consistent through evaluation of tables or text. Missing data does not include participants lost to follow-up. Missing data on variables that are not relevant is not  considered here (e.g., a question about household members that is not answered by participants living alone is not considered relevant). | This safeguard was met if missing data was less than 20%. If the proportion of missing data was not explicitly stated, this safeguard was unmet. | 8 |
| **7. Analysis accounted for missing data**  This safeguard is considered present if the analysis includes imputation or inverse probability weighting to account for missing data or there was no missing data to require such an analysis. The specific method used must be specified (e.g., sample mean substitution, hot deck imputation, single imputation, or multiple imputation etc.). | This safeguard was met if they accounted for missing data. It was also marked as met if they tested and found no differences between the missing sample and the analytic sample that would impact the relationship of interest. | 21 |
| **8. Exposure variations / treatment deviations were less than 20%**  This applies to exposure or treatment deviations from what was defined in the study. For example, treatment deviations due to non-compliance or change in a patient’s wish to continue the treatment. This safeguard is considered present if the exposure/ treatment variations/ deviations were less than 20%. Nonadherence to treatment is any deviation on the part of the patient or treatment provider to the trial treatment protocol, or any treatment change agreed with care providers or investigators but not permitted by the trial protocol. Variations in exposure may be due to variations in the behavior of a participant (e.g., amount of alcohol drunk or extent of smoking) while nonadherence can take the form of not starting a treatment at all, taking treatment at the incorrect time, “drug holidays,” or diminished adherence between clinician appointments. Complete withdrawal from treatment and withdrawal from the study (lost to follow-up) are separate as in the latter, follow-up data is unavailable. This safeguard needs to be mentioned by the authors in terms of what was done to monitor this and what was found. If this has not been mentioned, the safeguard is considered present if the exposure is a permanent attribute (e.g., a genetic marker or sex) or if a treatment cannot be withdrawn or changed (e.g., surgery). | This safeguard was not applicable, and was always unmet. | 0 |
| **9. Variations in exposure or withdrawals after start of the study were addressed by the analysis**  This safeguard is present if such analyses are included in the study or if this was not required for changes after the start of the study. In randomized experiments, this safeguard is addressed for withdrawals by an instrumental variable analysis, the instrument being the allocation sequence after randomization (intention-to-treat principle) or similar analysis. In observational studies, this safeguard is met if there was any analytic stratification, or adjustment by an indicator variable for the withdrawal. Variations in exposure can be handled by a dose-response analysis. | This safeguard was met if they analysed the effects of attrition and loss to follow up, i.e. stratification. It was also met if they tested and found no differences between the attritted and the analytic sample that would impact the relationship of interest. | 13 |
| **Equal ascertainment** |  |  |
| **10. Procedures for data collection of covariates were reliable and the same for all participants**  This safeguard is considered present if procedures for data collection of variables other than exposure/intervention and outcome were reliable and the same for all participants. For example, if some participants were interviewed and others filled in a questionnaire (containing all other variables for the study) this safeguard would be considered absent. This may include variables such as confounding variables and demographic variables, for example. It is okay for different procedures to be used for different variables so long as they were the same for all participants. | This safeguard was met if they collected the same data for all participants, even if it was gathered from multiple sources. | 28 |
| **11. The outcome was objective and/ or reliably measured**  This safeguard is considered present if the outcome measured was a hard outcome (e.g., death) or was reliably measured (e.g., using a validated tool, test-retest, piloting, validation in a previous study etc.), or clearly not a subjective assessment (e.g. ‘soft’ outcomes such as non-validated patient-reported outcome measures, or use of surrogate or proxy outcome measures, such as records, or a composite outcome measure). | This safeguard was met if the outcome was a hard measurement (even of a subjective construct). This safeguard was also met if the measure is both reliable and reproducible. | 14 |
| **12. Exposures/ interventions were objectively and/ or reliably measured**  This safeguard is considered present if both the active and control exposures were objectively defined to be clearly reproducible by researchers. If a tool was used to measure exposure variables, it should be a clearly reproducible tool. For interventions, a clear definition of treatment and control interventions is required so that they are reproducible by readers. Consistency of implementation from subject to subject is not assessed here. | This safeguard was met if both the measure of CA and the measure of the mediator were hard measurements (even of subjective constructs). This safeguard was also met if the measures were both reliable and reproducible. | 17 |
| **13. Outcome assessor(s) were blinded**  This safeguard is considered present if the outcome assessor(s) was blind to which participants were in the intervention/exposure group and control/ non-exposed groups or a hard outcome was assessed. The adequacy of blinding should be assessed for the relevant outcome (or exposure in case-control and similar studies). Outcome assessors could be participants (e.g., self-reported outcomes), data collectors (e.g., blinded research staff), or technicians. The adequacy of the blinding procedure will depend on the main outcome. For example, for participant-reported outcomes the blinding procedure is adequate for outcome assessors if it is adequate for participants and care-providers, such as being blind to the control treatment’s characteristics, consequences of the treatments, clinical manifestations, and monitoring or is similar in each group and also when there is no contact between participants and assessors. | This safeguard was not applicable, and was always unmet. | 0 |
| **14. Participants were blinded**  This safeguard is considered present if the participants were blind to which study group they were in. | This safeguard was not applicable, and was always unmet. | 0 |
| **15. Caregivers were blinded**  This safeguard is considered present if those caring for participants were unaware or kept blind to which study group participants were in. Caregivers are those administering the intervention, such as physicians, nurses, allied health professionals, surgeons, those administering co-interventions and following participants etc. For example, caregivers may be blinded by use of the same equipment in both treatment and control groups or ensuring the control treatment’s characteristics are indistinguishable from the experimental treatment, and the consequences of treatments, and monitoring are similar in each group. | This safeguard was not applicable, and was always unmet. | 0 |
| **16. Analyst(s) were blinded**  This safeguard is considered present if the person conducting the analyses for the study was unaware or kept blind to which participants were in the intervention/ exposure and control/ nonexposed groups. | This safeguard was not applicable, and was always unmet. | 0 |
| **Equal implementation** |  |  |
| **17. Care was delivered equally to all participants**  This safeguard is considered present if care delivery was implemented in the same setting or by the same staff such that it is unlikely to have been variable in quality and extent across participants. In assessing equal care, caregivers’ experience or skill should be considered as well as the monitoring of participants and other supportive care. This safeguard would fail be implemented and is considered absent in a multicenter trial. | This safeguard was not applicable, and was always unmet. | 0 |
| **18. Cointerventions that could impact the outcome were comparable between groups or avoided**  Co-interventions are the provision of additional care to either of the comparison groups. All co-interventions that may plausibly impact the outcome should be administered equally in intervention/ exposure and control groups and if so, this safeguard is considered present. This safeguard is also present if there were no co-interventions. | This safeguard was marked as met if the analysis controlled for other interventions that could have impacted the relationship of interest. | 1 |
| **19. Control and active interventions/ exposures were sufficiently distinct**  This safeguard is considered present if there was no contamination across control and active interventions/ exposures. Contamination occurs when the members of one group in a trial receive the treatment or are exposed to the intervention that is meant solely for the other group thereby minimizing any real difference that exists between the groups. | This safeguard was not applicable, and was always unmet. | 0 |
| **20. Exposure/intervention definition was consistently applied to all participants**  This safeguard is considered present if the same definition of exposure or intervention was used for all participants and did not change during the timeframe of the study. | This safeguard was met if the definition of CA and the mediator were the same for all participants. In whole of population studies, this was always met. | 28 |
| **21. Outcome definition was consistently applied to all participants**  This safeguard is considered present if the outcome definition remained the same for all participants during a study. For example, if during a psychiatry study the diagnostic manual was updated from DSM-IV to DSM-V, although objective,  this would be an inconsistent outcome definition and thus the safeguard would be considered absent. | This safeguard was met if the definition of the outcome was the same for all participants. In whole of population studies, this was always met. | 28 |
| **22. The time period between exposure and outcome was similar across patients and between groups or the analyses adjusted for different lengths of follow-up of patients**  The prospectively defined schedule for follow-up measures of the outcome should be similar between groups to ensure equal implementation. If this has not occurred, the analyses must adjust for different lengths of follow-up of patients (in a dynamic study). This safeguard is considered present if the time period between the exposure and outcome is similar across patients and between groups or the analysis adjusts for different lengths of follow-up of patients (e.g., time-to-event analysis). | This safeguard was met if the time passed between CA and outcome was the same, and stated explicitly. It was also met if they accounted for the differences in time passed. | 1 |
| **Equal prognosis** |  |  |
| **23. Design and/or analysis strategies were in place that addressed potential confounding**  This safeguard is considered present if the design accounts for confounding through restriction, matching or stratification on key confounding variables or alternatively randomization specified in the study design. Note, randomization is included here in addition to its own category elsewhere. In observational designs this safeguard is also met if consecutive patients (including interrupted, sequential etc.) were enrolled. Known important confounders can be controlled by statistical adjustment after completion of data collection using specific analytic strategies (e.g., covariate adjustment, propensity score, instrumental variable, etc.). This safeguard is considered present if there were analytic strategies in place to avoid confounding by key important variables, or analytic strategies to adjust for confounding were not required. Analytic strategies should also be in place to avoid confounding by indication if this is an observational study or if it is a non-randomized trial (randomized trials are exempt from confounding by indication). | This safeguard was met if they adjusted for confounding using an appropriate method. | 24 |
| **24. Key confounders addressed through design or analysis were not common effects of exposure and outcome**  This safeguard refers to the method of selection of key confounders and is considered absent if adjustments were made for “collected variables” but there was no justification for their confounder status (e.g. from the literature or through a DAG). To be a confounder, the variable must be a common cause of exposure and outcome and must NOT be a common effect of exposure and outcome | This safeguard was unmet if they adjusted for confounders that were known to be common effects of both CA and the outcome.  It was marked as met if all confounders were measured before both CA and the outcome were measured. | 22 |
| **25. Key baseline characteristics / prognostic indicators for the study were comparable across groups**  This safeguard is considered present if the distribution of relevant baseline characteristics across groups were balanced at the start of the study. The number and type of baseline characteristics are dependent on the research question. Baseline characteristics are found in the table or text. | This safeguard was not applicable, and was always unmet. | 0 |
| **26. Participants were randomly allocated to groups with an adequate randomization process**  This safeguard is only present in randomized experiments and is considered present if the allocation sequence to assign participants to groups was adequately generated to be at random. If participants were their own control, then treatment  order should have been randomized. A random number table or random number generator performed by computer, a coin toss or shuffling cards is acceptable. Methods such as sequence generated by odd or even date of birth or sequence  generated by other similar rules do not meet this safeguard definition. | This safeguard was not applicable, and was always unmet. | 0 |
| **27. Allocation procedure was adequately concealed**  This safeguard is considered present if the allocation procedure used to assign participants to intervention/ exposure and control groups prevents participants and investigators foreseeing the treatment assignments. Allocation concealment may be adequate if it was performed by use of centralized randomization, opaque sealed envelopes, numbered or coded devices. If the method is described but inadequate (e.g., use of open allocation schedule, unsealed or non-opaque envelopes, date of birth of participants etc.) then participants and investigators may be able to foresee group assignment and this safeguard is considered absent. | This safeguard was not applicable, and was always unmet. | 0 |
| **28. Conflict of interests were declared and absent**  Conflict of interests usually represents bias in favor of the intervention (e.g., drug companies running or funding clinicaltrials). This safeguard is considered present if conflict of interests were not deemed to be an important issue. Conflicts of interest exist when professional judgment concerning a primary interest (such as validity of research) may be influenced by a secondary interest (such as financial gain or personal relationships). This can be looked for by assessing relationships between authors and interventions which may be indicated in the beginning or end of the article text (sometimes beneath the references) and also by checking the author names and funding sources or affiliations (e.g., there may be no funding source for the study but the author works for the drug company). | This safeguard was marked as met if they explicitly stated that no conflicts of interest are present. | 14 |
| **Sufficient analysis** |  |  |
| **29. Analytic method was justified by study design or data requirements**  This safeguard would be absent if, for example, relative risk was used in a case-control design, or cross-over designs or cluster designs were properly handled etc. This safeguard also protects against violated assumptions, multicollinearity,  misspecification errors, unit of analysis errors, poor approaches to sensitivity analysis, and interactions that were not considered. Justification for the choice of model should be given and appropriate if it is not a standard approach for the  study design. | This safeguard was met if the analytic method was appropriate for the research question. | 28 |
| **30. Computation errors or contradictions were absent**  This safeguard is considered present if the analyses and text or tables were free of any computational errors or contradictions. Computational errors or contradictions can be checked by looking at whether the statistical analysis of numbers was correct (whether the numbers add up), errors that invalidate the results were avoided, and the data analysis was credible for the analysis to be deemed sufficient. | This safeguard was unmet if there were any discrepancies between statistics reported in the body of the paper and in the tables. | 28 |
| **31. There was no discernible data dredging or selective reporting of the outcomes**  Data dredging is present when data are analyzed ad hoc in many ways seeking any possible relationships between data. Selective outcome reporting occurs when the primary outcomes of a trial protocol are changed or omitted in the paper.  This safeguard is considered present if there was no data-dredging or selective reporting of the outcomes. This can be assessed by checking the outcomes were specified a priori and are relevant to the study hypothesis. The analysis must  begin with a hypothesis that specifies the outcomes before data are available for analysis (often found in a study protocol) and then follows with an examination of the data. Data dredging or selective reporting of the outcomes may have occurred if the outcome being assessed was likely to have been selected from multiple outcome measurements, relevant outcomes were omitted, outcomes were not directly related to the hypothesis, there were multiple analyses of the data, multiple or ad-hoc subgroup analyses, subgroups were defined in unusual ways, analyses were selected from a larger cohort of data, or the decision to validate a study’s result was dependent on the findings of the study. | This safeguard was met if they reported results for all analyses they proposed in their methods.  This safeguard was unmet if there were additional analyses after the main analysis that influenced the result of the main analysis. | 28 |
| **Temporal Precedence** |  |  |
| **32. All subjects were selected prior to intervention/ exposure and evaluated prospectively**  This safeguard is considered present if subjects were selected (or not excluded) before the intervention/ exposure began and was evaluated prospectively. This safeguard is applicable to experimental and retrospective/ prospective cohort study designs and nested case-control designs. It captures a prospective sequence of exposure to outcome whereby data from the intervention/ exposed and control/ nonexposed groups are collected and followed concurrently. A prospective sequence may not be applicable for certain designs, such as classic case-control or cross-sectional study designs and hence this safeguard is deemed to be absent by default. | This safeguard was met if data on all variables of interest was collected prospectively. It was unmet if data was collected retrospectively. | 7 |
| **33. Carry-over or refractory effects were avoided or considered in the design of the study or were not relevant**  This safeguard is considered present if there were no carry over effects from interventions prior to the start of the study (e.g., there was a long enough refractory period to separate the effects of different interventions). Carry-over effects occur in within-subject research designs, such as cross-over trials, and dose-response studies, dose-titration studies, and open-evaluation studies. They may also occur in a randomized trial if the intervention groups were randomized by continuation / discontinuation of previous treatments. Carry-over effects can occur due to fatigue, habituation, sensitization, and adaptation. Methods to overcome carry-over effects that can be looked for in the reported article are counterbalancing (interventions are given in different orders for different participants and carry-over effects will cancel each other out) and including treatment order as an independent variable in the analysis to measure the size of the carry-over effect. | This safeguard was met if the mediator and outcome were conceptually distinct. | 24 |
| **34. The intervention/ exposure period was long enough to have influenced the study outcome**  This safeguard is considered present if the intervention/ exposure period is temporally sufficient to have affected or influenced the outcome (e.g., smoking for a few weeks is unlikely to influence lung cancer). | This safeguard was met if there was an appropriate time passed between CA and the mediator. This depends on what constructs were measured. | 27 |
| **35. Dose of intervention/ exposure was sufficient to influence the outcome**  This safeguard is considered present if the dose of intervention/ exposure can reasonably be temporally related to an outcome (e.g., NSAID at low dosage and frequency in relation to future kidney injury) or a dose-response relationship  was documented. | This safeguard was not applicable, and was always unmet. | 0 |
| **36. Length of follow-up was not too long or too short in relation to the outcome assessment**  The follow-up period determines the temporal relationship between finishing the intervention and outcome assessment. If, for example, a drug was administered for three months and outcome was assessed after a year but there was no expectation that the effect could temporally be expected to continue post discontinuation of intervention and in this situation the safeguard is considered absent. Conversely, if following an exposure like diabetes onset cancer is looked for after 3 months that is clearly an insufficient duration and the safeguard is considered absent | This safeguard was met if there was appropriate time passed between CA, the mediator and the outcome. This depends on what constructs were measured. | 19 |

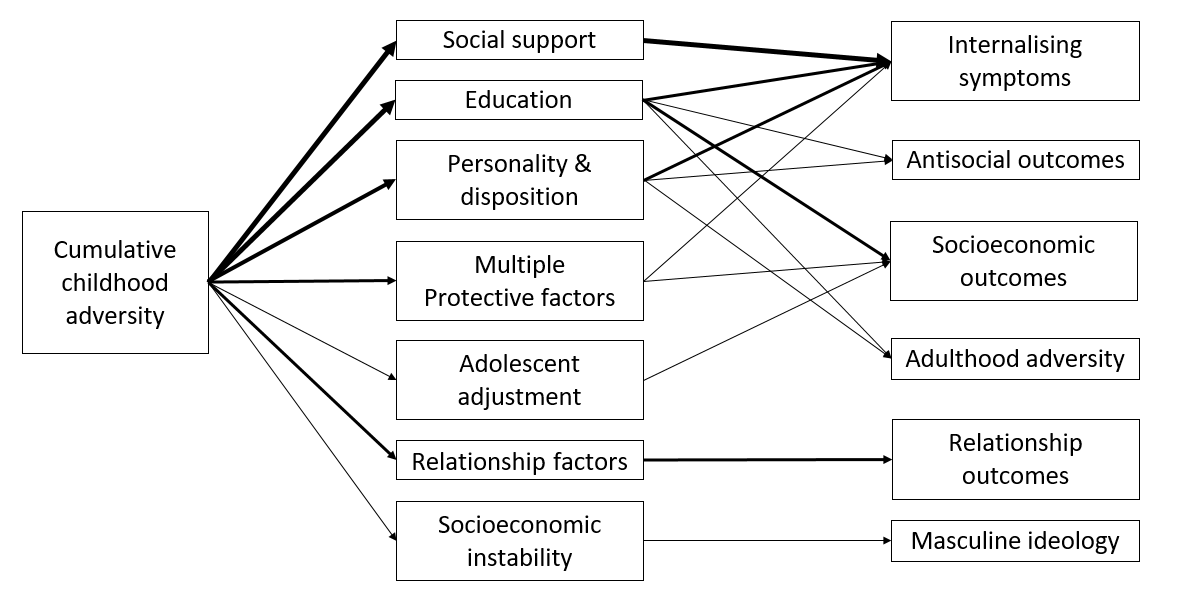
Appendix D – GRADE assessment

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Question | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | Overall |
| social support (6 papers) mediates the impact of CA | -1 | -2 | 0 | -2 | 0 | +1 | +1 | +1 | Very Low |
| educational factors (5 papers) mediates the impact of CA | -1 | -2 | 0 | -1 | 0 | +1 | +1 | +1 | Very low |
| personality and dispositional factors (5 papers) mediates the impact of CA | 0 | -2 | 0 | -1 | 0 | 0 | +1 | +1 | Very low |
| factors related to romantic relationship (2 papers) mediates the impact of CA | 0 | -2 | 0 | -1 | 0 | 0 | +1 | +1 | Very low |

Appendix E – PRISMA checklist

| **Section and Topic** | **Item #** | **Checklist item** | **Location where item is reported** |
| --- | --- | --- | --- |
| **TITLE** | | |  |
| Title | 1 | Identify the report as a systematic review. | Page 4 |
| **ABSTRACT** | | |  |  |  |
| Abstract | 2 | See the PRISMA 2020 for Abstracts checklist. | Page 3 |
| **INTRODUCTION** | | |  |  |  |
| Rationale | 3 | Describe the rationale for the review in the context of existing knowledge. | Page 4-5 |
| Objectives | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | Page 5 |
| **METHODS** | | |  |  |  |
| Eligibility criteria | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | Page 6-7 |
| Information sources | 6 | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | Page 6 |
| Search strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | Appendix B |
| Selection process | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | Page 6-7 |
| Data collection process | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | Page 9 |
| Data items | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | Table 2 |
| 10b | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | Table 2 |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | Page 7-8 |
| Effect measures | 12 | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. | N/A |
| Synthesis methods | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). | Page 7 |
| 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | N/A |
| 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | Page 7 |
| 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. | Page 7 |
| 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | N/A |
| 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | N/A |
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | Page 7-8 |
| Certainty assessment | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | Page 8 |
| **RESULTS** | | |  |
| Study selection | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. | Figure 1 |
| 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | N/A |
| Study characteristics | 17 | Cite each included study and present its characteristics. | Tables 3-6 |
| Risk of bias in studies | 18 | Present assessments of risk of bias for each included study. | Tables 3-6 |
| Results of individual studies | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | N/A |
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | Page 9-12 |
| 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | N/A |
| 20c | Present results of all investigations of possible causes of heterogeneity among study results. | N/A |
| 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | N/A |
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | Tables 3-6 |
| Certainty of evidence | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | Tables 3-6 |
| **DISCUSSION** | | |  |
| Discussion | 23a | Provide a general interpretation of the results in the context of other evidence. | Page 13 |
| 23b | Discuss any limitations of the evidence included in the review. | Page 13-14 |
| 23c | Discuss any limitations of the review processes used. | Page 14 |
| 23d | Discuss implications of the results for practice, policy, and future research. | Page 14 |
| **OTHER INFORMATION** | | |  |
| Registration and protocol | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | Page 6 |
| 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | Page 6 |
| 24c | Describe and explain any amendments to information provided at registration or in the protocol. | Appendix A |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | Page 2 |
| Competing interests | 26 | Declare any competing interests of review authors. | Page 2 |
| Availability of data, code and other materials | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | N/A |

Appendix F – Acyclic graph of protective factors and outcomes



Note: line boldness represents the number of studies observed for each bivariate pathway.