Sensitive periods in development and risk for psychiatric disorders and related endpoints: a systematic review of child maltreatment findings

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Lancet Psychiatry 2022; 9: 978–91

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Variation in the mental health of people who have experienced childhood maltreatment is substantial. One hypothesis is that this variation is attributable, in part, to the timing of maltreatment—specifically, whether maltreatment occurs during sensitive periods in development when the brain is maximally sensitive to particular types of environmental input. To determine whether there is scientific consensus around when periods of peak sensitivity occur, we did a systematic review of human observational studies. Although 89 (75%) of the 118 unique cross-sectional or longitudinal cohort studies we identified reported timing effects, no consistent sensitive periods were identified for any of the most studied outcomes. Thus, observational research on childhood maltreatment has yet to converge on a single period (or set of periods) of increased vulnerability. We identified study characteristics that might contribute to these between-study differences and used observations from our Review to suggest a comprehensive set of recommendations for future research.

Introduction

Psychiatric disorders affect an estimated 16–26% of the global population each year and 70–80% of the population at some point during their lifetime.[1–3] A major driver of psychiatric disorders is childhood maltreatment, a form of early adversity that encompasses the absence of expected inputs and responses from parents or caregivers (eg, physical or emotional neglect) and the presence of harmful, threatening inputs and responses (eg, physical, sexual, or emotional abuse).[4,5] Childhood maltreatment is common, with worldwide prevalence estimates ranging from 13% (sexual abuse) to 36% (emotional abuse). People with a history of maltreatment have, on average, at least twice the risk of developing a psychiatric disorder,[6] an effect that appears to be causal.[7,8] Nevertheless, it is clear that not all maltreated children are equally affected. One important determinant of the effects of maltreatment might be its developmental timing—specifically, whether it occurs during sensitive periods in development, meaning life stages when particular environmental inputs might be more influential. Identifying when these periods exist could have major benefits, including advancing understanding of the mechanisms linking maltreatment to later psychopathology and informing the development of targeted strategies to facilitate more timely intervention.

Neuroplasticity, which refers to the brain's dynamic capacity to undergo structural and functional maturation and change in response to experience,[9] is a powerful determinant of the extent to which different life experiences can become biologically embedded. So-called critical and sensitive periods are states of elevated plasticity when the effect of experience on neurodevelopment is especially strong and lasting.[5–7] Critical periods have long been viewed from a deterministic perspective: after the critical period ends, the effects of experience are permanent and irreversible; the window of plasticity closes and remains shut. But windows of sensitive-period plasticity do not fully close; rather, some degree of plasticity remains, although considerably more effort is required to produce change after a sensitive period ends than when that window was open. Therefore, we favour the term sensitive period in this Review, because of the potential for symptomatic improvement, remission, or recovery in nearly all common forms of psychopathology.

The neurobiological mechanisms that create sensitive periods are complex and encompass mechanisms that inhibit, initiate, and later slow, plasticity.[10] These mechanisms involve processes that govern the initial wiring of the brain (eg, synapse formation and overproduction) and those that shape consolidation of neural networks (eg, synapse elimination and pruning).[9] The associated psychological literature also commonly groups these mechanisms into those that are time limited and activated by universal experiences across the human species (sometimes labelled as experience expectant), and other ongoing learning mechanisms thought to be unique to the individual and their environment (ie, experience dependent).[11] The experience-expectant category is more commonly implicated in the formation of sensitive periods; however, the distinction between the two types of mechanisms is not necessarily precise and this framework does not capture all types of plasticity.[12]

Scientific interest in sensitive periods started nearly a century ago, when the concept was first articulated by Charles Stockard, an embryologist. Stockard observed that birth defects in fish offspring occurred only when mothers were exposed to extreme temperatures and toxic chemicals just as a specific embryonic organ was developing, labelling these time periods as moments of supremacy or critical moments.[13] In 1935, ethologist Konrad Lorenz was the first to apply this concept to animal behaviour, noting that young ducklings, goslings, and chicks would not imprint in the typical way for their species if their encounter with a moving object was delayed.[14] In the second half of the 20th century, animal

researchers also began generating evidence to support the existence of critical socialisation periods when specific social inputs were necessary for typical social and emotional functioning.[15] Harry Harlow's 1965 study[16] showed rhesus monkeys kept in social isolation between ages 3 months and 12 months had clear, enduring social and emotional deficits (whereas isolation at later ages appeared not to have such an effect), and in 1970, Nobel laureates David Hubel and Torsten Wiesel began establishing critical periods in the development of sensory systems.[17] These early animal socialisation studies, in particular, informed human research on attachment and approach learning, and the hypothesis that early caregiving relationships have a crucial role in determining later emotional and behavioural health.[18]

Since the 1950s, studies mentioning sensitive or critical periods have steadily increased. Articles additionally mentioning maltreatment are fewer but increased by 40 times in less than two decades (appendix 1 p 4). Published reviews investigating timing effects for maternal deprivation or institutionalisation suggest a sensitive period between ages 6 months and 24 months.[19] However, periods of peak vulnerability to maltreatment remain unknown.[20,21]

In this systematic review, we investigated whether evidence has converged to identify sensitive periods when the developing brain is most susceptible to the effects of childhood maltreatment. Specifically, we investigated the questions: (1) what proportion of studies testing for timing effects of maltreatment find such effects, and how consistent are the periods of peak vulnerability across studies? (2) Some researchers have postulated that sensitive periods are a property of individual biological systems (eg, neural circuits) rather than complex phenotypes, such as mental health disorders;[22] are findings more consistent in studies at more "biological" levels of analysis? (3) Do findings become more consistent when studies are stratified by different study characteristics (eg, sample size, statistical approach, or assessment methods)? (4) Research has repeatedly suggested a high degree of multifinality in psychopathology, wherein the same risk factor increases risk for multiple types of disorder simultaneously;[23] does this principle extend to studies of the timing effects of maltreatment (ie, do multiple disorder types show similar timing effects)? (5) Relatedly, the principle of equifinality suggests that the same mental health problems can arise through multiple different developmental histories and risk factors;[23] does this principle extend to studies of timing effects (ie, do different types of maltreatment show similar timing effects)? (6) Are there sex or gender differences in the periods identified across studies?

Methods

Search strategy and selection criteria

Using PRISMA guidelines,[24] we did a systematic review of human observational studies that tested for maltreatment timing effects by searching MEDLINE, PsycINFO, and the Cumulative Index to Nursing and Allied Health. Because some researchers have speculated that sensitive periods might be more readily identified for more biological outcomes, we sought to identify studies examining whether timing of maltreatment was related to psychopathology (eg, psychiatric disorder diagnosis or high scores on symptom scales) as well as studies connecting timing of maltreatment to related constructs within other levels of analysis, including neuroimaging (ie, brain structure or functioning), epigenetics (ie, DNA methylation), psychophysiology (eg, cortisol reactivity or cortisol awakening response), and behaviour (eg, personality or cognitive test performance). In addition to covering multiple levels of analysis, we selected search terms to capture a range of Research Domain Criteria constructs, including negative valence systems, positive valence systems, cognitive systems, See Online for appendix 1

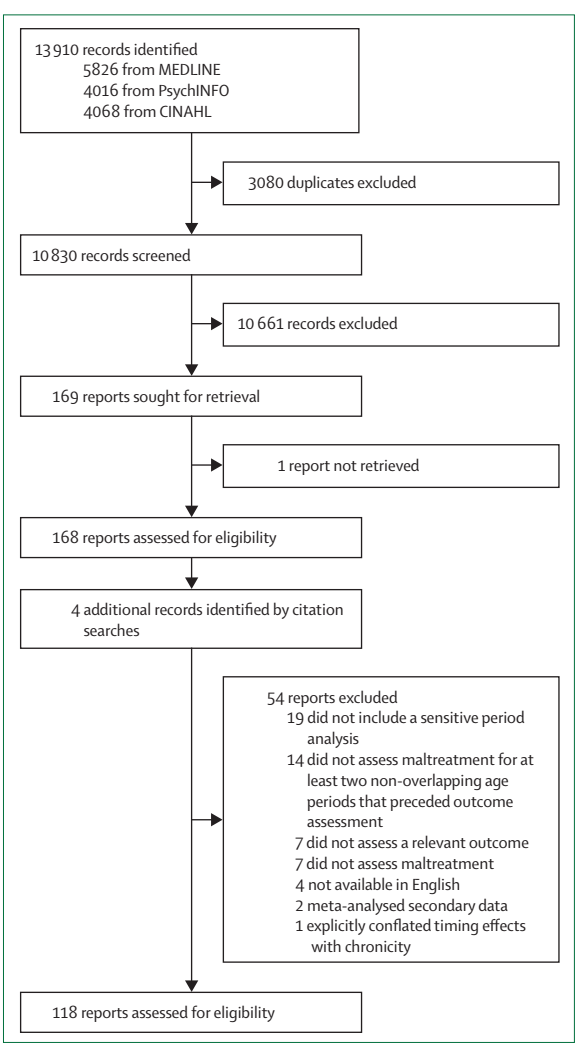
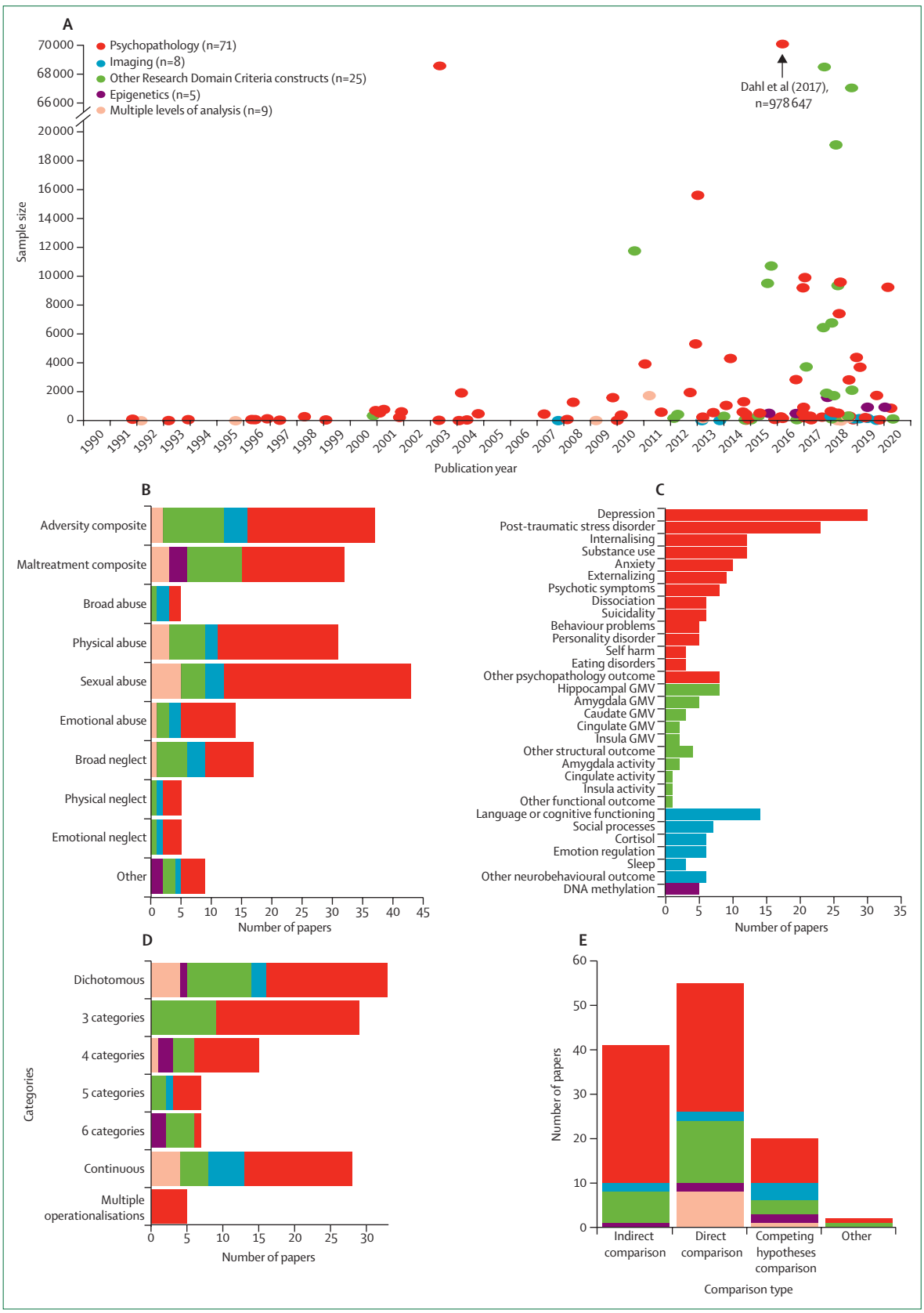


Figure 1: **Study profile**
CINAHL=Cumulative Index to Nursing and Allied Health.



social processes, arousal and regulatory systems, and sensorimotor systems.[25]

The inclusion criteria used in this Review were that studies reported results from human participants; the research was published in English; participants were assessed for one or more relevant outcomes; participants were assessed for exposure to maltreatment alone or alongside other measures of adversity; maltreatment exposure was assessed for at least two non-overlapping time periods that each preceded the outcome assessment (studies assessing maltreatment exposure across a continuous range of ages were considered to meet this criterion); and the article reported results for at least one test of sensitive period effects, whether that was an implicit (ie, non-statistical) or explicit comparison of associations between maltreatment occurring during two or more different age periods and a given outcome. Studies were labelled as being of "maltreatment" if they assessed any of these exposures: physical abuse, sexual abuse, emotional or verbal abuse, physical neglect, or emotional neglect. Although we required studies to assess maltreatment occurring at ages before age 18 years, we did not exclude studies for also assessing maltreatment after this point or based based solely on participant age (because many were retrospective studies of adults). These criteria and definitions were established before doing our systematic search; however, the search procedure was not preregistered and a public protocol was not prepared.

Our search proceeded in four steps. First, we searched each database from inception to Aug 9, 2020, using strings related to child abuse, maternal deprivation, neglect, sexual, physical, or emotional abuse, maltreatment, adverse childhood experiences, and victimization, as well as strings related to age, timing, and sensitive or critical periods, to psychopathology or mental disorders, to other Research Domain Criteria such as negative or positive valence, and to neuroimaging; full strings are shown in appendix 1 (pp 5–9). We exported articles to the systematic review application, Rayyan.[26] Second, two authors (JDS and ECD) independently screened titles and abstracts of articles retrieved from the search before reviewing the text of potentially eligible studies. Third, two authors (JDS and ECD) screened the text of retrieved articles to identify those meeting all inclusion criteria. Fourth, two authors (JDS and ECD) independently extracted study characteristics and our primary outcome (the sensitive periods identified). Discrepancies at each step were resolved by discussion. We arranged studies into subgroups based on key characteristics, including the outcome of interest, maltreatment type assessed, and other study design features, and then we searched the references of all included studies.

We evaluated all studies for risk of bias with two independent raters (two of three raters for each study: JDS, TWC, and Samantha Stoll) using an adapted Quality Assessment Tool for observational cohort and cross-sectional Studies developed by the National Heart, Lung, and Blood Institute.[27] Discrepancies were resolved by the third rater. Finally, we used permutation testing to statistically evaluate sensitive periods for the most studied outcomes in each level of analysis (ie, depression, language or cognitive ability, and hippocampal volume; appendix 1 pp 2–3).

Results

Our search identified 10 830 studies, of which 114 were eligible to be included and a further four studies were identified through citation searches, such that 118 independent reports met our inclusion criteria (figure 1). Of these studies, 71 (60%) tested for associations of maltreatment timing with psychopathology, 8 (7%) with neural indices, 5 (4%) with DNA methylation, 25 (21%) with other Research Domain Criteria units of analysis, and 9 (8%) examined outcomes at multiple levels (appendix 2 p 1).

See Online for appendix 2

Despite a shared focus on maltreatment, the 118 studies differed substantially. First, sample sizes were highly variable, ranging from 15 to 978 647 participants. 100 (85%) studies included more than 100 participants, with 37 (31%) reporting more than 1000 participants (figure 2A).

Second, maltreatment exposure was measured with reports of individual maltreatment types, maltreatment clusters, and maltreatment experiences co-occurring with other childhood adversities (figure 2B). Only 28 (24%) of the 118 studies employed prospective assessments; the remainder used cross-sectional or retrospective designs. 61 (52%) studies used measures that aggregated across different maltreatment types or combined maltreatment with other kinds of adversity and 50 (42%) examined only specific maltreatment types (most commonly sexual abuse). The remaining 7 (6%) studies used both aggregated and specific measures.

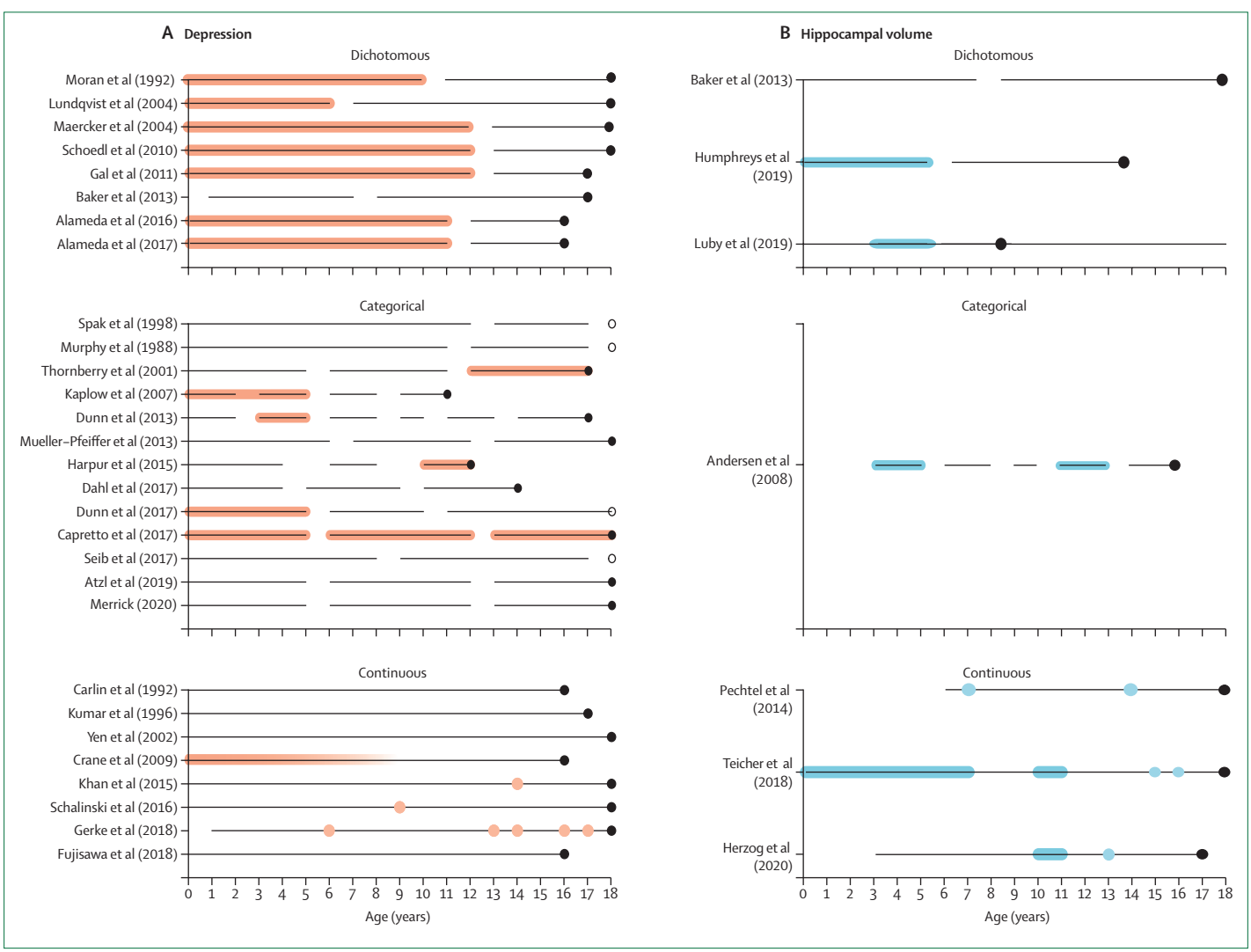
Figure 2: **Overview of the literature on sensitive periods for child maltreatment**

Full details on the 118 studies are in appendix 2. (A) Scatterplot of increases in sample size across sensitive period studies. (B) Frequency of child maltreatment exposures examined across sensitive period studies. Studies could be counted more than once if they examined multiple maltreatment types. Maltreatment composite studies combined multiple types of maltreatment into a single exposure measure, and adversity composite studies combined maltreatment and other non-maltreatment adversities into a single exposure measure. (C) Frequency of specific outcomes examined across sensitive period studies. Studies could be counted more than once if they examined multiple outcomes. (D) Use of exposure timing, including dividing age into two to six categories or examining year of age (continuous). (E) Frequency of analytical strategies used in sensitive period studies. Indirect comparison studies described rather than tested differences in the magnitude of the association between exposure and outcome as a function of exposure timing; direct comparison studies statistically evaluated whether the effect of exposure at one point differs from that at another; and competing hypotheses studies directly evaluated alternative theoretical explanations, including accumulation, chronicity, or recency. GMV=grey matter volume.

Third, several dozen outcomes were studied; psychopathology was the most common. Within our three major outcome categories (psychopathology, imaging, and other Research Domain Criteria units of analysis), the most common outcomes were depression, hippocampal volume, and language or cognitive ability (figure 2C).

Fourth, researchers defined maltreatment timing differently. Definitions of timing included the age at first or worst exposure; the presence or absence of maltreatment during different periods of development (eg, age 0–11 years *vs* age 12–18 years); scores showing the extent of exposure during different periods of development (eg, frequency, severity, total number of maltreatment events, or number of types of maltreatment); and grouping by recency of maltreatment, often combined with the onset of maltreatment (eg, early maltreatment *vs* early-and-recent or recent-only maltreatment). Timing was most often treated as a categorical measure, with development divided into periods roughly corresponding to early childhood, middle childhood, and adolescence. Considerably fewer studies used dichotomous or continuous measures of age (figure 2D).

Fifth, studies varied in the analytical rigour with which they identified sensitive periods. The least rigorous type of study, which we labelled as indirect comparison studies (n=41 [35%]), described rather than statistically tested differences in the magnitude of the association between maltreatment and outcome as a function of exposure timing. Direct comparison studies (n=55 [47%]) provided a stronger test of the sensitive period hypothesis by statistically evaluating whether the effect of exposure at one point in development differed from the effect of exposure at another. The most rigorous type, competing hypotheses studies (n=20 [17%]), directly compared the effects of maltreatment happening during two or more



(Figure 3 continues on next page)

time periods and evaluated alternative explanations for observed timing effects, including maltreatment accumulation (number of exposure types or times exposed), chronicity (duration), or recency (only timing of the most recent exposure). Two (2%) of the 118 studies did not fit into any of these categories (figure 2E).

Our assessment of study quality showed that the risk of biased results from this literature was high overall (appendix 2 p 2). Across studies, the mean number of study quality criteria met was 5·5 (SD 1·9) of 13. The most common item that did not pass the risk of bias assessment was whether the paper presented a justification for selecting or recruiting the number of participants included or discussed statistical power. Only 21 (18%) studies included this information, of which 15 (71%) indicated they were likely to be underpowered for at least some of the analyses done.

Across all 118 studies, 89 (75%) reported at least one sensitive period. Although sensitive periods appeared more consistent when exposure age was dichotomised, no consistent sensitive periods were identified for each of the most commonly studied outcomes in each major level of analysis (depression, hippocampal volume, and language or cognitive ability; figure 3). This observation was supported with permutation testing, which indicated insufficient evidence to reject the null hypothesis that childhood maltreatment was not associated with the outcome at each age (appendix 1 p 11). No clear timing patterns were observed among the next most studied outcomes within each level, although the number of studies within these domains was too small for permutation testing (appendix 1 pp 12–13).

Although some experts have suggested that sensitive periods might be more readily found for more "biological" outcomes,[22] we observed only weak evidence supporting this hypothesis. For example, whereas neuroimaging and epigenetic studies were more likely to report sensitive period effects than studies of psychopathology (8 [100%] of the 8 neuroimaging studies were positive *vs* 4 [80%] of 5 epigenetics studies *vs* 54 [76%] of 71 psychopathology studies), these differences did not reach statistical significance, which was probably due to the small number of studies in some groups (χ^2=2·45, df=2, p=0·293).

There was also no clear relationship between likelihood of reporting positive findings and analytical rigour. The proportion of studies reporting at least one sensitive period was statistically comparable across competing hypotheses studies and indirect comparison studies (18 [90%] of 20 competing hypotheses studies and 35 [85%] of 41 indirect comparison studies; χ^2=0·25, df=1, p=0·615). However, direct comparison studies reported significantly fewer positive findings (35 [64%] of 55) than both competing hypotheses studies (χ^2=4·918, df=1, p=0·027) and indirect comparison studies (χ^2=5·616, df=1, p=0·018).

Because of the range of factors that could contribute to the mixed findings we observed, stratifying papers by outcome alone might be insufficient to investigate between-study heterogeneity. Therefore, we tried organising papers on depression (the most common study outcome) in other ways—including by sample size, analytical rigour, maltreatment assessment approach, study design, and use of diagnosis versus symptom outcomes—to see whether more consistent findings would emerge (figure 4). They did not. Similarly, no clear patterns emerged when grouping studies according to timing of the outcome assessment (ie, whether depression was measured in adolescence, young adulthood, or in heterogeneous age groups; appendix 1 p 14).

We tested whether multiple types of mental health problems might share similar sensitive periods by reviewing studies assessing internalising and externalising disorders. Although these outcomes overlap, they are more causally and symptomatically distinct than disorders within the same diagnostic group (eg, anxiety and depression). Although we found substantial between-study variation in the sensitive periods observed for both internalising and externalising disorders, individual studies tended to find similar periods of peak vulnerability for both outcomes (appendix 1 p 15).

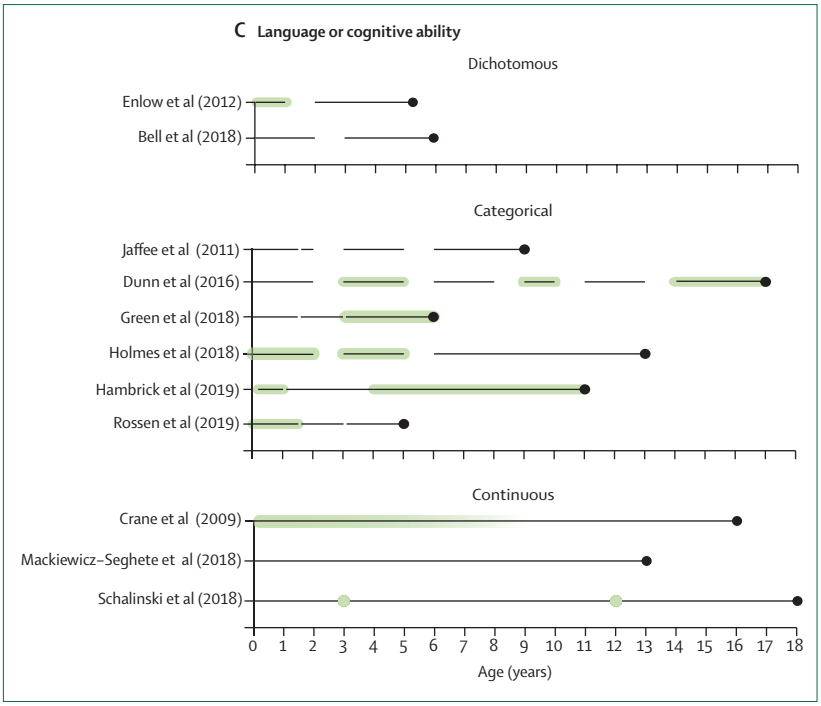


***Figure 3*: Summary of maltreatment-related sensitive period findings for depressive symptoms or depression diagnosis (A), hippocampal volume (B), and cognitive or language ability (C), by timing as dichotomous, categorical, or continuous age**

Each line shows the results from one study,[83-127] with the length and position of the line showing the ages when maltreatment was assessed. Thicker, colour-coded line segments indicate the specific sensitive periods identified by the study. Solid dots show the end of the maltreatment exposure assessment window. Open dots indicate studies in which maltreatment exposure was assessed beyond age 18 years. Coloured gradients show sensitive periods from studies using age as continuous and reporting that outcomes were associated with an earlier or later sensitive period without denoting specific ages.

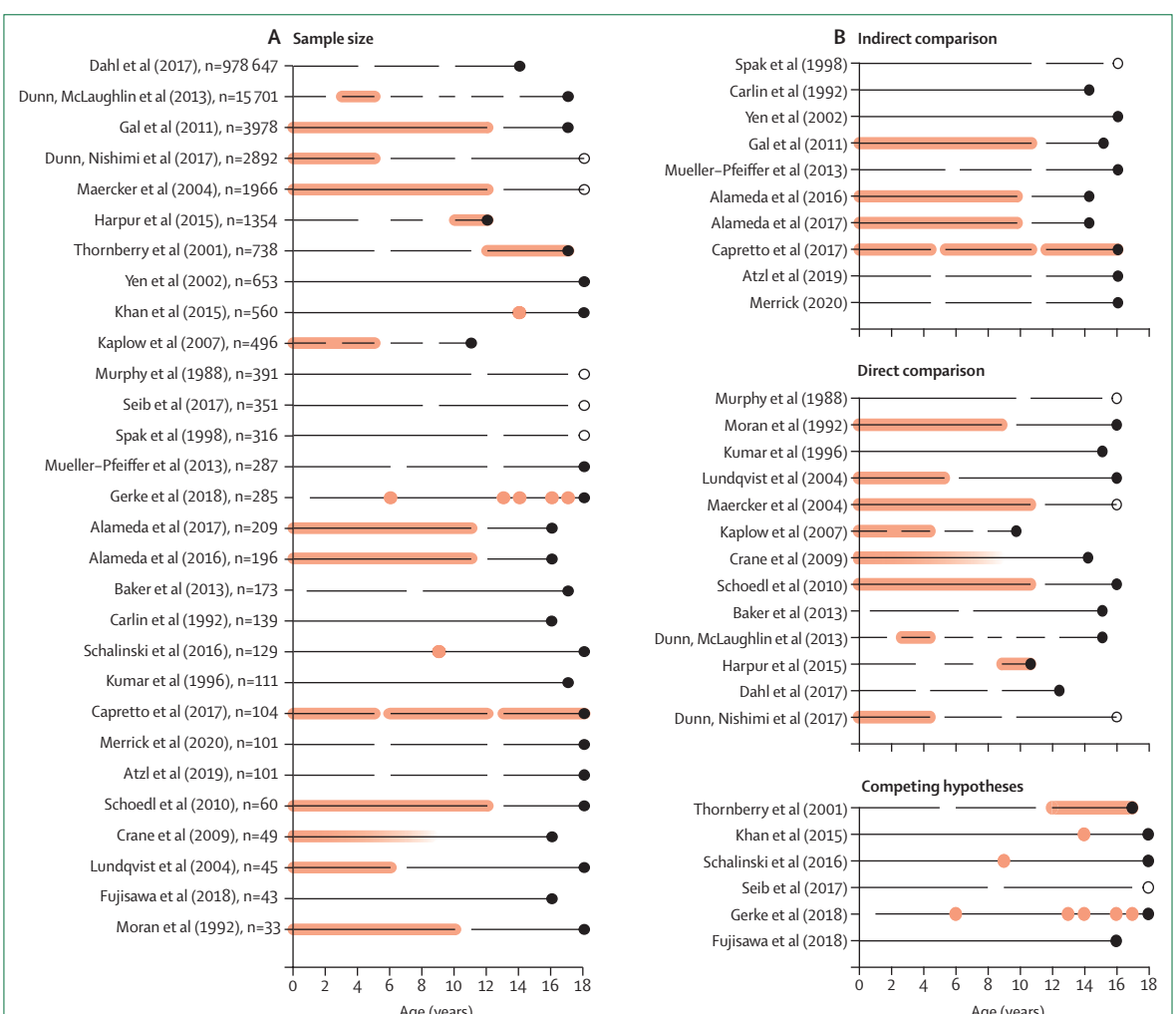
To investigate whether different maltreatment types share similar sensitive periods, we identified 20 studies that tested sensitive period effects for at least two maltreatment types. Of these studies, 15 (75%) reported at least one positive sensitive period finding, with all but two (both of which used a dichotomous measure of age) also finding that sensitive periods differed at least somewhat across maltreatment type (figure 5). However, there was little consistency across these studies in the sensitive periods identified for specific types of maltreatment (eg, physical *vs* sexual abuse) or broader maltreatment categories (eg, abuse *vs* neglect).

Sex differences in the timing of sensitive periods could also be expected, because of known sex differences in maltreatment prevalence and timing,[4,83] brain development,[84] psychopathology risk,[85,86] and sex-specific critical periods for hormonal and corticolimbic system functioning in rodents.[87,88] The few studies examining sex differences were almost equally split on whether sex differences in the effects of timing were found (appendix 1 pp 16–17).

Discussion

Although three-quarters of the 118 studies included in this systematic review reported timing effects, we found little converging evidence for maltreatment-related sensitive periods. Sensitive periods were not more consistent in studies with similar characteristics, including outcome type, operationalisation of maltreatment timing, or study rigour.

Possible explanations for why we observed such low convergence include that the timing and magnitude of sensitive periods has been shown to vary as a function of both genes and environmental input (this variability probably complicates efforts to identify universal periods of enhanced neuroplasticity),[86,89] or that sensitive periods in childhood are less numerous and their effects more nuanced than those occurring prenatally or perinatally. Periods of neuroplasticity that occur later in development might therefore be considerably more difficult to identify in observational work.



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However, neither of these explanations would explain why our maltreatment results contrast those found in studies examining maternal deprivation or institutionalisation, which suggest larger effects on future psychopathology during the first 6–24 months of life.[20] This discrepancy might partly be because maternal deprivation and institutionalisation both represent omissions of expected care, whereas the category of maltreatment is more heterogeneous, encompassing both omission of expected care (ie, neglect) and unexpected harm (ie, abuse). However, the literature on deprivation and institutionalisation is characterised by considerable complexity, with some reports indicating a second sensitive period in pre-adolescence,[90] and both

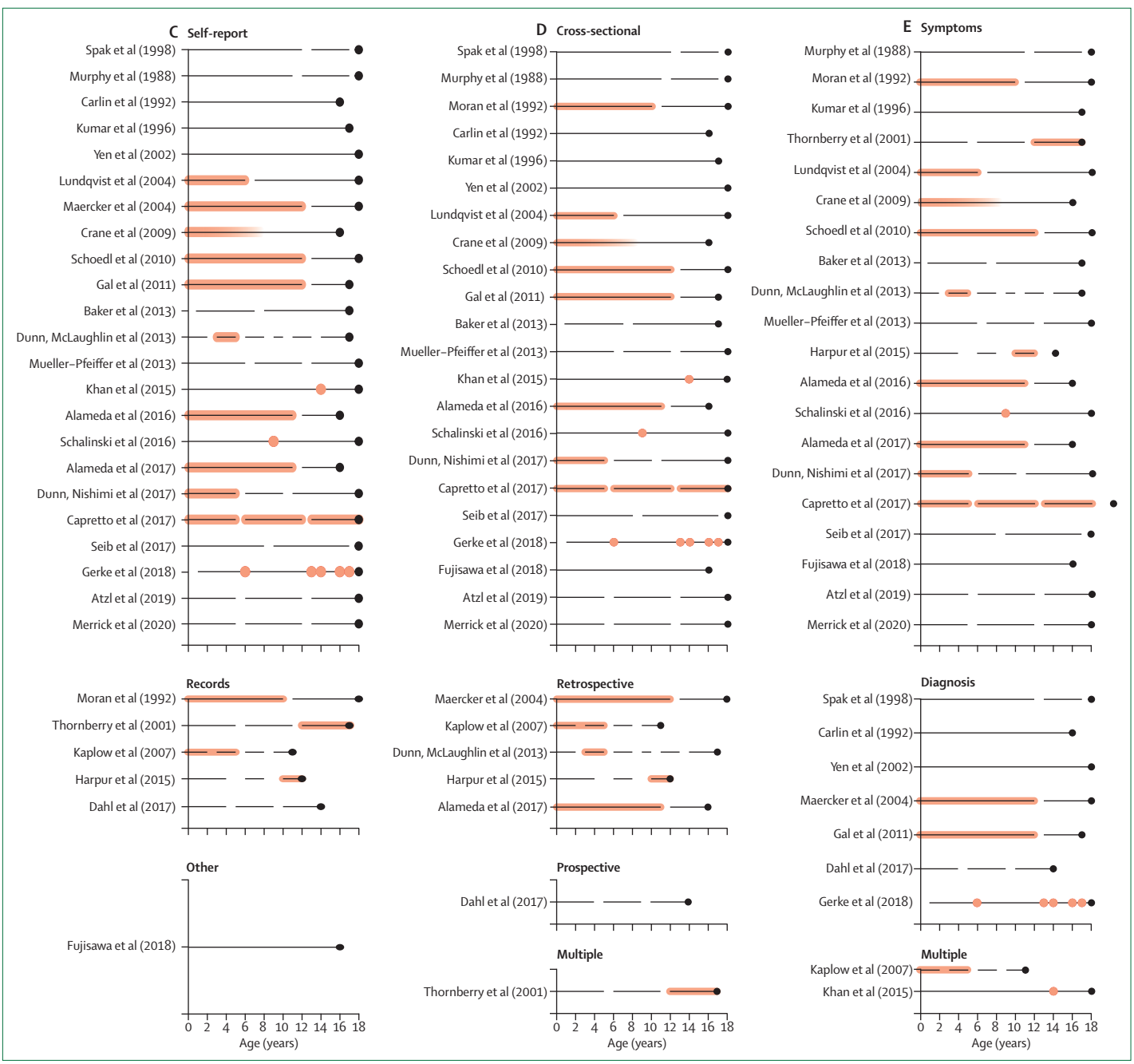

Figure 4: **Maltreatment-related sensitive period studies for depressive symptoms or depression diagnosis, by sample size (A), analytical strategy (B), maltreatment assessment approach (C), study design (D), and diagnosis versus symptom outcomes (E)**

Each line shows the results from one study, [83-127] with the length and position of the line showing the ages when maltreatment was assessed. Thicker line segments indicate the specific sensitive periods identified by the study. Solid dots show the end of the maltreatment exposure assessment window. Open dots indicate studies in which maltreatment exposure was assessed beyond age 18 years. Coloured gradients show sensitive periods from studies with age as continuous and reporting that outcomes were associated with an earlier or later sensitive period.

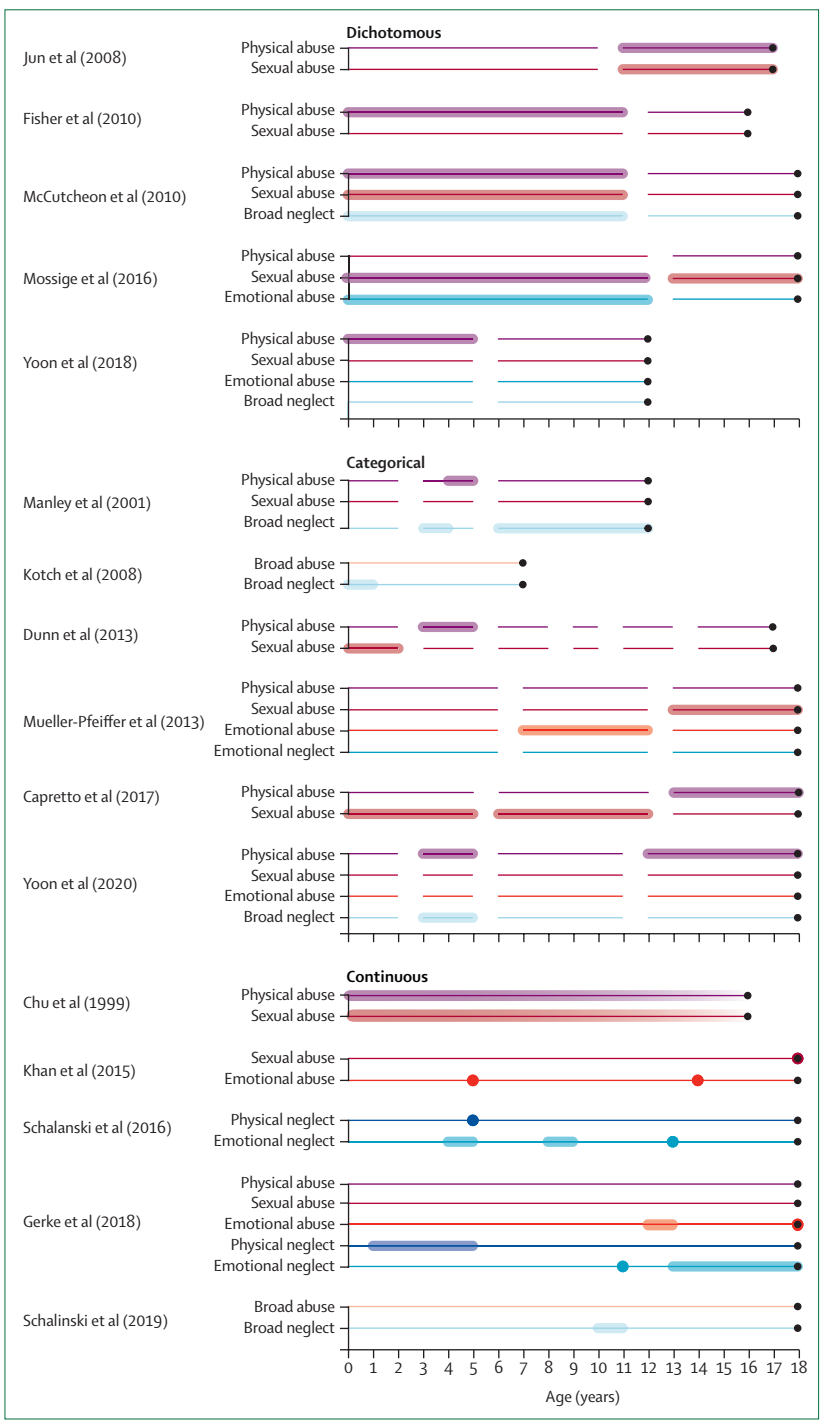

Figure 5: **Sensitive periods identified by studies assessing two or more different types of maltreatment and psychopathology outcomes, by timing as dichotomous, categorical, or continuous age**

Results of each study[128–137] are shown as a group of coloured lines, with the length and position of the lines showing the ages at which maltreatment was assessed and colour showing maltreatment type. Thicker segments indicate the specific sensitive periods identified for each outcome, whereas thinner segments indicate no sensitive periods were identified for that age range. Solid dots show the end of the exposure assessment window. Gradients show sensitive periods from studies using age as continuous and reporting that worse outcomes were associated with an earlier or later sensitive period. Results are shown only from studies with at least one positive sensitive period finding.

sex-specific and sleeper (or latent) effects.[8,91,92] Even studies using randomised assignment to study the effects of institutionalisation have been unable to disentangle the effects of exposure duration from developmental timing.[19] These sources of complexity also extend to studies of maltreatment, perhaps further contributing to inconsistent findings across studies.

Another possible contributor, cited in nearly all systematic reviews, is methodological heterogeneity. We attempted to understand this heterogeneity by grouping studies with similar characteristics. However, these efforts were hindered in many instances by the small number of studies in some subsets. The possibility of heterogeneity that was unaccounted for even within these subsets makes it difficult to discern if conflicting findings indicate a true absence of sensitive periods or simply methodological and statistical confounds. At the very least, our findings suggest that if maltreatment timing effects exist, they are likely to be sensitive to aspects of study design. In the panel, we outline some of the most probable contributors to these discrepancies and steps to mitigate them in future research.

We found that 75% of studies assessing children for multiple types of maltreatment reported distinguishable sensitive periods associated with each type. This observation aligns with theories organising exposures along distinct continuums of adversity that differentially affect neural systems and behaviour (eg, the Dimensional Model of Adversity and Psychopathology).[93,94] Thus, our findings suggest sensitive periods might be clarified by examining specific forms of maltreatment or dimensions of adversity rather than broad or aggregated composites.

Our results additionally suggest a need for increased precision in assessments of maltreatment timing. Dichotomous operationalisations of age seemed to contribute to a false sense of consistent findings, which disappeared when more precise measures of maltreatment timing were used. Studies with more precise measures of timing using instruments such as the Maltreatment and Abuse Chronology of Exposure scale[83] might help to identify relatively brief (eg, <3 years) sensitive periods that would otherwise be missed.[95–97]

Studies using objective outcome measures (eg, brain morphometry or stress physiology) were not statistically more likely to identify sensitive periods than studies using subjective outcomes (eg, psychiatric symptoms). However, the small number of high-quality studies using objective outcomes combined with heterogeneity in the outcomes studied limited our ability to make strong inferences about whether shifting focus to more transdiagnostic, biological measures would better show maltreatment timing effects.

Regarding subjective outcomes, we observed that individual studies assessing both internalising and externalising symptoms generally identified overlapping sensitive periods for these constructs. This finding might reflect within-study correlations of these

outcomes, and also suggests that sensitive periods relevant to maltreatment could manifest as increased vulnerability to the development of general psychopathology, rather than specific disorders or diagnostic families. This explanation aligns with decades of research indicating that the effects of maltreatment are non-specific, increasing risk for multiple types of psychiatric disorders simultaneously.[7,98,99] Consequently, our understanding of maltreatment timing effects might benefit from first examining outcomes at the level of general psychopathology, unless there are compelling theoretical reasons to examine disorder-specific measures.

Risk of bias was high in the studies we reviewed, with many not meeting even half of the criteria in our quality assessment tool. One salient limitation was that few studies reported being adequately statistically powered. This finding suggests it would be premature to interpret the null or mixed findings summarised in this systematic review as strong evidence that there are no sensitive period effects. Future studies on sensitive periods should address this limitation by estimating statistical power and preregistering analytical plans on open science platforms to reduce concerns about multiple testing. Studies should also try to assess and communicate how much the reported frequency of a particular exposure (eg, sexual abuse) varies across development, because this variation could affect power to detect sensitive periods at specific ages (eg, early in development when infantile amnesia limits maltreatment recall).

Only 24% of the studies had a prospective assessment strategy. Although sensitive periods for depression from prospective studies were not more reliable than from retrospective studies, known challenges with retrospective measures suggest their predominance is a limitation of the field. Compared with prospective measures, retrospective measures typically overestimate maltreatment effects on subjective outcomes and underestimate maltreatment effects on objective outcomes.[100,101] Retrospective and prospective measures of maltreatment occurrence also show low levels of agreement.[102] To our knowledge, agreement between retrospective and prospective measures of maltreatment timing has not been systematically studied, but it might be even lower due to cognitive biases, including telescoping effects (the tendency to perceive recent events as more remote and more distant events as more recent).[103] We therefore encourage investigators examining maltreatment timing effects to use prospective assessment strategies whenever possible.

In addition to more rigorous measurement of maltreatment, we encourage innovation in the development of new and more objective measures of early-life stressors, as these could reduce measurement error and increase statistical power to detect timing effects. For example, combining self-report and parent-report measures of maltreatment with glucocorticoid levels sampled repeatedly across development might help researchers to account partly for some of the known issues within the literature on maltreatment (eg, recall failure and cognitive biases).[104] Children's primary teeth have also recently been proposed as a promising new tool, because of their unique ability to record the timing of early-life stressors at a daily and weekly resolution.[105] Teeth might well be a new and non-invasive biospecimen that records life experiences objectively and can guide causally informative research on how and why psychiatric disorders emerge after experiences of adversity.[106]

When assessing sensitive periods in observational studies, two key challenges exist: multicollinearity and multiple testing. Multicollinearity arises because maltreatment exposure can be highly correlated across adjacent

***Panel:* Key challenges and recommendations for future research on maltreatment timing effects**

- Timing effects probably differ for different types of maltreatment, which peak in frequency and severity at different ages and work through partly separable neural mechanisms. Researchers should therefore stratify maltreatment analyses by maltreatment type or broad dimensions of adversity (eg, deprivation *vs* threat) when possible
- Over-reliance on crude measures of age of exposure (eg, dichotomised into early *vs* late) might obscure brief sensitive periods and contribute to a false sense of consistency that disappears when more precise measures of age are used. Researchers should therefore avoid dichotomous operationalisations of age in favour of multicategorical or continuous options
- The effects of maltreatment on psychopathology are likely to be general (ie, increasing risk of multiple types of mental health problems) rather than specific, and yet most sensitive period studies examine disorder-specific outcomes.Unless compelling reasons exist to examine disorder-specific measures, researchers should consider first examining outcomes at the level of general psychopathology or broad psychiatric spectra (eg, internalising symptoms)
- Risk of biased findings appears high because many studies are of poor quality. Researchers can take steps to improve quality by adopting the changes described, and ensuring adequate statistical power and preregistering analyses
- Over-reliance on retrospective measures of maltreatment, which show poor agreement with prospective measures, typically overestimate maltreatment effects on subjective outcomes, and might generate biased estimates of maltreatment timing. Researchers should therefore use prospective assessment strategies with frequent assessments whenever possible, and consider incorporating objective measures of exposure (eg, biomarkers)
- Observational studies of sensitive periods face statistical challenges, including multicollinearity (because maltreatment exposure tends to be highly correlated across adjacent ages), multiple testing (when numerous age ranges or regression models are compared), and many ways to operationalise relevant constructs. Researchers should therefore consider using advanced analytical approaches including the Structured Life Course Modeling Approach, random forest regression, or specification curve analysis
- Ruling out alternative explanations is crucial; what appears to be developmental differences in plasticity could instead reflect myriad other age-related differences (eg, rates of exposure or child-coping resources). Although no study will be able to account for all potential alternative explanations, researchers could increase confidence in their findings by testing as many plausible competing hypotheses as their data allow

ages. Multiple testing problems arise when several age ranges or regression models are compared. To mitigate these issues, new analytical strategies have been developed to test sensitive period effects with accumulation-of-risk and other theories, including the structured life course modelling approach[107,108] and machine-learning approaches (eg, random forest regression).[109] In addition, specification curve analysis can address methodological heterogeneity issues, because this technique examines how effect sizes vary across hundreds or even thousands of models that operationalise key parameters (eg, maltreatment type or timing) in different ways.[110]

Eliminating alternative explanations for apparent sensitive period effects is crucial. What appears as developmental differences in plasticity could instead reflect age-related differences in rates, severity, or accumulation of maltreatment exposure, or other factors that vary by age, such as child coping resources and cognitive capacity (eg, younger children might internalise maltreatment because they do not have the cognitive or socioemotional sophistication to attribute it to parental characteristics). Ruling out all alternative explanations is only possible in an experimental context. Nevertheless, investigators with observational data could increase confidence in their findings by testing as many plausible competing hypotheses as possible.

Although theories on the importance of developmental timing exist in multiple fields, including life-course epidemiology,[111] developmental neuroscience,[22] and developmental psychopathology,[112] this systematic review shows that these theories are not yet consistently supported by evidence from human observational studies on childhood maltreatment. We hope this Review inspires more rigorous research to investigate these timing effects, which, if known, could inform the optimal timing of intervention efforts aimed at improving mental health at the individual and population levels.

Conclusions

Researchers and clinicians should be cautious before deeming a particular phase of development a sensitive period for the effects of childhood maltreatment on psychopathology and associated constructs, because existing research does not align on any single period of increased vulnerability. This observation should not be interpreted as conclusive evidence that maltreatment-related sensitive periods do not exist, because it could also be due to methodological heterogeneity, study designs characterised by high risk of bias, and low analytical rigour. Studies that directly address these limitations are needed before information regarding maltreatment timing can be productively incorporated into causal models and clinical decision making.

Contributors

JDS and ECD did the literature search; JDS made the tables and figures; JDS, TWC, and ECD all contributed to data analysis and interpretation, and the writing and editing of the manuscript.

Declaration of interests

JDS received funding from the National Institute on Drug Abuse (award number T32DA050560). ECD received funding from the National Institute of Mental Health of the National Institutes of Health (award number R01MH113930). TWC declares no competing interests.

Acknowledgments

We thank Susan T Landry for her assistance in copyediting the manuscript and Dr Andrew Simpkin for consultation on statistical methods, as well as Janine Cerutti, Emma Glickman, Olivia Sterns, Samantha Stoll, and Amy Riegelman for their assistance in literature searches and data extraction for this Review. The sources providing funding for each of the authors played no role in the study design; collection, analysis, and interpretation of data; writing of the report; or decision to submit the paper for publication. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Schaefer JD, Cheng TW, Dunn EC. Sensitive periods in development and risk for psychiatric disorders and related endpoints: a systematic review of child maltreatment findings. *Lancet Psychiatry* 2022; **9:** 978–91.

Appendix for the Article:

Sensitive periods in development and risk for psychiatric disorders and related endpoints: A systematic review of child maltreatment findings

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This material supplements, but does not replace, the peer-reviewed paper in

Lancet Psychiatry

Supplemental Methods

Data Extraction

The primary outcomes of interest in our review were the periods of development identified as sensitive periods for maltreatment within each study. We also extracted data regarding study size, participant sex (% male), type(s) of maltreatment studied, ages during which maltreatment occurred, how maltreatment exposure was measured (e.g., self-report, parent-report, use of official records), which aspect of maltreatment "timing" was measured (e.g., onset, most severe instance, density, etc.), how timing was operationalized (e.g., with age as a dichotomy, ordinal series of categories, a continuum, etc.), the outcomes assessed, the ages at which these outcomes were assessed, and the analytic strategy used (e.g., indirect comparison, direct comparison, evaluation of competing hypotheses). All of these data are available in **Table S2** (see accompanying Excel file).

Risk of Bias Assessments

Three raters (including J.D.S. and T.W.C.) assessed studies for risk of bias using a modified version of the National Institutes of Health Quality Assessment Tool for Observational and Cohort Studies.(1) All studies were initially scored by two independent raters, with the third rater serving as a tie-breaker of rating discrepancies. Criteria and coding response options were as follows:

(1) research goals (with 1 indicating at least one clearly articulated research question and 0 indicating a lack of clearly articulated research questions),

(2) study population definition (with 1 indicating a clearly specified population and 0 indicating insufficient information),

(3) participation rate (with 1 indicating > 50% participation and 0 indicating < 50%),

(4) participant recruitment (with 1 indicating that maltreated and nonmaltreated children were drawn from the same population with the same inclusion and exclusion criteria and 0 indicating they were not),

(5) sample size justification (with 1 indicating the presence of a statement indicating that the study was adequately powered and 0 indicating the presence of a statement indicating that the study was underpowered),

(6) exposure assessment (with 1 indicating that maltreatment was assessed prior to the outcome and 0 indicating a cross-sectional design),

(7) exposure levels (with 1 indicating that maltreatment exposure was measured on a continuous or ordinal scale and 0 indicating it was measured only as present/absent),

(8) exposure assessment (with 1 indicating that maltreatment was assessed prospectively or using official records and 0 indicating that it was assessed only via retrospective report),

(9) repeated assessments (with 1 indicating that maltreatment was assessed more than once and 0 indicating it was assessed only once),

(10) outcome measures (with 1 indicating gold-standard assessment of the outcome and 0 indicating use of outcome measures with less objectivity, accuracy, and/or reliability),

(11) assessor blinding (with 1 indicating that outcome assessors did not know whether participants had been maltreated or not and 0 indicating no blinding),

(12) follow-up rate (with 1 indicating >80% follow-up during the study period and 0 indicating < 80% follow-up or a cross-sectional design),

(13) testing of alternative hypotheses (with 1 indicating that the study evaluated whether other maltreatment characteristics such as severity, frequency, or recency might better account for observed sensitive period effects and 0 indicating that they did not).

The criterion "sufficient timeframe to see an effect" from the original assessment tool was not included in our adapted instrument, given that all studies we included measured maltreatment exposure that occurred prior to the outcome assessment, even if this was done retrospectively (and therefore all studies would receive a "1" on this item). When there was insufficient information to assign a paper a "0" or a "1" for a specific criterion, we labeled it "NR" (not reported) or "NA" (if the criterion was not applicable). Finally, we summed across items to give each paper an overall quality rating from 0-13 ("NRs" and "NAs" were counted conservatively as "0" in these totals).

Permutation Testing

For each of the most studied outcomes in each major level of analysis (depression, hippocampal volume, and language/cognitive ability), we used permutation testing to quantitatively assess the presence of sensitive periods. Permutation testing is a statistical hypothesis test that shuffles the data labels of the observed data (here, reflecting age at maltreatment exposure) many times to generate a null distribution. The main advantage of this approach is that it carries very few assumptions; permutation testing does not require that the data are distributed in

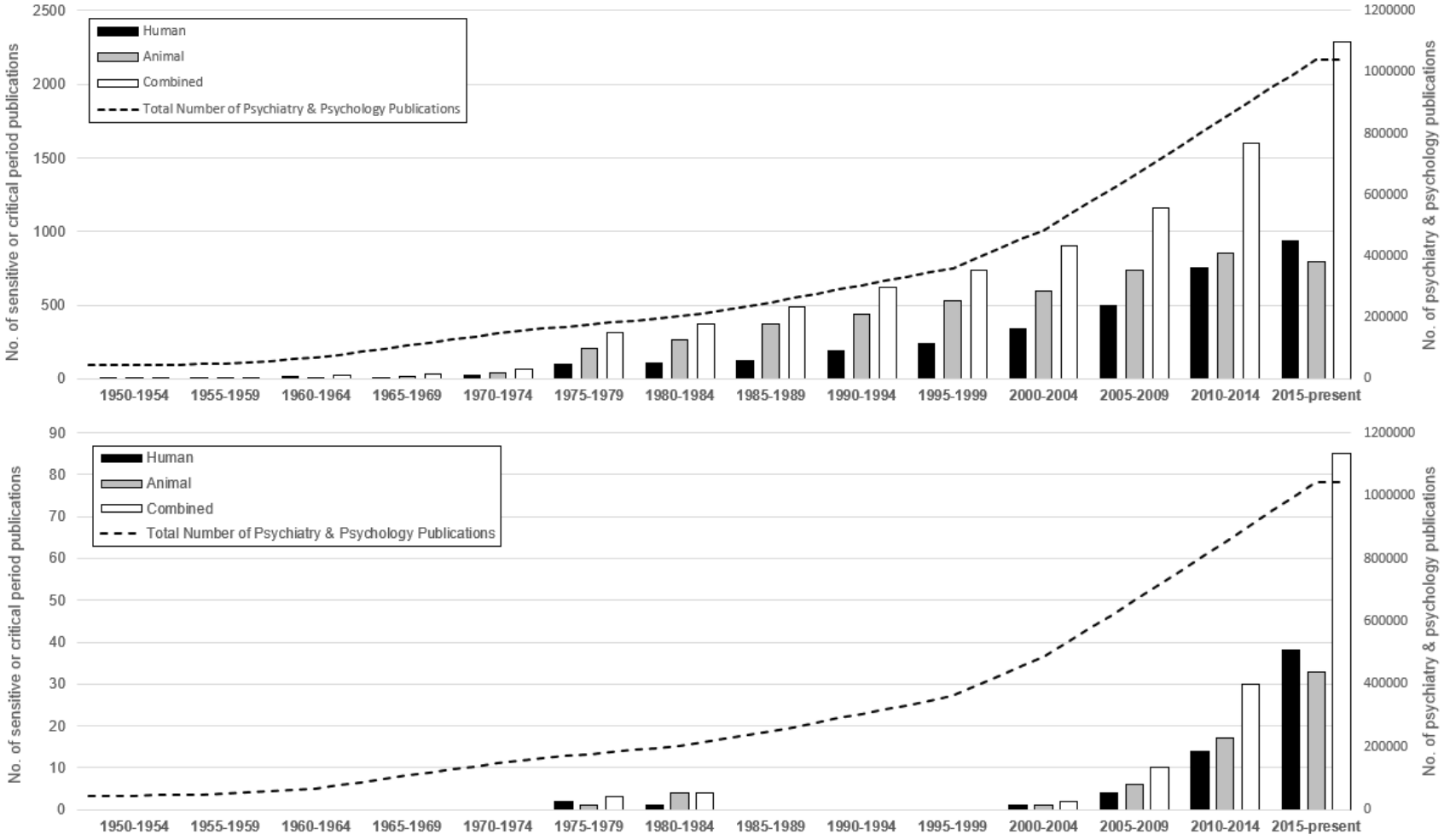
any particular way, but instead its major assumption is that the shuffled data are exchangeable, meaning that they maintain the same joint probability distribution before and after shuffling. P-values indicate the frequency with which a certain estimate (or a more extreme estimate) would be obtained by chance when the null hypothesis is true. By generating a null distribution from repeatedly shuffling the data labels, permutation testing can identify p-values associated with estimates obtained from the observed data.

There was heterogeneity in how timing effects were reported across studies, which made it difficult to combine data using standard meta-analysis approaches (e.g., pooling odds-ratios). We therefore used a crude binary variable to indicate whether each study reported a timing effect of maltreatment at each age between 0-18 (1 = reported timing effect; 0 = no reported timing effect). We then calculating the probability of identifying a timing effect at each age by summing this binary variable across studies and dividing that sum by the total number of studies that assessed timing effects at that age. Finally, we compared these values to a null distribution, which we generated by shuffling the values within each study. This test allowed us to assess the null hypothesis (that the likelihood of identifying associations between childhood maltreatment and various study outcomes did not vary by maltreatment age).

Studies with continuous age effects were excluded if they did not identify whether timing effects occurred at specific ages (i.e., they only reported general positive or negative age associations). A total of 4 out of 29 depression studies, 2 out of 11 language/cognitive ability studies, and 1 out of 7 hippocampal volume studies were excluded for this reason, leaving 25, 9, and 6 studies, respectively, in the analyses. Within each study, ages were rounded to the nearest whole number according to conventional rounding rules, except when decimal places were helpful to differentiate between adjacent time periods (e.g., when age brackets were 0-1.5 and 1.6-3, this was rounded to 0-1 and 2-3).

Data were permuted within study such that for each age block that identified sensitive period effects, the start year was randomly sampled from among the years assessed in that study (not all studies assessed at each year between 0-18). After each permutation, the probability of identifying a timing effect was calculated at each year. Data were permuted 1,000 times to generate a null probability distribution for each year. The actual effect probability was compared to this null distribution for each year, and the corresponding one-sided p-statistics are presented in **Table S4.** Results were evaluated at an α-threshold that was Bonferroni-corrected for multiple comparisons. Code for these analyses is available at https://github.com/thedunnlab/sens_periods_maltreatment.

Figure S1. Interest in maltreated-related sensitive period effects has increased over time.



Note. The upper panel of Figure 1 displays the number of published PubMed articles from inception to 4/26/2020 using the phrases "critical period" or "sensitive period" in the paper title or abstract. The lower panel shows the subset of published articles that also included the word "maltreatment" along with critical or sensitive period. Articles were classified as studying human, animal or combined populations (i.e., both human and animal subjects, or unclassified) using native PubMed filtering tools. Dotted lines and secondary y-axes display the increase in the total number of psychiatry and psychology publications searchable in PubMed (using the "Psychiatry and Psychology Category"[Mesh] search string) across the same period.

Table S1. Complete search terms used in the systematic search, divided by reference database

Category	OVID Search	PsycINFO Search	CINAHL Search
Maltreatment Search Terms			
Child Abuse	1. ((child* or youth or young or parent*) and (abuse* or abusing or abusive)).ti,ab. or exp Child Abuse/	1. ((child* or youth or young or parent*) and (abuse* or abusing or abusive)).ti,ab. or exp Child Abuse/	TI ((child* or youth or young or parent*) and (abuse* or abusing or abusive)) OR AB ((child* or youth or young or parent*) and (abuse* or abusing or abusive)) OR MH ("Child Abuse+")
Abuse Survivor	2. (survivor* and (child* or youth or young or parent*) and abuse).ti,ab. or exp "Adult Survivors of Child Abuse"/	2. (survivor* and (child* or youth or young or parent*) and abuse).ti,ab.	or TI (survivor* and (child* or youth or young or parent*) and abuse) OR AB (survivor* and (child* or youth or young or parent*) and abuse) OR MH ("Child Abuse Survivors")
Maternal Deprivation	3. ((mother* or maternal) and depriv*).ti,ab. or exp Maternal Deprivation/	3. ((mother* or maternal) and depriv*).ti,ab. or exp Deprivation/ or exp Mother Absence/	or TI ((mother* or maternal) and depriv*) or AB ((mother* or maternal) and depriv*) or MH ("Psychosocial Deprivation")
Neglect	4. (neglect* and (physical* or emotional*)).ti,ab.	4. (neglect* and (physical* or emotional*)).ti,ab. or exp Child Neglect/	or TI (neglect* and (physical* or emotional*)) or AB (neglect* and (physical* or emotional*)) or MH ("Neglect (Omaha)")
Sexual Abuse	5. ("sexual abuse" or "sex abuse").ti,ab. or exp Sex Offenses/	5. ("sexual abuse" or "sex abuse").ti,ab. or exp Sexual Abuse/	or TI ("sexual abuse" or "sex abuse") or AB ("sexual abuse" or "sex abuse") or MH ("Sexual Abuse")
Physical Abuse/Harsh Discipline	6. ((physical* and (abuse* or abusing or abusive)) or "harsh discipline" or "harsh physical discipline").ti,ab.	6. ((physical* and (abuse* or abusing or abusive)) or "harsh discipline" or "harsh physical discipline").ti,ab. or exp Physical Discipline/	or TI (((physical* and (abuse* or abusing or abusive)) or "harsh discipline" or "harsh physical discipline")) or AB (((physical* and (abuse* or abusing or abusive)) or "harsh discipline" or "harsh physical discipline"))
Emotional Abuse	7. (emotional and (abuse* or abusing or abusive)).ti,ab.	7. (emotional and (abuse* or abusing or abusive)).ti,ab. or exp Emotional Abuse/ or exp Verbal Abuse/	or TI ((emotional and (abuse* or abusing or abusive))) or AB ((emotional and (abuse* or abusing or abusive))) or MH ("Verbal Abuse")
Maltreatment (broad)	8. (maltreat* or mistreat*).ti,ab.	8. (maltreat* or mistreat*).ti,ab.	or TI (maltreat* or mistreat*) or AB (maltreat* or mistreat*)
ELS or ACE	9. ("early life stress*" or "adverse childhood experience*").ti,ab.	9. ("early life stress*" or "adverse childhood experience*").ti,ab. or exp Early Experience/	or TI ("early life stress*" or "adverse childhood experience*") or AB ("early life stress*" or "adverse childhood experience*") or MH ("Adverse Childhood Experiences")

Victimization	10. victimi*.ti,ab.	10. victimi*.ti,ab. or exp Victimization/	or TI (victimi*) or AB (victimi*)
	11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	
Sensitive/Critical Period Search Terms			
Age Factors	12. "age factors".ti,ab. or exp Age Factors/	12. "age factors".ti,ab. or exp Age Differences/	TI ("age factors") or AB ("age factors") or MH (“Age Factors”)
Sensitive Period	13. (sensitiv* and period*).ti,ab.	13. (sensitiv* and period*).ti,ab.	or TI (sensitiv* and period*) or AB (sensitiv* and period*)
Critical Period	14. (critical and period*).ti,ab.	14. (critical and period*).ti,ab.	or TI (critical and period*) or AB (critical and period*)
Sensitive Age	15. (sensitiv* and age*).ti,ab.	15. (sensitiv* and age*).ti,ab.	or TI (sensitiv* and age*) or AB (sensitiv* and age*)
Critical Age	16. (critical and age*).ti,ab.	16. (critical and age*).ti,ab.	or TI (critical and age*) or AB (critical and age*)
Timing	17. ("time factors" or timing).ti,ab. or exp Time Factors/	17. ("time factors" or timing).ti,ab.	or TI ("time factors" or timing) or AB ("time factors" or timing) or MH (“Time Factors”)
Developmental Period	18. ("developmental period" or “period of development”).ti,ab.	18. ("developmental period" or “period of development”).ti,ab.	or TI ("developmental period" or “period of development”) or AB ("developmental period" or “period of development”)
Combining	*19. 12 or 13 or 14 or 15 or 16 or 17 or 18*	*19. 12 or 13 or 14 or 15 or 16 or 17 or 18*	
Psychopathology Search Terms			
Mental Disorders	20. (mental and (disorder* or illness* or health)).ti,ab. or exp Mental Disorders/	20. (mental and (disorder* or illness* or health)).ti,ab. or exp Mental Disorders/ or exp Psychiatric Symptoms/ or exp Abnormal Psychology/ or exp Internalizing Symptoms/ or exp Externalizing Symptoms/	TI (mental and (disorder* or illness* or health)) or AB (mental and (disorder* or illness* or health)) or MH (“Behavioral Symptoms+” or “Mental Disorders+”)
Psychopathology	21. psychopathology.ti,ab. or exp Psychopathology/	21. psychopathology.ti,ab. or exp Psychopathology/	or TI (psychopathology) or AU (psychopathology) or MH (“Psychopathology”)
Mental Health	22. exp Mental Health/	22. exp Mental Health/	or MH (“Mental Health”)
Combining	*23. 20 or 21 or 22*	*23. 20 or 21 or 22*	
Other Research Domain Criteria (RDoC) Search Terms			
Negative Valence	24. ("negative valence" or emotion* or affect* or anxiet* or fear* or "acute threat" or "potential threat" or "sustained threat" or "frustrative nonreward" or "frustrative non-reward" or "emotion regulation" or "emotional regulation").ti,ab. or exp Emotions/ or exp	24. ("negative valence" or emotion* or affect* or anxiet* or fear* or "acute threat" or "potential threat" or "sustained threat" or "frustrative nonreward" or "frustrative non-reward" or "emotion regulation" or "emotional regulation").ti,ab. or exp Emotions/ or exp Affect/ or	or TI ("negative valence" or emotion* or affect* or anxiet* or fear* or "acute threat" or "potential threat" or "sustained threat" or "frustrative nonreward" or "frustrative non-reward" or "emotion regulation" or "emotional regulation") or AB ("negative valence" or emotion* or affect* or anxiet* or fear* or "acute

	Affect/ or exp Anxiety/ or exp Fear/	exp Anxiety/ or exp Fear/ or exp Frustration/	threat" or "potential threat" or "sustained threat" or "frustrative nonreward" or "frustrative non-reward" or "emotion regulation" or "emotional regulation") or MH (“Emotions+”)
Positive Valence	25. ("positive valence" or "reward respons*" or "reward anticipat*" or "reward sati*" or "reward learning" or "reward predic*" or "habit" or "reward valu*" or "reward evalu*" or "delay discount*" or "effort" or anhedonia).ti,ab. or exp Anhedonia/ or exp Affective symptoms/	25. ("positive valence" or "reward respons*" or "reward anticipat*" or "reward sati*" or "reward learning" or "reward predic*" or "habit" or "reward valu*" or "reward evalu*" or "delay discount*" or "effort" or anhedonia).ti,ab. or exp Anhedonia/	or TI ("positive valence" or "reward respons*" or "reward anticipat*" or "reward sati*" or "reward learning" or "reward predic*" or "habit" or "reward valu*" or "reward evalu*" or "delay discount*" or "effort" or anhedonia) or AB ("positive valence" or "reward respons*" or "reward anticipat*" or "reward sati*" or "reward learning" or "reward predic*" or "habit" or "reward valu*" or "reward evalu*" or "delay discount*" or "effort" or anhedonia) or MH (“Anhedonia” or “Reward” or “Delay Discounting”)
Cognitive	26. (cogniti* or learning or memory or executive function* or self-regulation or "self regulation" or self-control or "self control" or Intelligence or IQ).ti,ab. or exp Attention/ or exp cognition/ or exp cognition disorders/ or exp neurocognitive disorders/ or exp language/ or exp memory/ or exp perception/ or exp self-control/	26. (cogniti* or learning or memory or executive function* or self-regulation or "self regulation" or self-control or "self control" or Intelligence or IQ).ti,ab. or exp Attention/ or exp Cognition/ or exp Cognitive Ability/ or exp Cognitive Impairment/ or exp Neurocognitive Disorders/ or exp Language/ or exp Memory/ or exp Perception/	or TI (cogniti* or learning or memory or executive function* or self-regulation or "self regulation" or self-control or "self control" or Intelligence or IQ) or AB (cogniti* or learning or memory or executive function* or self-regulation or "self regulation" or self-control or "self control" or Intelligence or IQ) or MH (“Cognitive Ability (Iowa NOC)” or “Cognition Disorders” or “Cognition+” or “Executive Function” or “Language Processing” or “Mentalization” or “Perception+” or “Distraction” or “Attention+” or “Learning+” or “Habits+”)
Social Processes	27. (social process* or affiliation or attachment or "social communication" or "facial communication" or "self-perception" or "self perception" or agency or self-knowledge or "self awareness" or self-awareness or "self monitoring" or self-monitoring or "theory of mind").ti,ab. or exp social	27. (social process* or affiliation or attachment or "social communication" or "facial communication" or "self-perception" or "self perception" or agency or self-knowledge or "self awareness" or self-awareness or "self monitoring" or self-monitoring or "theory of	or TI (social process* or affiliation or attachment or "social communication" or "facial communication" or "self-perception" or "self perception" or agency or self-knowledge or "self awareness" or self-awareness or "self monitoring" or self-monitoring or "theory of mind") or AB (social process* or affiliation

	perception/ or exp social skills/ or exp self concept/ or exp Interpersonal relations/ or exp Social behavior/ or exp Mentalization/	mind").ti,ab. or exp Social Skills/ or exp Social Cognition/ or exp Social Communication/ or exp Social Interaction/	or attachment or "social communication" or "facial communication" or "self-perception" or "self perception" or agency or self-knowledge or "self awareness" or self-awareness or "self monitoring" or self-monitoring or "theory of mind") or MH ("Attachment Behavior+" or "Communication+" or "Social Behavior+" or "Social Skills" or "Social Interaction Skills (Iowa NOC)" or "Self Concept+" or "Theory of Mind")
Arousal/Regulatory	28. (arousal or "regulatory system*" or circadian or sleep or wake*).ti,ab. or exp homeostasis/ or exp wakefulness/ or exp sleep/ or exp "sleep initiation and maintenance disorders"/	28. (arousal or "regulatory system*" or circadian or sleep or wake*).ti,ab. or exp Homeostasis/ or exp Wakefulness/ or exp Sleep/ or exp Sleepiness/ or exp Sleep Wake Cycle/	or TI (arousal or "regulatory system*" or circadian or sleep or wake*) or AB (arousal or "regulatory system*" or circadian or sleep or wake*) or MH ("Arousal+" or "Sleep+" or "Sleep Disorders+" or "Circadian Rhythm")
Sensorimotor	29. (sensorimotor or sensory or motor).ti,ab. or exp psychomotor performance/	29. (sensorimotor or sensory or motor).ti,ab. or exp Psychophysiology/ or Exp Motor Performance/	or TI (sensorimotor or sensory or motor) or AB (sensorimotor or sensory or motor) or MH ("Sensory Motor Integration" or "Psychomotor Performance+")
Personality/Other	30. (personality or temperament).ti,ab. or exp Mental Processes/ or exp physiolog*/ or exp psychophysiolog*/ or exp Personality/ or exp neurobehavioral manifestations/	30. (personality or temperament).ti,ab. or exp Psychophysiology/ or exp Personality/	or TI (personality or temperament) or AB (personality or temperament) or MH ("Personality+")
DNA Methylation	31. exp Epigenetics/ or (epigen* or "DNA methylation" or "methylation" or "epigenetic ag*").ti,ab.	31. exp Epigenetics/ or (epigen* or "DNA methylation" or "methylation" or "epigenetic ag*").ti,ab.	or (MH "Epigenomics") or (MH "Methylation") or TI ("DNA Methylation") or AB ("DNA Methylation") or TI ("epigen") or AB ("epigen") or TI ("epigenetic ag*") or AB ("epigenetic ag*")
Combining	*32. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31*	*32. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31*	
	Neuroimaging Search Terms		
Neuroimaging Techniques	33. exp Brain/ or exp Magnetic Resonance Imaging/ or exp Diffusion Magnetic Resonance Imaging/ or exp Neuroimaging/ or exp Functional Neuroimaging/ or	33. exp Brain/ or exp Neuroimaging/ or (Magnetic Resonance Imaging or Diffusion Magnetic Resonance Imaging or Neuroimaging or Functional Neuroimaging or	or MH ("Brain" or "Magnetic Resonance Imaging" or "Electroencephalography" or "Tomography, Emission-Computed") or TI (Magnetic Resonance Imaging or Diffusion Magnetic Resonance

	exp Electroencephalography/ or exp Positron-Emission Tomography/ or exp Diagnostic Imaging/ or (Magnetic Resonance Imaging or Diffusion Magnetic Resonance Imaging or Neuroimaging or Functional Neuroimaging or Electroencephalography or Positron-Emission Tomography).ti,ab.	Electroencephalography or Positron-Emission Tomography).ti,ab.	Imaging or Neuroimaging or Functional Neuroimaging or Electroencephalography or Positron-Emission Tomography) or AB (Magnetic Resonance Imaging or Diffusion Magnetic Resonance Imaging or Neuroimaging or Functional Neuroimaging or Electroencephalography or Positron-Emission Tomography)
Neuroimaging Parameters	34. ("gray matter" or "grey matter" or "white matter" or "brain connectivity" or "functional connectivity").ti,ab.	34. ("gray matter" or "grey matter" or "white matter" or "brain connectivity" or "functional connectivity").ti,ab.	or TI ("gray matter" or "grey matter" or "white matter" or "brain connectivity" or "functional connectivity") or AB ("gray matter" or "grey matter" or "white matter" or "brain connectivity" or "functional connectivity") or MH (“Brain Mapping”)
Combining	*35. 33 or 34*	*35. 33 or 34*	
	Combining & Filtering Search Terms		
	36. 11 and 19 and (23 or 32 or 35)	*36. 11 and 19 and (23 or 32 or 35)*	
	37. review.ti.	*37. review.ti.*	
	38. meta-analysis.ti.	*38. meta-analysis.ti.*	
	39. 36 not (37 or 38)	*39. 36 not (37 or 38)*	*NOT (TI (“review” or “meta-analysis”))*
	40. 39 not (exp Animals/ not humans.sh.)	*40. 39 NOT (Animal NOT Human).po.*	*NOT (((MH "Animals+") OR (MH "Animal Studies") OR (TI "animal model*")) NOT (MH "human"))*
TOTAL HITS	**5826**	**4016**	**4068**

Notes. “Total hits” for each database includes overlapping studies that appeared in one or more of the other databases.

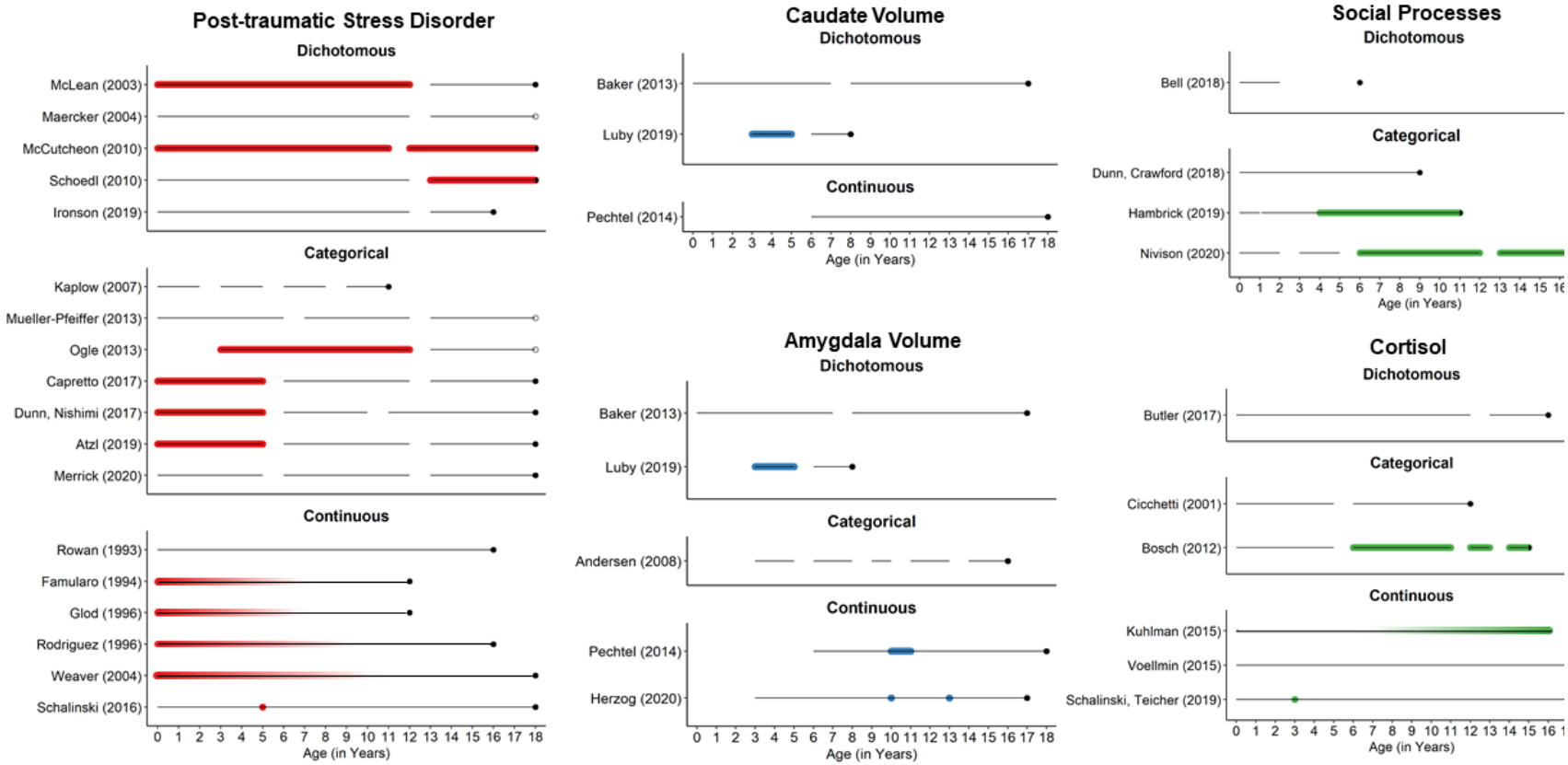
Tables S2 & S3 can be found in the Supplementary Excel File

Table S4. Results from permutation testing

Age	Depression	Language/cognitive	Hippocampal volume
0 (first year of life)	0.043	0.130	NA
1	0.070	0.118	NA
2	0.078	0.735	NA
3	0.026	0.114	0.026
4	0.026	0.127	0.058
5	0.016	0.131	0.103
6	0.211	0.510	1.000
7	0.653	0.771	0.845
8	0.671	0.791	1.000
9	0.364	0.301	1.000
10	0.403	0.307	0.688
11	0.612	NA	0.243
12	0.813	NA	0.702
13	0.997	NA	0.263
14	0.979	NA	0.465
15	1.000	NA	1.000
16	0.999	NA	1.000
17	0.981	NA	NA
18	1.000	NA	NA

Notes. Table displays p-values per year for three outcome types. These p-values reflect the test of the null hypothesis (that there are no effects of timing for that year of analysis). As shown, there were no ages where we found p-values small enough to be considered statistically significant (defined as $p < .003$, based on $\alpha = 0.05$, divided by Bonferroni-correction for 19 tests (one for each year) per outcome type). Only years with four or more studies reporting effects were included; *NA* values indicate that this minimum study threshold was not met.

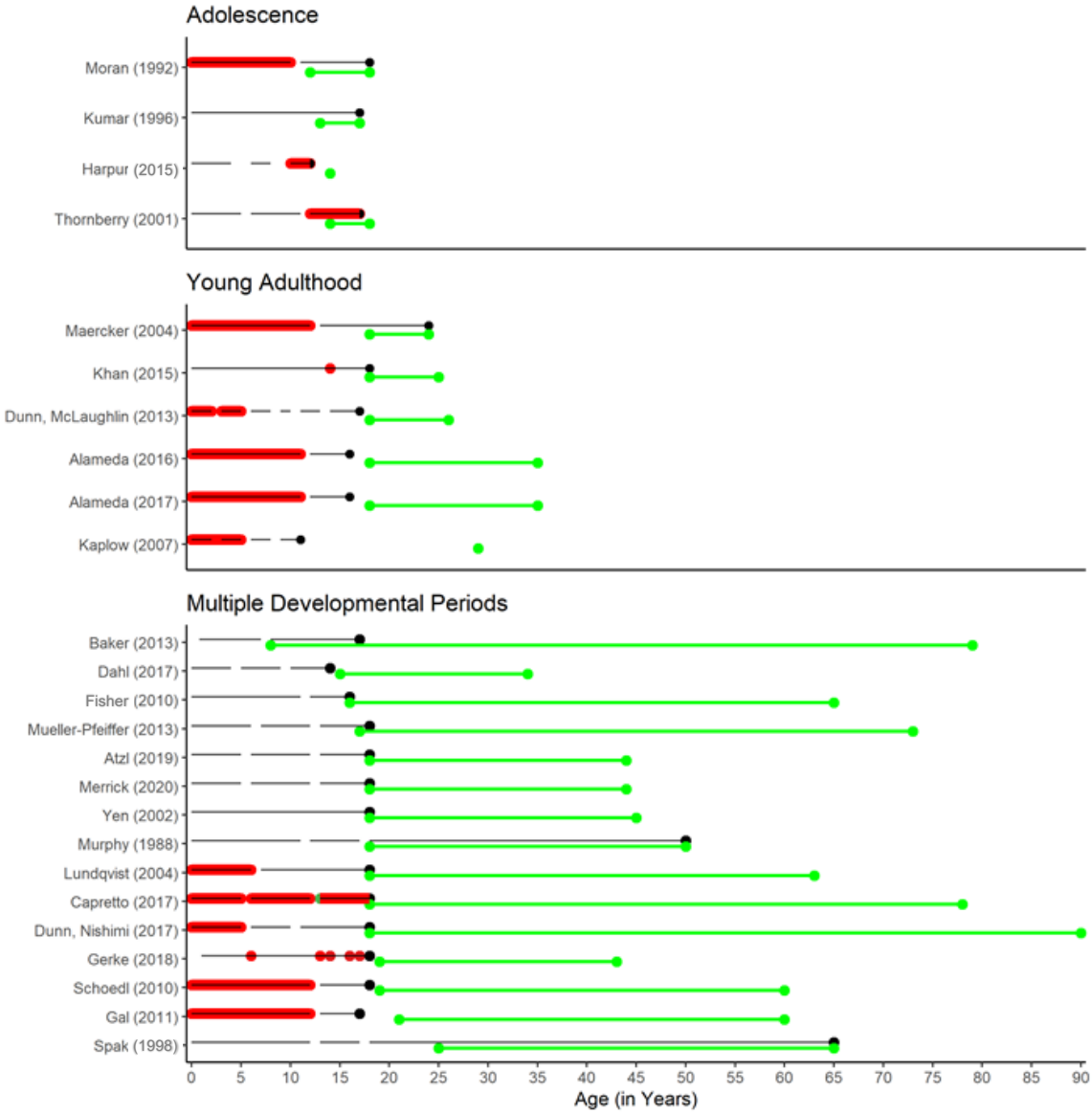
Figure S2. Sensitive periods identified for second-most commonly-studied outcomes



Note. This figure summarizes results from studies testing for timing-of-child-maltreatment effects on other commonly-studied outcomes across three different levels of analysis: (1) post-traumatic stress disorder symptoms or diagnoses, (2) caudate volume, (3) amygdala volume, (4) social processes (which encompasses measures of attachment, social competence, etc.), and (5) cortisol (which encompasses measures of free salivary cortisol; within-person variation such as the magnitude of the cortisol awakening response, diurnal change, or change in cortisol levels in response to stress; and hair cortisol concentration). Within each outcome, studies are organized by the operationalization of timing (e.g., dichotomous, categorical, or continuous). Results of each study are depicted on one line, with the length and position of the line showing the ages when maltreatment was assessed. Thicker line segments indicate the specific sensitive periods identified by the study, if any. Solid black dots denote the end of the maltreatment exposure-assessment window. Open black dots indicate studies where maltreatment exposure was assessed beyond age 18. Colored gradients depict sensitive periods from studies using a continuous operationalization of age and reported that worse outcomes were associated with an "earlier" or "later" sensitive period (i.e., without denoting specific ages)

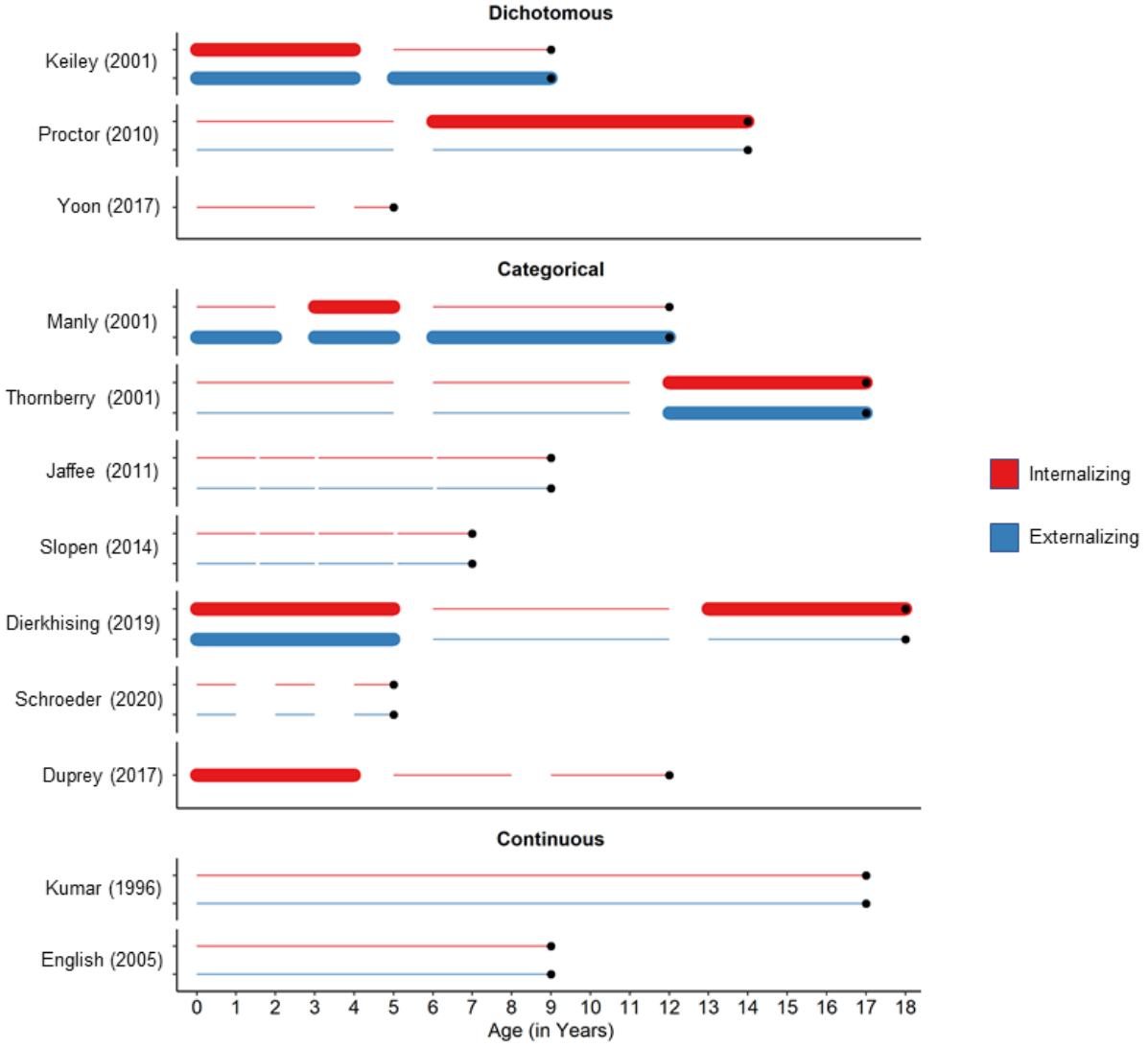
(see (2) as an example). Studies employing alternative operationalizations of maltreatment timing that could not be easily converted into years of age (e.g., before or after starting elementary school) or that combined outcomes falling into multiple categories are not shown.

Figure S3. Sensitive periods for depression organized by timing of outcome assessment



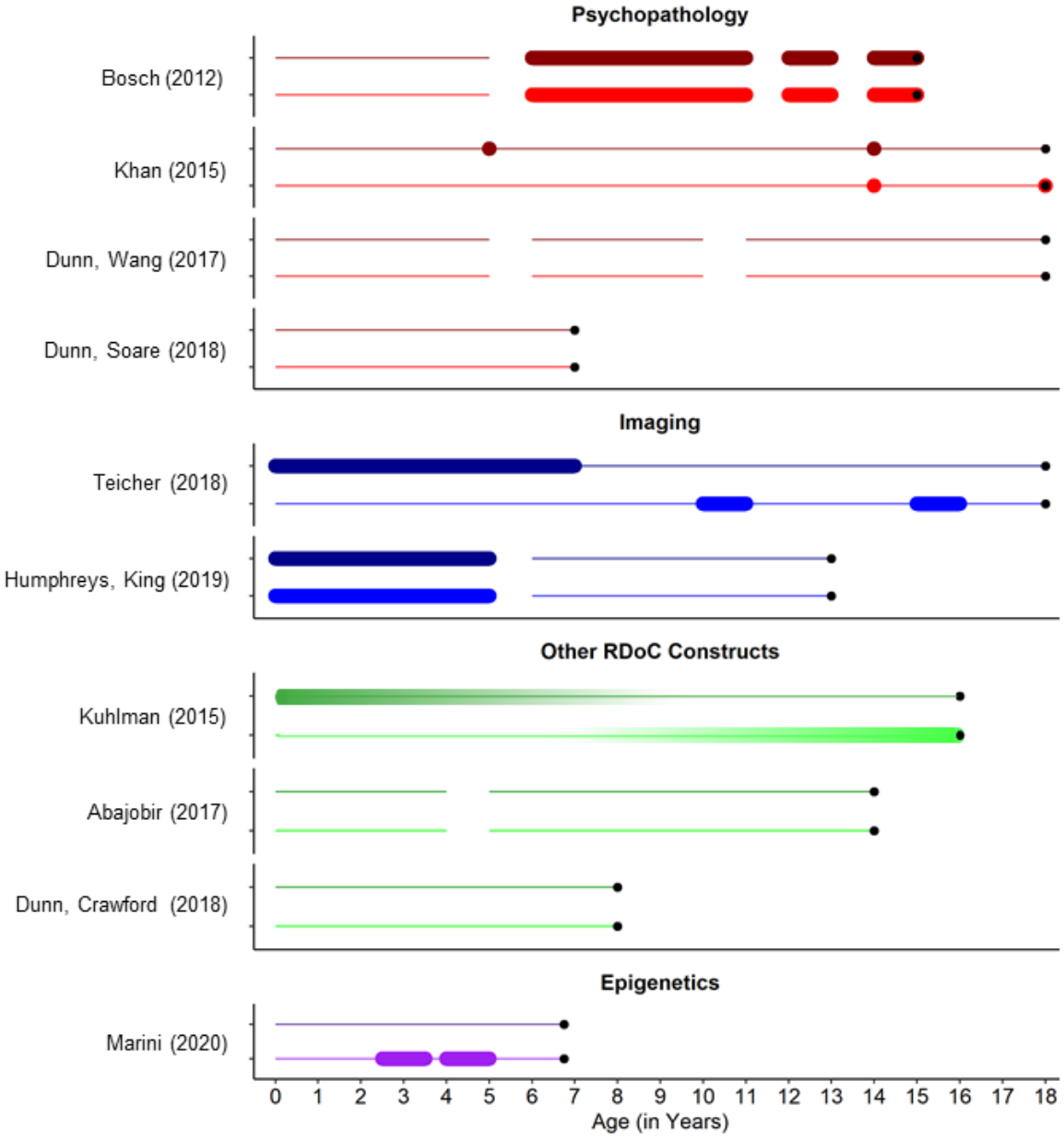
Notes. This figure displays studies testing for sensitive periods in the relationship between maltreatment and depression, organized by the timing of depression assessment (i.e., adolescence, young adulthood, or across multiple developmental periods). The length and position of each black line shows the ages at which maltreatment was assessed in each study. Shaded red segments indicate the specific sensitive periods identified, if any. Solid black dots denote the end of the exposure-assessment window. Green lines just beneath each black line show the ages at which participants were assessed for depression.

Figure S4. Sensitive periods for internalizing and externalizing symptoms.



Notes. This figure displays results from studies that tested for sensitive periods effects influencing the relationship between maltreatment and both internalizing and externalizing symptoms, organized by operationalization of age (e.g., dichotomous, categorical, or continuous). Results from internalizing and externalizing sensitive period analyses from each study are depicted on each set of red and blue lines, with the length and position of the lines showing the ages when maltreatment was assessed. Thicker segments indicate the specific sensitive periods identified for each outcome, if any, whereas thinner segments indicate no sensitive periods were identified for that age range. Solid black dots denote the end of the exposure-assessment window. Despite assessing the appropriate outcomes, Cicchetti (2013) and Cicchetti (2014) were excluded from this figure because they employed alternative operationalizations of maltreatment timing that could not be easily converted into years of age (e.g., early vs. late vs. persistent maltreatment).

Figure S5. Sensitive periods identified for men and women in studies reporting on sex differences.



Notes. Of the 118 studies we reviewed, only 14 reported examining whether sensitive periods differed for men and women. Of these 14, 11 reported results separately by sex without testing explicitly for sex differences, two tested interactions between sex and timing, and one study did both. Studies examining sex differences were roughly evenly split, with eight studies (57%) finding evidence supporting sex differences, and six failing to find support (43%). This figure displays results from studies that tested for sensitive periods effects separately in men and women, organized by level of analysis (e.g., psychopathology, imaging, or other RDoC construct). Results from each study are displayed as a pair of two lines, with the upper, darker-colored line in each pair depicting findings for men and the bottom, lighter-colored line in each pair depicting findings for women. The length and position of each line show the ages when maltreatment was assessed. Thicker segments indicate the specific sensitive periods identified for each outcome, whereas thinner segments indicate no sensitive periods were identified for that age range. Solid black dots denote the end of the exposure-assessment window. Despite also reporting results separately by sex, four studies were excluded from the figure because they employed alternative

operationalizations of maltreatment timing that could not be easily converted into years of age (e.g., before or after starting elementary school).(3–6)

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