Orri M, Gunnell D, Richard-Devantoy S, Bolanis D, Boruff J, Turecki G, Geoffroy MC. In-utero and perinatal influences on suicide risk: a systematic review and meta-analysis. Lancet Psychiatry. 2019 Jun;6(6):477-492. doi: 10.1016/S2215-0366(19)30077-X. Epub 2019 Apr 24. PMID: 31029623.

In-utero and perinatal influences on suicide risk: a systematic review and meta-analysis

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Summary

Background. Adverse in-utero and perinatal conditions may contribute to a heightened suicide risk throughout the lifespan, however existing evidence is sparse and contradictory. We did a systematic review and meta-analysis to investigate in-utero and perinatal exposures associated with suicide, suicide attempt, and suicidal ideation.

Methods. We searched MEDLINE, Embase, and PsycINFO from inception to January 24, 2019 for population-based prospective studies investigating the association between in-utero and perinatal factors and suicide, suicide attempt, and suicidal ideation. We calculated pooled odds ratio (ORs) with 95% CIs using random-effects models and used meta-regression to investigate heterogeneity.

Findings. We identified 42 studies; they had a low risk of bias (median quality score 9/9; range 5-9). Family/parental characteristics, such as high birth order (eg, pooled ORs fourth or later born vs first born 1.52, 1.21-1.88), teenage mothers (1.80, 1.52-2.14), single mothers (1.57, 1.31-1.89), indices of socioeconomic position such as low maternal (1.36, 1.28-1.46) and paternal (1.38, 1.27-1.51) education, and foetal growth - low birthweight (1.30, 1.09-1.55) and small-for-gestational-age (1.18. 1.00-1.40) were associated with higher suicide risk. Father's age, low gestational age, obstetric characteristics (eg, caesarean section), and condition/exposure during pregnancy (eg, maternal smoking or hypertensive disease) were not associated with higher suicide risk. Similar patterns of associations were observed for suicide attempt and suicidal ideation; however, these results were based on a lower number of studies. In meta-regression, differences in length of follow-up explained most between-study heterogeneity.

Interpretation. These findings suggest that prenatal and perinatal characteristics are associated with increased suicide risk during the life course, supporting the developmental origin of health and diseases hypothesis for suicide. The low number of studies for some risk factors, especially for suicide attempt and ideation, leaves gaps in knowledge that need to be addressed. The mechanisms underlying the reported associations, and their causal nature still remain unclear.

Funding. European Union's Horizon 2020.

Introduction

Suicide is an important cause of mortality worldwide, with an estimated global burden of 800 000 deaths each year,[1] and its prevention is of paramount importance. The need for prevention extends to non-fatal suicide attempt and severe suicidal ideation, as both carry serious long-term consequences[2] including increased risk of suicide death.[3]

Suicide is a complex and multifactorial phenomenon with both proximal (eg, mental disorders, economic breakdowns) and distal (eg, childhood adversities) risk factors.[4] In keeping with the developmental origins of health and disease (DOHaD) model,[4–8] an increasing number of studies have reported associations of in-utero and perinatal factors with suicide and mental disorders.[9,10] While the contribution of in-utero and perinatal conditions is well established for a range of non-communicable diseases such as cardiovascular and metabolic comorbidities,[11–13] evidence is less consistent for psychiatric disorders and suicide.[14,15] For example, prior studies have reported an increased risk of suicide for individuals born with a low birthweight[16] or individuals exposed to maternal smoking during pregnancy,[17] whereas others have failed to replicate these associations.[18,19] Such inconsistencies may be accounted for by heterogeneity of studies in terms of country of origin, study design and length of follow-up. Further, as both suicide and most in-utero/perinatal factors (such as low birthweight) are rare at the population-level, failure to find an association in some studies may be attributable to the lack of statistical power despite large sample sizes. We are unaware of any systematic review of the in-utero and perinatal influences on suicide using statistical approaches increasing the statistical power (such as meta-analysis).

We conducted a systematic review and meta-analysis of the available evidence on the association between in-utero and perinatal risk factors (including in-utero conditions, maternal-related factors, and socioeconomic conditions at birth) and suicide, suicide attempt, and suicidal ideation. Findings from such a study may provide insight supporting the DOHaD hypothesis for suicide risk, thus informing public health preventive interventions focusing on early maternal and child care.

Methods

Search strategy and selection criteria

This systematic review was conducted in accordance with Meta-analyses Of Observational Studies in Epidemiology (MOOSE) guidelines.[20] The protocol was registered in PROSPERO (number CRD42018091205). A health science librarian (JB) searched the following databases from their inception until January 24, 2019 for published studies on in-utero and perinatal factors and suicide: MEDLINE, Embase, and PsycINFO. The search was restricted to studies

published in English. Additionally, we searched the reference lists of all identified publications and hand searched key journals. Only published studies were considered. A search strategy was developed for MEDLINE and modified for the other databases. Using a combination of free text and controlled vocabulary terms (see **appendix**), we searched terms from three categories: in-utero and perinatal factors (eg, "birthweight", "parent* age", "foetal growth"), suicide-related outcomes (eg, "suicide*", "suicide attempt", "suicidal ideation", "self-harm"), and studies with a prospective design (eg, "longitudinal", "registries", "epidemiological studies"), combined using the Boolean operator "and".

Two investigators (MO and DB) independently screened the identified records for eligibility, first by title or abstract, followed by assessing the full-text (agreement on inclusion, weighted k = 0.98); discrepancies were resolved by discussion with a third investigator (MCG). Studies were included if they: (1) were population-based longitudinal studies or case-control studies nested in a cohort (ie, linkage of population registries or population-based cohort studies), and (2) reported on associations between any in-utero (any gestational period) and perinatal (measure up to one year of age) exposures or conditions and suicide, suicide attempt or suicidal ideation. Studies assessing self-harm defined as non-suicidal self-injuries were excluded.

Data extraction and quality assessment

Two investigators (MO and DB) independently extracted the following information from the selected articles: name of the first author, year of publication, name of the cohort (or information about the register), study location (country), number of participants, birth year of the participants, year at which the outcomes were assessed, participants' age at outcome assessment, risk factors investigated, outcome(s) investigated, number of cases and non-cases among exposed and non-exposed to each risk factor. If information was unavailable or unclear from a published report, corresponding authors were contacted to obtain the relevant data.

Study quality was assessed using the Newcastle-Ottawa Quality Assessment Scale for cohort studies.[21] The scale assesses the quality of three domains of a study: participant selection (eg, representativeness of the exposed cohort), comparability of exposed and non-exposed groups (eg, whether the analysis accounted for confounding factors), and ascertainment of outcome (eg, adequacy of follow-up). For each characteristic within these three domains, a point was given if the criterion was fulfilled, except for comparability criterion that could score 0, 1 or 2 points (score range, 0-9). Two investigators (MO and DB) independently assessed the quality of the articles. Agreement between the investigators was high (weighted k = 0.86), and remaining discrepancies were resolved by discussion with a third investigator (MCG).

Data analysis

We did separate meta-analyses to estimate the association between each identified risk factor and suicide, suicide attempt, and suicidal ideation when raw data were provided for at least 2 studies. When it was not possible to pool the estimates, or information to perform meta-analysis was lacking (ie, single studies), we summarized evidence narratively. Our procedure to harmonize exposure categorization across studies is described in **appendix**. For exposures investigated in more than one study from the same cohort/linkage, we selected the study with the longest follow-up. We calculated crude odds ratios (OR) and 95% confidence intervals (CIs) to compare lifetime suicide risk of individuals exposed to a given risk factor versus those non-exposed. Pooled ORs with 95% CIs were calculated using random-effect models.[22] Given the range of different measures used to compute adjusted associations (eg, hazard ratios, odds ratios), adjustment variables investigated (eg, socioeconomic position, mental health), and exposure categorisation (eg, mother's age <20 versus ≥20 in one study, and <20 versus 20-25 versus ≥25 in another), we were not able to pool consistent adjusted estimates. However, we narratively reported whether adjusting for confounding variables yielded changes in the crude estimates in the single studies and performed sensitivity analyses. Forest plots were generated showing ORs with corresponding 95% CIs for each study and the overall random-effect pooled estimate. We assessed heterogeneity across studies using the Cochrane Q statistic and the I^2 statistic (higher values representing higher heterogeneity),[23] and used meta-regression and subgroup analyses to explore potential sources of heterogeneity (ie, age at follow-up, study design, and differences in the categorization of the exposure variables) and the influence of individual studies. Risk of publication bias was assessed with visual inspection of the funnel plots, and further inspected using the Egger test[24] and the Duval and Tweedie trim-and-fill method.[25]

Role of funding sources

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 793396 and the Canadian Institutes of Health Research. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

From the initially retrieved 3013 unique records, 42 articles met our inclusion criteria (**Figure 1**) and were retained for this study. The articles consisted of data that were drawn from 21 different cohorts (n=10 cohort studies and n=11 population registers) from Europe (n=15), North America (n=3), Taiwan (n=1), and New Zealand (n=1), and Brazil (n=1). Sample sizes ranged from 140 to 3 300 708, and follow-up from 2 to 70 years. Suicide mortality was an

outcome in 14 of 21 cohorts, suicide attempt in 9 of 21, and suicidal ideation in 4 of 21 (**Table 1**). Methodological quality of the retained studies was high for observational studies (overall satisfactory quality of evidence; **Table 2**): most studies showed limited evidence of selection bias, had long follow-up and were based on secure records for the assessment of exposures and outcomes (eg, linkage of hospital or death registers).

Figure 2 shows the perinatal factors investigated in the included studies. Studies investigating the association between family and parental characteristics and suicide risk suggested that suicide risk was heightened for second or later born individuals compared to first born individuals. The pooled OR for this comparison was 1.22 (95%CI 1.12-1.34; n=10 studies; **Figure 3**). Restricting the analysis to 7 of the 10 studies allowed us to test dose-response associations between birth order and suicide: the pooled OR for the comparison between second-to-third born versus first born was 1.18 (1.07-1.30) and for the comparison between fourth or later born and first born was 1.51 (1.21-1.88), suggesting an increased suicide risk for increasing birth order. Most studies adjusting for confounding factors in multivariate analyses (such as maternal age, socioeconomic status, and sex), reported dose-response associations between increasing birth order and suicide, with adjusted associations being 10-20% stronger than crude associations. There was also evidence of an association in two within-family studies comparing siblings from the same family (thus accounting for family-related confounding factors).[26,27] One study showed that suicide risk was similar when the analyses were stratified according to the time since the birth of the previous child (eg, adjusted hazard ratio [HR] were 1.41 when the previous child was born 2 years earlier, 1.24 when the child was born 2-3 years earlier, and 1.49 when the child was born >3 years earlier),[26] while another study showed that suicide risk persisted when the analyses were stratified by sibship size.[28] The association, however, was less clear for suicide attempt. The risk of suicide attempt was not heightened for second or later born children compared to first born children, with a pooled OR of 1.17 (0.97-1.41, n=5 studies; **Figure 4**). One study only found statistical evidence for an association between birth order and suicidal ideation for the comparison between fourth or later born children versus first born children (adjusted OR 1.48, 1.06-2.07).[29] For mother's age at child birth, suicide risk was heightened for offspring of younger mothers (<20 years of age) compared to those born to older mothers (≥20 years of age), with a pooled OR of 1.80 (1.52-2.14, n=7 studies). Adjustment for various confounding factors in single studies (eg, birth order, socioeconomic status) did not account for this association. Associations were also found for suicide attempt and younger mothers (pooled OR 1.81, 1.32-2.50, n=4 studies) but not for suicidal ideation (pooled OR 1.28, 0.84-1.94, n=2 studies). No evidence of increasing suicide risk was found for individuals born to young (<25 years) or older fathers (>35 years) compared to those born to fathers aged 25-35, with pooled ORs of 1.24 (0.90-1.71, n=4 studies) and 1.05 (0.88-1.25, n=4 studies),

respectively. However, subgroup analyses stratified by age at outcome assessment indicated that indicated that in studies with >30 years follow-up there was evidence of increased risk amongst those with older fathers. Additionally, one study using a robust within-sibling design reported heightened risk of suicide attempt for offspring born to fathers aged 45 years or older compared to fathers aged 20-24 years (HR 2.72, 2.08-3.56).[30] For household composition at child birth, the pooled OR for the comparison between single-mother households (ie, single, widowed, divorced mothers at child birth) versus non-single mother households was 1.57 (1.31-1.89, n=7 studies). Most studies adjusted for relevant confounding factors, such as socio-economic status, child sex, and other family variables (eg, maternal age), and no major variations in the estimates was detected. These results were consistent for suicide attempt (pooled OR 1.78, 1.29-2.45, n=3 studies), but no association was reported for suicidal ideation in one study (OR 1.21, 0.86-1.37).[31]

For variables describing family socioeconomic position at birth, the pooled OR for higher versus lower parental education (ie, up to primary/lower secondary school) was similar for mothers (1.36, 1.28-1.46, n=3 studies) and fathers (1.38, 1.27-1.51, n=2 studies). Adjustment for confounding factors (eg, parental age, birthweight and birth order) did not explain associations in any of the studies. Suicide attempt (OR 1.33, 0.96-1.83)[32] and suicidal ideation (OR 0.94, 0.82-1.14)[31] were not associated with maternal education in the two studies that investigated this, although for suicide attempt the strength of the association (OR 1.33) was consistent with that seen for suicide. Individuals from low socioeconomic status at birth (parents' unskilled/manual work) were at increased risk of suicide (pooled OR 1.27, 1.00-1.61, n=6 studies) or suicide attempt (pooled OR 1.75, 1.45-2.09, n=5 studies) but not suicidal ideation (OR 1.23, 0.76-1.57),[31] compared to individuals with higher socioeconomic status.

Several studies investigated the association between various indices of foetal growth and suicide risk. Evidence of increased risk was found across five studies comparing suicide risk for individuals with low (<2500 g) versus normal birthweight (≥2500 g), with a pooled OR of 1.30 (1.09-1.55). Such risk was not explained by other in-utero and maternal confounding variables (eg, gestational age, obstetric characteristics, mother's age and parity). Consistently, there was an increased risk of suicide attempt (pooled OR 1.39, 1.23-1.56, n=2 studies) and suicidal ideation (pooled OR 1.73, 1.04-2.86, n=2 studies) for individuals born with low birthweight. Low gestational age at birth (ie, prematurity) was not associated with suicide, with a pooled OR of 1.11 (0.98-1.25; n=5 studies) for low (<36/38 weeks) versus non-low gestational age (≥36/38 weeks). However, an association was found for being small for gestational age at birth, with a pooled OR of 1.18 (1.00-1.40, n=4 studies). Concerning suicide attempt, an association was reported for low gestational age in two studies (pooled OR 1.09, 1.04-1.15), although this comparison

was mainly influence by one study (99.8% weights). One study reported a higher risk in the lowest category of birth length (<47 cm) relative to the reference category (50–51 cm), with a crude HR of 1.36 (1.01-1.84) for suicide and an adjusted HR of 1.29 (1.18-1.41) for suicide attempt.[16] One study reported no association between small head circumference at birth (<32 cm versus ≥32 cm) and suicide,[17] but another study reported an association with suicide attempt (adjusted OR 2.2, 1.1-4.6). [33]

Several studies investigated associations between obstetric characteristics and suicide but found no statistical evidence of an association with caesarean section versus vaginal delivery (pooled OR 1.13, 0.92-1.40, n=2 studies) and placenta abruption (adjusted HR 1.60, 0.51-4.98).[17] Similarly, a study found no statistical evidence of an association between 5-min Apgar score <7 and suicidal ideation (adjusted OR 1.9, 0.73-5.0),[33] whereas another study reported an association between caesarean section and suicide attempt (OR 1.09, 1.00-1.18).[16]

Finally, maternal physical and psychological prenatal conditions and exposures during pregnancy were investigated for their association with suicide risk. Four studies investigated associations between maternal smoking during pregnancy and suicide mortality. The pooled OR for the comparison between mothers smoking ≥1 cigarettes/day versus mothers smoking <1 cigarettes/day was 1.56 (0.99-2.46, n=4 studies). Studies investigating the number of cigarettes/day did not report a clear dose response association.[17,34] It is worth noting that these studies revealed potential confounding effects of perinatal and family variables: in one study, the effect of maternal smoking was only seen for the comparison between mother smoking >10 vs <1 cigarettes/day after adjustment for child's sex, gestational age, birthweight, 5-minute Apgar score, maternal age, parity, and mother's psychiatric diagnosis before the child's birth.[34] In another study, the effect of maternal smoking was attenuated when the analysis was restricted to sibling pairs discordant for suicidal acts and prenatal smoking exposure.[17] Weak evidence for an association with suicide was reported for mother chronic illness[35] and exposure to diethylstilboestrol during pregnancy,[36] and for both suicide and suicide attempt for bereavement stress during preconception (ie, death of a first-degree relative),[37] mother hypertensive disease (pooled OR suicide 1.09, 0.69-1.72, n=2 studies; HR suicide attempt 1.27, 1.00-1.63),[16] mother's antenatal depressive mood,[38] and unwanted pregnancy.[38] It is worth noting, however, that these comparisons were based on relatively few events.

We found high heterogeneity for most pooled estimates. Meta-regression suggested that 36 to 100% of this heterogeneity could be explained by the age at follow-up (≤30 years versus >30 years), but accounting for this factor would not alter our results (**appendix**). No heterogeneity was explained by study design, and differences in the

categorization of the exposure variables. When single studies explaining the remaining heterogeneity were removed, the pooled estimate did not change (**appendix**).

Subgroup analyses, although based on a small number of studies, suggested that associations of maternal age and single motherhood were more pronounced among studies with shorter follow-up (≤30 years), whereas associations for birth order, paternal age and parental education were more pronounced among studies with longer follow-up (>30 years) (**Figure 5**). For all comparisons, we found little evidence that publication bias could have influenced our results (**appendix**). Sensitivity analyses suggested that confounding factors are unlikely to explain the reported associations.

Discussion

To our knowledge, this is the first systematic review and meta-analysis summarizing the available evidence of the in-utero and perinatal influences on suicide. We showed that in-utero and perinatal influences, especially family/parental characteristics, socioeconomic characteristics, and indices of foetal growth, are associated with increased suicide risk several decades later. Although such findings are consistent with DOHaD hypothesis,[4,10] in-utero and perinatal factors are generally absent from most of the current models of suicide. Integrating the contribution of these early-life factors would improve our understanding of the aetiology of suicide and inform population-based suicide prevention efforts. However, some important issues remain to be clarified in future research.

First, many risk factors such as obstetric characteristics and conditions/exposures during pregnancy remain under-investigated. Although single studies were of high quality, additional evidence is needed to draw firm conclusions about their role on the aetiology of suicide. Moreover, no data was available for several other potentially relevant factors, such as maternal psychopathology, substance use, infections, and birth complications, that were shown to contribute to the aetiology of other mental disorders.[14]

Second, suicide attempt and suicidal ideation were under-investigated outcomes. It is important for future studies to test whether early-life factors associated with suicide are similarly associated with non-fatal suicide attempt. Our meta-analysis suggests that while some associations are similar for suicide and suicide attempt (eg, mother's young age), for other factors (eg, birth order) the available evidence does not allow us to draw firm conclusions. Additionally, as the literature showed that many childhood/adolescence risk factors for suicidal thoughts differ from those for suicidal acts,[39] future studies should clarify whether this applies to in-utero and perinatal influences as well.

Given the low number of studies investigating suicidal ideation as an outcome, additional evidence on this point is needed.

Third, future studies are needed to establish the causality of associations. Although most studies adjusted for relevant confounding factors, causation cannot be established as unmeasured factors may account for observed associations.[40] For example, associations of adverse maternal conditions with suicide risk could be due to parental psychiatric disorders influencing both adverse maternal conditions (eg, teenage pregnancy, single motherhood) and mental health disorders in the offspring. Among the 42 included studies, only 8 investigated the confounding role of parental psychopathology (**appendix**). Although it is difficult to reach firm conclusions, we observed that associations between early-life factors and suicide outcomes persisted after adjustment for parental mental disorders, including in sibling designs. This is in line with findings from a recent study that indicates that parental psychopathology is unlikely to fully explain the association between early-life influences and mental disorders.[41] Additionally, although experimental studies are unfeasible or unethical, quasi-experimental approaches, based on instrumental variables or twin/sibling designs, are available.[40,42] Few such studies were identified in this review, and provided evidence suggesting that the association of birth order and maternal age on suicide was causal.[26,27] However, one study reported that the association between low birthweight and suicide attempt was fully attenuated using a sibling design.[43] These quasi-experimental studies account for factors that sibling share within the family, including parental psychopathology. Future studies should use such designs to prompt causal conclusions.

Fourth, suicide rather than being a single condition, is a behaviour resulting from a combination of vulnerability factors and immediate precipitant factors. Therefore, the observed associations are likely to reflect both the influence of early risk factors on mental disorder strongly associated with suicide (eg, schizophrenia, major depression), and the influence of early risk factors on behaviours, such as impulsive-aggression, that are specifically associated with suicide.[44] Therefore, future studies are needed to clarify whether the in-utero and perinatal risk factors for suicide identified in our meta-analysis are also related to adolescence/adult psychiatric disorders comorbid with suicide, or whether they are specific to suicide. The association between family and maternal characteristics at child birth and suicide risk is consistent with studies that found: (i) a negative dose-response association of higher birth order with adult psychiatric admissions[45] and mental illness,[29] (ii) associations of young mother's age and single mother household with behavioural and mental health problems,[46,47] and (iii) the association between socioeconomic adversity in childhood and adverse social, health, and mortality outcomes.[48] However, the absence of association between advanced father's age and suicide risk differs from the documented association between young paternal age

with behaviour syndromes and psychosis and advanced paternal age with pervasive developmental disorders/autism spectrum disorder.[49] On the other hand, one study suggested an increased risk of suicide attempt for individuals born from a father aged >45 years,[30] which calls for further investigations to ascertain whether advanced paternal age is specifically linked with non-fatal suicidal behaviours. Similarly, our meta-analysis also provides evidence for an association between low birthweight and risk for suicide, suicide attempt, and suicidal ideation that is consistent with what has been reported for ADHD, autism,[43] and schizophrenia,[14] but inconsistent with a meta-analysis that failed to report an association with depression.[50]

Finally, the mechanisms underlying associations between in-utero/perinatal factors and suicide should be clarified. Hypothesised mechanisms are conceptually represented in **Figure 6**. First, factors such as young mother's age, teenage mothers, single motherhood, and low socioeconomic position at birth may reflect an adverse psychosocial environment which increased level of stress in pregnant mothers.[9] Maternal stress may affect foetal brain development through epigenetic mechanisms (eg, alterations in the glucocorticoid receptor and the central corticotrophin hormone) or gene-by-environment interactions mechanisms (eg, via Oxytocin pathways)[51] leading to persistent neurobiological alterations of the hypothalamic-pituitary-adrenal axis.[4,52,53] Second, socioeconomic adversity in the prenatal and perinatal period is likely to continue during childhood (limiting children's access to social capital, educational resources, and adequate cognitive stimulation) and adulthood, yielding an increased risk for mental disorder, adverse experiences (including trauma), low social support, and suicide risk.[54] Third, inadequate maternal nutrition in pregnancy due to low family resources, or impoverished foetal nutrition of later-born children due to depletion of maternal nutritional reserves during prior pregnancies (thrifty-phenotype hypothesis),[55] may be associated with future mental disorders increasing the suicide risk. Therefore, knowledge of these mechanisms is of utmost importance as they may inform population-based prevention interventions targeting such mechanisms.

This study is based on a systematic literature search with no date limit, and the good quality of the included studies positively affected the quality of the meta-analytic results. Despite these strengths, this study has limitations. First, the large majority of the included studies came from high-income countries, especially from Northern-Europe, with under-representation of low and middle-income countries. This is a fundamental gap that needs to be addressed, as the investigated associations might be different in other socio-economic contexts. Second, our meta-analysis only reported crude associations, therefore the pooled ORs might have overestimated the association between in-utero and perinatal risk factors and suicide risk because of inadequate adjustment for confounding. Third, although most heterogeneity has been explained by differences in age at follow-up across studies, data were not sufficient to conduct

detailed subgroup analyses. Fourth, it was not possible to investigate sex differences. Finally, unpublished studies were not included in our analyses, which might have generated bias.

In conclusion, the available evidence suggests that prenatal and perinatal characteristics are associated with increased suicide risk during the life course, with some differences between suicide-related outcomes (ie, suicide mortality, suicide attempt, and suicidal ideation) that need to be further investigated. These findings emphasize the role of conception and pregnancy as crucial periods for disease prevention from a public health perspective.

Figures

Figure 1. Flow chart of study selection
Note: The number of studies included in the quantitative analyses varied by early-life factor and outcome considered.

Figure 2. Assessed risk factors across the included studies
Note: The figure reports the number of studies in which each individual risk factor was analysed, and includes multiple studies published using the same data.

Figure 3. Pooled Odds Ratios for the association between in-utero and perinatal risk factors and suicide
Note: The figure shows forest plots reporting the association between in-utero and perinatal risk factors and suicide for each single study entered in the analysis and the pooled random-effect estimate. Study published using the same data are considered only once.

Figure 4. Pooled Odds Ratios for the association between in-utero and perinatal risk factors and suicide attempt and suicidal ideation
Note: The figure shows forest plots reporting the association between in-utero and perinatal risk factors and suicide attempt and suicidal ideation for each single study entered in the analysis and the pooled random-effect estimate. Study published using the same data are considered only once.

Figure 5. Subgroup analysis by age at follow-up
Note: The figure shows the pooled estimates for each comparison, stratified by age at follow-up.

Figure 6. Conceptual model of the potential mechanisms linking in-utero and perinatal risk factors and suicide risk
Note: This conceptual model describes possible pathways explaining associations of early-life factors with suicide, as suggested in the reviewed literature. Biological (eg, epigenetic, genetic), environmental (eg, adverse exposure in childhood, low resources) and gene-x-environment mechanisms are suggested.

Authors' contribution

MO, DG, SRD, GT, MCG designed the study; JB elaborate the search strategy and performed the initial search; MO, DB, and MCG performed study selection and quality assessment; MO performed statistical analyses and wrote the first draft of the manuscript; MCG supervised the study; all authors critical reviewed the manuscript and contribute to data interpretation.

Conflict of interest statement

The authors declare no conflict of interest.

Acknowledgements

DG is supported by the NIHR Biomedical Research Centre at University Hospitals Bristol NHS Foundation Trust and the University of Bristol, England. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health and Social Care. MCG is fellow of the Fonds de Recherche en Santé du Québec (FRSQ) and is supported by the American Foundation for Suicide Prevention (AFSP). Dr Turecki holds a Canada Research Chair (Tier 1) and a NARSAD Distinguished Investigator Award. He is supported by grants from the Canadian Institute of Health Research (CIHR) (FDN148374 and EGM141899). Drs Geoffroy and Turecki are supported by the Fonds de recherche du Québec - Santé (FRQS) through the Quebec Network on Suicide, Mood Disorders and Related Disorders. We thank Christine Neilson, University of Manitoba, for peer review of the MEDLINE search strategy.

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Research in context

Evidence before this study

We systematically searched Medline without data and language limitations up to March 6, 2018, using the following keywords: (suicid* OR "suicide attempt" OR "attempted suicide" OR "suicidal ideation" OR "suicide thoughts" OR "suicidal behavior" OR "suicidal behaviours" OR "completed suicide" OR "suicide risk" OR "suicidality") AND ("birth order" OR "parity" OR "multiparity" OR "family size" OR "sibship size" OR "number of siblings" OR "birth weight" OR "underweight" OR "maternal age" OR "mother age" OR "paternal age" OR "father age" OR "parent* age" OR "foetal fetal growth" OR "fetal growth" OR "early life" OR "early-life" OR perinatal OR prenatal) AND (longitudinal OR "population-based" OR cohort OR observational OR prospective OR "registry" OR "register-based"). Most of the retrieved studies investigated risk factors measured during childhood, and a few investigated risk factors during the in-utero and perinatal periods, resulting in 20 relevant studies. No systematic review or meta-analysis was identified. Most studies came from high-quality cohorts and population-based registers. Some studies suggested increased suicide risk for some risk factors (such as increased birth order, low socioeconomic position at birth). However, while similar in quality and design: (i) some studies reported different estimates for the same risk factor; (ii) some studies reported similar estimates (eg, similar Hazard/Odds Ratios) but different confidence intervals, so that only some of the studies could conclude for a statistically significant difference between individuals exposed and non-exposed to the same risk factor; (iii) some studies had different follow-up periods, ie, some extending until adolescence/young adulthood, others extending until adulthood; (iv) almost all studies presented both crude and adjusted estimates, but the choice of the adjustment variables was highly variable across studies; in particular, some studies adjusted for factors occurring between the exposure (eg, low birthweight) and the outcome (eg, suicide), which can bias the estimate of the contribution of the exposure. These differences preclude firm conclusions about the role of these factors on suicide risk.

Added value of this study

To our knowledge, this is the first systematic review and meta-analysis summarizing the available evidence about the in-utero and perinatal influences on suicide. We found that, across the high-quality included studies, family/parental characteristics at child birth (eg, higher birth order, low mother's age, single motherhood), low socioeconomic position (eg, low parental education and socioeconomic status), and restricted foetal growth (eg, low birthweight, small for gestational age) were associated with increased suicide risk. No evidence for an association was found for risk factors such as advanced father's age, low gestational age, obstetric characteristics, and mother's smoking in pregnancy. Moreover, accounting for the participant's age at follow-up explained the heterogeneity across studies for most comparisons, without changing the study conclusions.

Implications of all the available evidence

Evidence suggests that prenatal and perinatal characteristics are associated with increased suicide risk during the life course, with main influences represented by unfavourable family/parental characteristics and restricted foetal growth. However, more studies are necessary to establish the role of those risk factors on suicide attempt and ideation, extend the evidence to understudied influences, and probe their causal role.

Table 1. Characteristics of the included studies

Sample	Study	Study design	Level of analysis	Participants (n)	Year range at birth	Year range at outcome assessment	Follow-up range	Investigated outcomes	Investigated in-utero and perinatal factors
1958 British Birth Cohort									
1958 British Birth Cohort	Geoffroy 2014[18]	Cohort	Whole population	16 470	1958	1965-2009	7-51	Suicide	Birth order, maternal age, SES, gestational age, birth weight, smoking in pregnancy
1958 British Birth Cohort	Geoffroy 2018[29]	Cohort	Whole population	8 905	1958	2003	45-45	Ideation	Birth order, maternal age, SES, birth weight
ALSPAC									
	Easey 2019[56]	Cohort	Whole population	2571	1991-1992	up to 2008	up to 16	Attempt	Birth order
	Page 2014[32]	Cohort	Whole population	1 806	1991-1992	2007-2009	16-18	Attempt	SES, maternal education
Born in Washington State, US, in 1968–96	Li 2003[57]	Register	Whole population	23 882	1968-1996	NA	1-19	Suicide	Birthweight
CHDS									
CDHS	Fergusson 1999[58]	Cohort	Whole population	1 025	1977-1998	1992-1996	up to 18	Attempt	Maternal age
CDHS	Fergusson 2000[31]	Cohort	Whole population	1 265	1977-1998	1992-1998	up to 21	Attempt, ideation	Maternal age, single mother, SES, maternal education
Copenhagen Perinatal Cohort 1959-1961	Sorensen 2009[59]	Register	Whole population	7 177	1959-1961	1969-2005	10-46	Suicide	SES
Danish born in 1966–1996									
Danish born in 1966	Christofferssen 2003[60]	Register	Whole population	84 765	1966	1981-1993	14-27	Attempt	Maternal age
Danish born in 1966–1996	Mok 2017[61]	Register	Whole population	1 793 681	1966-1996	1981-2006	15-40	Suicide	Maternal age, paternal age
Danish Metropolit Cohort	Osler 2008[19]	Cohort	Whole population	9 359	1953	1972-2002	19-49	Suicide, attempt	Single mother, SES, birthweight
E3N Cohort 1990	Verdoux 2007[36]	Cohort	Sibling design	3 127	NA	up to 2004	NA	Suicide	Exposure to diethylstilboestrol
Finnish born in 1922-1989									
Finnish born in 1922-1987	Saarela 2016[62]	Register	Sibling design	254 059	1922-1987	1987-2011	0-89	Suicide	Birth order
Finnish born in 1987-1989	Ekblad 2010[34]	Register	Whole population	179 869	1987-1989	1987-2007	0-20	Suicide	Smoking in pregnancy
Helsinki Birth Cohort Study 1934–1944									
Helsinki Birth Cohort Study 1934–1944	Lahti 2014[63]	Register	Whole population	13 242	1934-1944	1969-2010	24-76	Suicide, attempt	Birth order
Helsinki Birth Cohort Study 1934–1944	Lahti 2015[64]	Register	Whole population	12 597	1934-1944	1969-2010	25-76	Suicide, attempt	Gestational age, SGA
Johns Hopkins Collaborative Perinatal Study	Nomura 2007[33]	Cohort	Whole population	1 525	1960-1964	1992-1994	27-33	Ideation	Gestational age, birthweight, head circumference, APGAR
National Longitudinal Survey of Children and Youth	Dykxhoorn 2017[65]	Cohort	Whole population	6 388	1994-2009	NA	12-25	Ideation	Maternal age, prenatal care after 20 weeks of gestation
Northern Finland Birth Cohort 1966									
Northern Finland Birth Cohort 1966	Alaräisänen 2012[38]	Cohort	Whole population	10 742	1966	1967-2005	up to 39	Suicide, attempt	Birth order, maternal age, single mother, SES, antenatal depression, unwanted pregnancy

Northern Finland Birth Cohort 1966	Miller 2010[66]	Cohort	Whole population	10 965	1966	1967-2005	up to 39	Suicide	Maternal age, SES, paternal age
Northern Finland Birth Cohort 1966	Sauvola 2001[67]	Cohort	Whole population	11 017	1966	1982-1994	16-28	Suicide	Single mother
Norwegians born in 1967–1997									
Norwegians born in 1967–1996	Bjørngaard 2013[26]	Register	Whole population and sibling design	1 690 306	1967-1996	1979-2008	12-41	Suicide	Birth order, maternal age, single mother, maternal education, paternal education, interbirth spacing
Norwegians born in 1967–1976	Gravseth 2010[68]	Register	Whole population	610 359	1967-1976	1986-2004	10-37	Suicide	Birth order, single mother
Norwegians born in 1967–1997	Risnes 2016[69]	Register	Whole population and sibling design	1 562 647	1967-1997	1981-2011	15-45	Suicide	Gestational age
Pelotas Birth Cohort	Barros 2018[70]	Cohort	Whole population	3 528	1982	2012	30	Attempt	SES
Scottish born in 1969-1988									
Scottish born in 1969-1986	Riordan 2006[71]	Register	Whole population	1 061 830	1969-1986	1981-2003	12-34	Suicide	Birth order, maternal age, SES, gestational age, birthweight
Scottish born in 1969-1986	Riordan 2012[45]	Register	Whole population	897 685	1975-1988	1987-2007	12-32	Suicide	Birth order, maternal age, SES, gestational age, birthweight, family size
Scottish longitudinal survey of young people	Young 2011[72]	Cohort	Whole population	2 157	1984	1999	up to 15	Attempt	Birth order, maternal age, birthweight, number of birth complications,
Swedish born in 1932-1997									
Swedish born in 1973-1997	Class 2014 (a)[43]	Register	Whole population and sibling design	2 308 032	1973-1997	2009	12-36	Attempt	Birthweight
Swedish born in 1973-1997	Class 2014 (b)[37]	Register	Whole population	2 197 707	1973-1997	1985-2009	12-36	Suicide, attempt	Prenatal stress
Swedish born in 1983-1996	Cnattingius 2011[17]	Register	Whole population and sibling design	1 449 333	1983-1996	1993-2007	10-24	Suicide	Birth order, maternal age, single mother, gestational age, birth length, birthweight, paternal age, smoking in pregnancy, maternal education, SGA, number of birth complications, head circumference, hypertensive disease, placenta abruption, mode of delivery
Swedish born in 1973-1997	D'Onofrio 2013[73]	Register	Whole population and sibling design	3 300 708	1973-1997	1985- 2009	12-37	Attempt	Gestational age
Swedish born in 1973-1997	D'Onofrio 2014[30]	Register	Whole population and sibling design	2 293 032	1973-1997	1985- 2009	12-37	Attempt	Paternal age
Swedish born in 1973-1979	Ekéus 2006[74]	Register	Whole population	292 129	1973-1979	1990-2002	17-29	Suicide, attempt	Maternal age
Swedish born in 1973-1980	Mittendorfen-Rutz 2004[16]	Register	Whole population	713 370	1973-1980	1983-1999	10-26	Suicide, attempt	Birth order, maternal age, birthweight, birth length, hypertensive disease, mode of delivery

Swedish born in 1973-1980	Mittendorfen-Rutz 2008[75]	Register	Whole population	318 953	1973-1980	1991-1999	18/19-26	Attempt	Gestational age, birthweight, birth length
Swedish born in 1973-1983	Niederkrotenthaler 2012[76]	Register	Case-control	14 976	1973-1983	1983-2004	10-31	Suicide, attempt	Birth order, maternal age, gestational age, birthweight, paternal age, SGA, birth length
Swedish born in 1932-1980	Rostila 2014[27]	Register	Sibling design	102 824	1932-1980	1981-2002	up to 70	Suicide	Birth order, maternal age
Swedish born in 1946-1968	Von Borczyskowski 2010[77]	Register	Whole population	2 936 224	1946-1968	1987-2001	19-55	Suicide	Maternal age, SES, paternal age
Swiss National Cohort	Steck 2018[78]	Register	Whole population	2 395 677	1990-2000	2000-2008	10-18	Suicide	Birth order, maternal age single mother, SES, paternal age, parental education
Taiwaneses born in 1978-1993	Chen 2013[28]	Register	Case-control	123 504	1978-1993	1993-2008	15-30	Suicide	Birth order, maternal age, single mother, maternal education, paternal education
Uppsala University Hospital in 1915-1929	Danziger 2011[79]	Register	Whole population	11 650	1915-1929	1960-2002	31-87	Suicide	Birth order, maternal education, single mother, SES, gestational age, birth weight, SGA

ALSPAC, Avon Longitudinal Study of Parents and Children; CHDS, Christchurch Health and Development Study; NA, not available; SGA, Small for gestational age; SES, Socioeconomic status

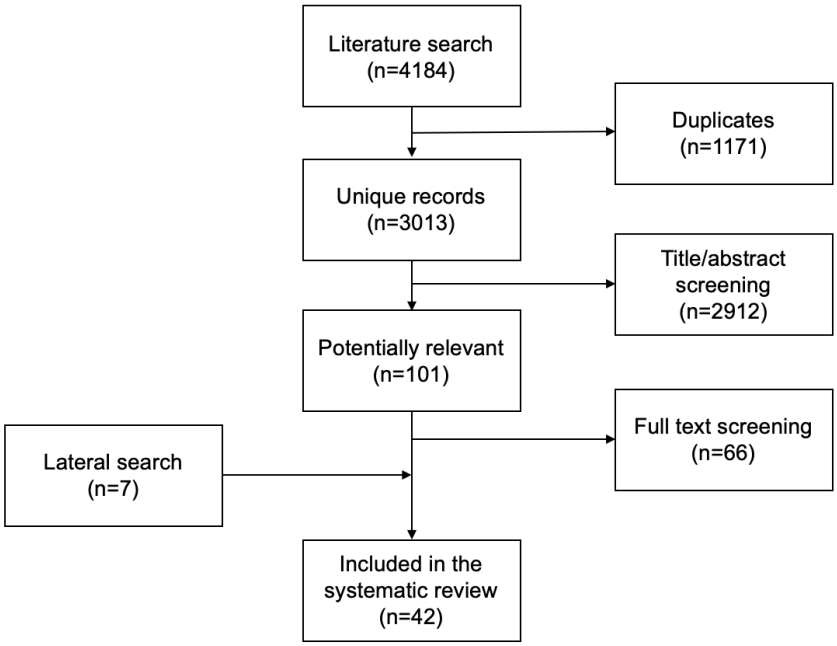
Table 2. Quality assessment according to the Newcastle-Ottawa Scale criteria

Sample	Study and year	Selection				Comparability	Outcome			Quality score (0-9)
		Representativeness (0-1)	Selection non exposed (0-1)	Ascertainment exposure (0-1)	Outcome not present at study start (0-1)	Case/control comparability (0-2)	Assessement of outcome (0-1)	Length of follow-up (0-1)	Adequacy of follow-up (0-1)	
1958 British Birth Cohort										
1958 British Birth Cohort	Geoffroy 2014[18]	1	1	0	1	2	1	1	1	8
1958 British Birth Cohort	Geoffroy 2018[29]	1	1	0	1	2	1	0	0	5
ALSPAC		1	1	0	1	2	0	1	0	6
ALSPAC	Easey 2019	1	1	1	1	2	0	1	1	8
ALSPAC	Page 2014[32]	1	1	1	1	2	0	1	1	8
Born in Washington State, US, in 1968–96	Li 2003[57]	1	1	1	1	1	1	1	1	8
CHDC										
CHDC	Fergusson 1999[58]	1	1	0	1	1	0	1	1	6
CHDC	Fergusson 2000[31]	1	1	0	1	2	0	1	1	7
Copenhagen Perinatal Cohort 1959-1961	Sorensen 2009[59]	1	1	1	1	1	1	1	1	8
Danish born in 1966–1996										
Danish born in 1966	Christofferssen 2003[60]	1	1	1	1	2	1	1	1	9
Danish born in 1966–1996	Mok 2017[61]	1	1	1	1	2	1	1	1	9
Danish Metropolit Cohort	Osler 2008[19]	1	1	1	1	0	1	1	0	6
E3N Cohort 1990	Verdoux 2007[36]	1	1	0	1	1	0	1	1	6
Finnish born in 1922-1989										
Finnish born in 1922-1987	Saarela 2016[62]	1	1	1	1	2	1	1	1	9
Finnish born in 1987-1989	Ekblad 2010[34]	1	1	1	1	2	1	1	1	9
Helsinki Birth Cohort Study 1934–1944										
Helsinki Birth Cohort Study 1934–1944	Lahti 2014[63]	1	1	1	1	2	1	1	1	9
Helsinki Birth Cohort Study 1934–1944	Lahti 2015[64]	1	1	1	1	2	1	1	1	9
Johns Hopkins Collaborative Perinatal Study	Nomura 2007[33]	1	1	1	1	2	0	1	1	8
NLSCY	Dykxhoorn 2017[65]	1	1	0	1	NA	0	1	0	4
Northern Finland Birth Cohort 1966										
Northern Finland Birth Cohort 1966	Alaräisänen 2012[38]	1	1	1	1	2	1	1	1	9
Northern Finland Birth Cohort 1966	Miller 2010[66]	1	1	0	1	2	1	1	1	8
Northern Finland Birth Cohort 1966	Sauvola 2001[67]	1	1	0	1	1	1	1	1	7
Norwegians born in 1967–1997										
Norwegians born in 1967–1996	Bjørngaard 2013[26]	1	1	1	1	2	1	1	1	9
Norwegians born in 1967–1976	Gravseth 2010[68]	1	1	1	1	1	1	1	1	8
Norwegians born in 1967–1997	Risnes 2016[69]	1	1	1	1	2	1	1	1	9
Pelotas Birth Cohort	Barros 2018	1	1	0	1	0	0	1	1	5
Scottish born in 1969-1988										

Scottish born in 1969-1986	Riordan 2006[71]	1	1	1	1	2	1	1	1	9
Scottish born in 1969-1986	Riordan 2012[45]	1	1	1	1	2	1	1	1	9
Scottish longitudinal survey of young people	Young 2011[72]	1	1	0	1	2	0	1	1	7
Swedish born in 1932-1997										
Swedish born in 1973-1997	Class 2014 (a)[43]	1	1	1	1	2	1	1	1	9
Swedish born in 1973-1997	Class 2014 (b)[37]	1	1	1	1	2	1	1	1	9
Swedish born in 1983-1996	Cnattingius 2011[17]	1	1	1	1	2	1	1	1	9
Swedish born in 1973-1997	D'Onofrio 2013[73]	1	1	1	1	2	1	1	1	9
Swedish born in 1973-1997	D'Onofrio 2014[30]	1	1	1	1	2	1	1	1	9
Swedish born in 1973-1979	Ekéus 2006[74]	1	1	1	1	2	1	1	1	9
Swedish born in 1973-1980	Mittendorfen-Rutz 2004[16]	1	1	1	1	2	1	1	1	9
Swedish born in 1973-1980	Mittendorfen-Rutz 2008[75]	1	1	1	1	2	1	1	1	9
Swedish born in 1973-1983	Niederkrotenthaler 2012[76]	1	1	1	1	2	1	1	1	9
Swedish born in 1932-1980	Rostila 2014[27]	1	1	1	1	2	1	1	1	9
Swedish born in 1946-1968	Von Borczyskowski 2010[77]	1	1	1	1	2	1	1	1	9
Swiss National Cohort	Steck 2018[78]	1	1	1	1	2	1	1	1	9
Taiwaneses born in 1978-1993	Chen 2013[28]	1	1	1	1	2	1	1	1	9
Uppsala University Hospital in 1915-1929	Danziger 2011[79]	1	1	1	1	2	1	1	1	9

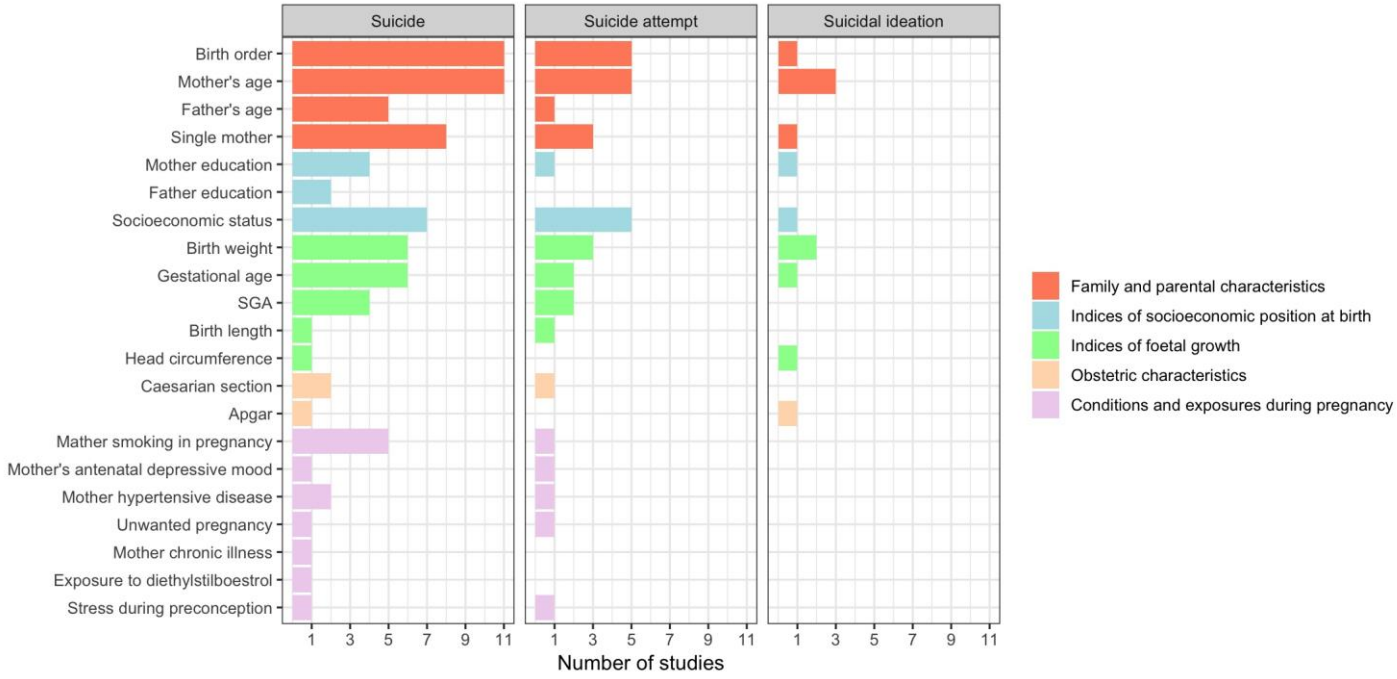
ALSPAC, Avon Longitudinal Study of Parents and Children; CHDS, Christchurch Health and Development Study; NA, not applicable

Figure 1. Flow chart of study selection



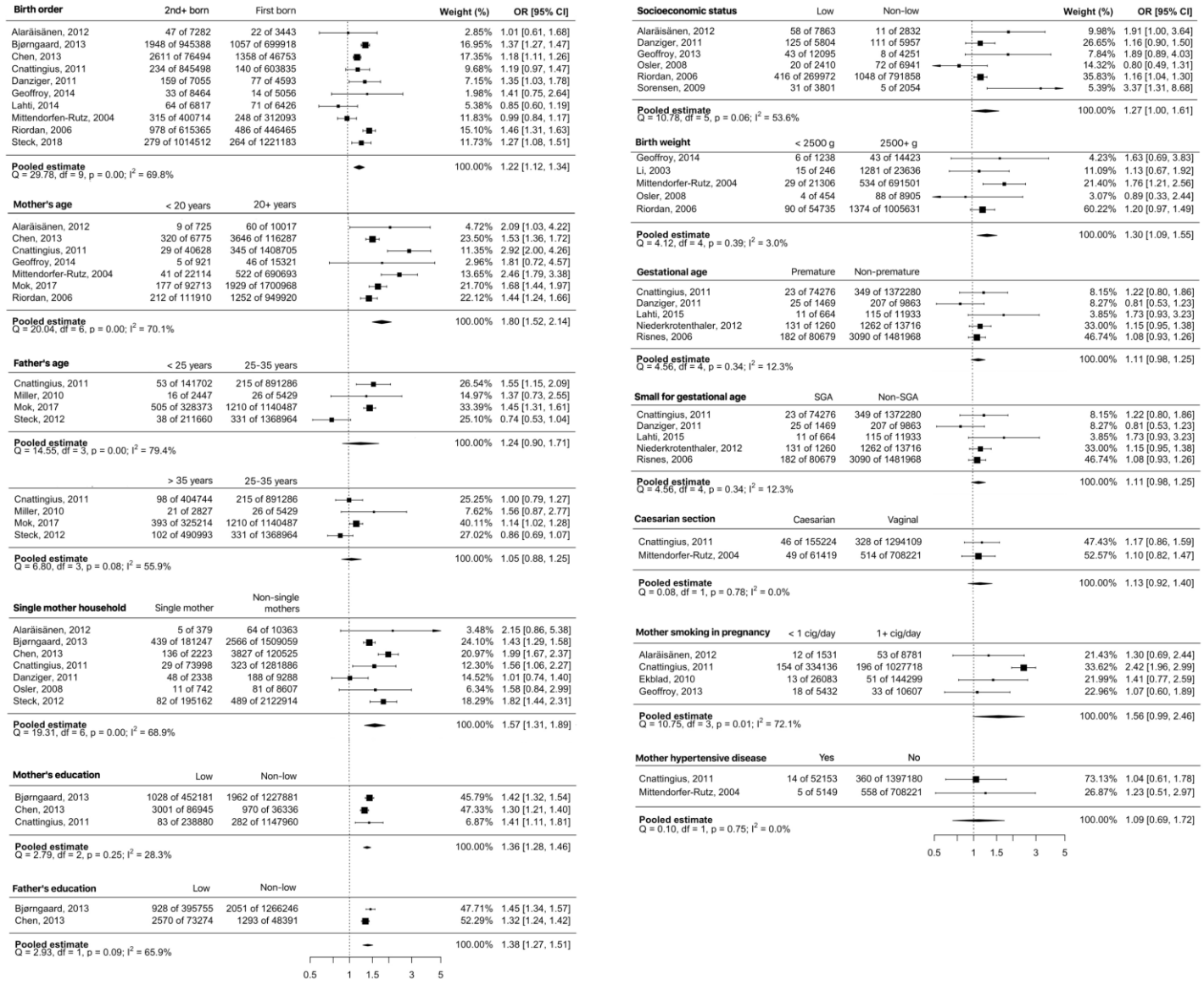
The number of studies included in the quantitative analyses varied by early-life factor and outcome considered.

Figure 2. Assessed risk factors across the included studies



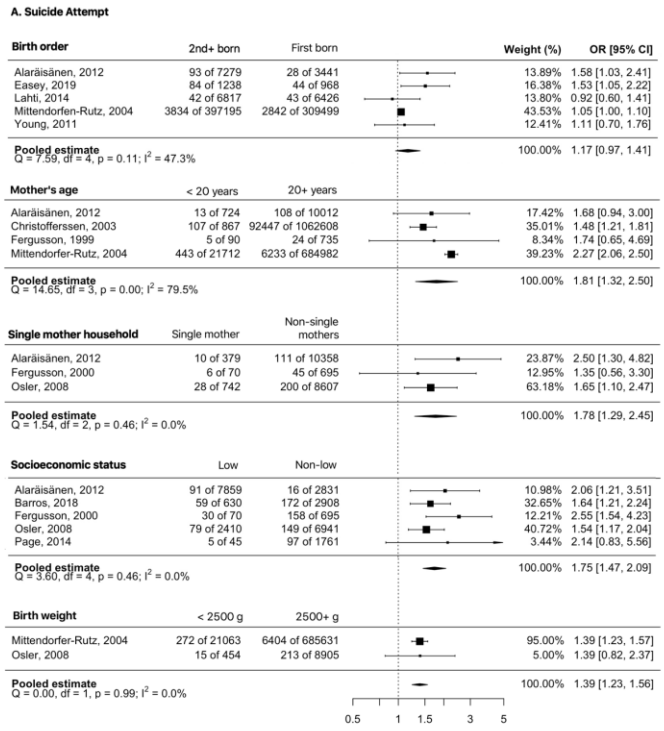
The figure reports the number of studies in which each individual risk factor was analysed, and includes multiple studies published using the same data.

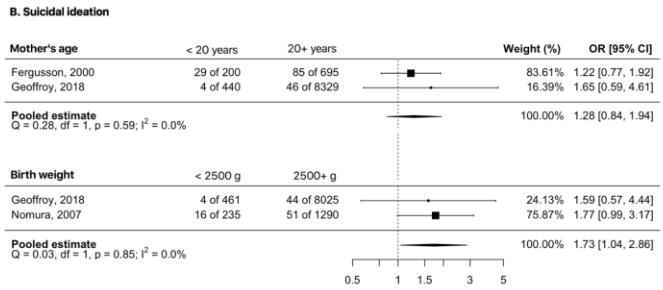
Figure 3. Pooled Odds Ratios for the association between in-utero and perinatal risk factors and suicide



The figure shows the forest plot reporting the association between in-utero and perinatal risk factors and suicide for each single study entered in the analysis and the pooled random-effect estimate. Study published using the same data are considered only once.

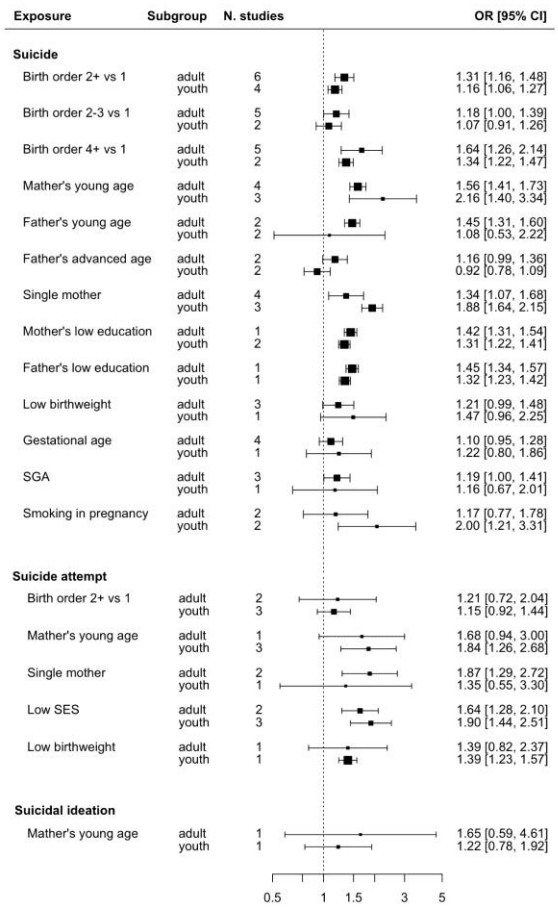
Figure 4. Pooled Odds Ratios for the association between in-utero and perinatal risk factors and suicide attempt and suicidal ideation





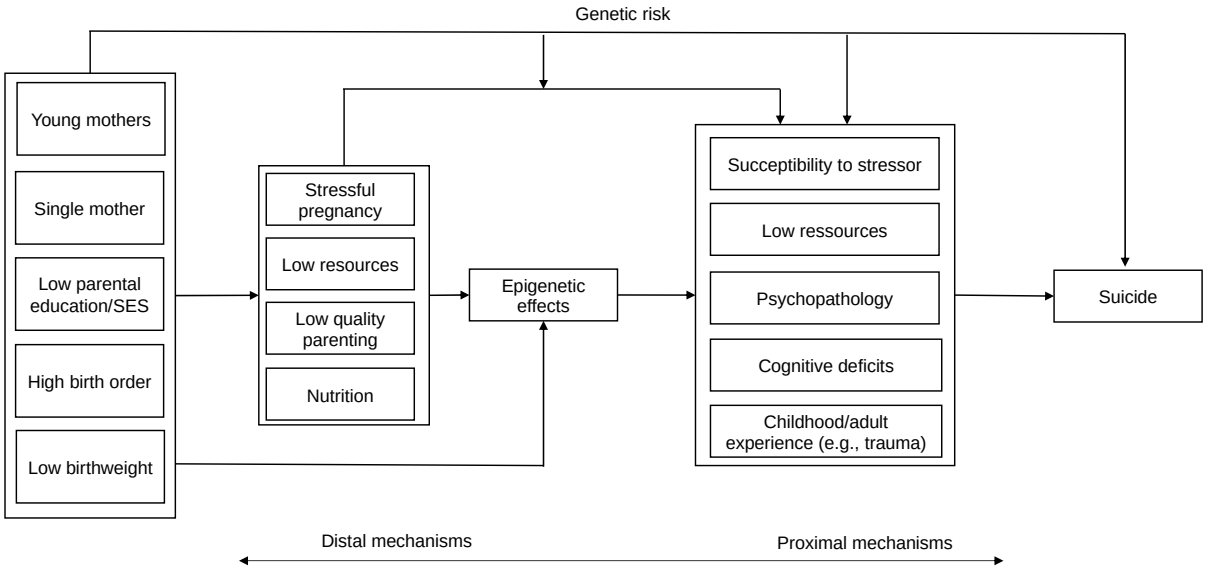
The figure shows the forest plot reporting the association between in-utero and perinatal risk factors and suicide attempt and suicidal ideation for each single study entered in the analysis and the pooled random-effect estimate. Study published using the same data are considered only once.

Figure 5. Subgroup analysis by age at follow-up



The figure shows the pooled estimates for each comparison, stratified by age at follow-up.

Figure 6. Conceptual model of the potential mechanisms linking in-utero and perinatal risk factors and suicide risk



This conceptual model describes possible pathways explaining associations of early-life factors with suicide, as suggested in the reviewed literature. Biological (eg, epigenetic, genetic), environmental (eg, adverse exposure in childhood, low resources) and gene-x-environment mechanisms are suggested.

Supplementary appendix

In-utero and perinatal influences on suicide risk: a systematic review and meta-analysis

Massimiliano Orri, David Gunnell, Stephane Richard-Devantoy, Despina Bolanis, Jill Boruff, Gustavo Turecki & Marie-Claude Geoffroy

Methods

Literature search

A health sciences librarian (JB) conducted searches in MEDLINE, EMBASE and PsycInfo, from database inception to May 3, 2018 using the combination of keywords and subject headings presented in **supplementary table 1**. The search strategy was developed for MEDLINE and modified for the other databases using the observational studies methodological filter from the Scottish Intercollegiate Guideline Network.[1] The search strategy was peer reviewed by another health sciences librarian (CN) using the Peer Review of Electronic Search Strategies checklist.[2] Additionally, we searched the reference lists of all identified studies and hand searched key journals (ie, JAMA, JAMA Psychiatry, The Lancet, The Lancet Psychiatry, BMJ, International Journal of Epidemiology, The American Journal of Psychiatry, British Journal of Psychiatry, Psychological Medicine, Acta Psychiatrica Scandinavica, American Journal of Public Health, Social Psychiatry and Psychiatric Epidemiology). Search results were exported into EndNote and all duplicates were removed. A PRISMA flow chart was used to track the number of studies in each stage of the review (see figure 1 in manuscript). Citations were imported into the web software Rayyan,[3] which facilitated independent and blind screening of the studies by two researchers (MO and DB), and subsequent comparisons.

Harmonisation of in-utero and perinatal factors

Supplementary tables 2 to 13 show categorisation of in-utero and perinatal exposure factors assessed in the studies included in the meta-analysis and how they were harmonised across studies. Data were harmonised in order to maximize the number of studies included in the meta-analysis with homogeneous assessment of the exposure.

Birth order was categorized as 1st versus 2nd or later born (**supplementary table 2**) and dose-response association was examined using birth order categorised as 1st versus 2nd and 3rd born versus 4th or later born for a subgroup of studies (n=6) (**supplementary table 3**).

Mother's age at child birth was categorised as younger age, ie, <20 years, versus older age, ie, ≥20 years (n=8), except for 1 study in which maternal age was categorised as <18 years versus ≥18 years (**supplementary table 4**). Father's age at child birth was categorised as follows: younger age, ie, <25 years, versus average age, ie, 25-35 years, versus older age, ie, ≥35 years (**supplementary table 3**).

Household composition was categorised as single-parent family versus non-single-parent family (**supplementary table 4).** Single-parent family mainly included single mothers (ie, not living with the biological father of the child at child birth), separated or divorced at child birth, and widowed at child birth. While most studies assessed mother's status, 2 studies did not specify whether the single parent was the mother or the father.

Mother's and father's levels of education at child birth were categorised into lower (ie, primary/lower education or lack of formal education, or <10 years of education) versus higher (**supplementary tables 7 and 8**).

Socioeconomic status was categorised as lower versus higher (**supplementary table 9**). However, as detailed in supplementary table 9 included studies relied on heterogeneous indicators of low socioeconomic status, eg, father's unskilled or manual work, low level of socioeconomic status according to Elley & Irving (1976) scale of socioeconomic status, professional occupation according to UK classification (Class I to VI).

Birthweight was categorised as low, ie, <2500 grams, versus normal, ie, 2500 grams (**supplemental table 10**).

Gestational age at birth was categorised as low, ie, <37 or 38 weeks, versus normal, ie, ≥37 or 38 weeks (**supplemental table 11**). Small for gestational age (ie, gestational age adjusted for birthweight) was categorised as small, ie, lower tertiles of the distribution or -2 SD from the distribution mean, versus normal (**supplementary table 12**).

Mother smoking during pregnancy was categorised as smoker, defined as mother smoking > 1 cigarette per day during pregnancy versus no smoker (**supplementary table 13**).

Analysis of the between-study heterogeneity

Meta-analysis was performed using the DerSimonian and Laird inverse-variance-weighted random-effect models.[4] The heterogeneity across studies was investigated using the (1) Cochrane Q statistic and (2) I^2 statistic (**supplementary table 14**). (1) Cochran's Q statistic tests whether variability in observed effect sizes is larger than expected based on sampling variability alone (significant test suggesting heterogeneity). (2) I^2 statistic represents the percentage of variation across studies that is due to heterogeneity rather than chance and was computed as follows: $I^2 = 100\% \times (Q-df)/Q$. Supplementary table 14 also reports results of the meta-regression analyses investigating the influence of age at follow-up (≤30 years versus >30 years) as moderator, tested using the Q statistics, the proportion of heterogeneity explained by the moderator in the meta-regression model (R^2), and the proportion of residual heterogeneity (I^2) after considering the effect of the moderator.

Risk of publication bias analysis

Supplemental table 15 and the funnel plots in **supplementary figures 1 and 2 show** report risk of publication bias results. The asymmetry of the funnel plots was tested using the Egger's regression test for random-effect models. When publication bias was suggested by a significant Egger's test, we used the Trim and Fill method to further explore the extent of the possible bias. The Trim and Fill is a nonparametric (rank-based) data augmentation technique method; it first estimates the number of studies missing from a meta-analysis due to suppression of the most extreme results on one side of the funnel plot, then augments the observed data so that the funnel plot is more symmetric, and finally recalculates the summary estimate based on the complete data. This analysis indicated possible publication bias for mother smoking during pregnancy ($p = 0.002$ for the Egger test) and maternal age at child birth ($p = 0.034$ for the Egger test). For mother smoking during pregnancy, explorations using the Trim and Fill method suggested that two studies were potentially missing due to publication bias. Including those studies would make the

comparison between mother smoking during pregnancy versus non-smoking statistically significant - whereas mother smoking during pregnancy was not associated with suicide mortality in main analysis (figure 3 in the manuscript). The funnel plot for mother smoking during pregnancy in figure 1 represents the estimated effect size (log OR, x-axis) and corresponding standard error (y-axis) of the analysed studies (indicated by black dots) and of the potentially missing studies according to the Trim and Fill analysis (indicated by white dots). It is important to note that (1) our review suggested that this association is likely to be confounded by other concurrent factors, and (2) the comparison is strongly influenced by one study (Cnattingius *et al.* 2011) that, if removed, would render the pooled OR for the three remaining studies non-significant (see sensitivity analyses). For maternal age at child birth, explorations using the Trim and Fill method suggested that three studies were potentially missing due to publication bias. However, differently from maternal smoking, including those study would not change the result of the meta-analysis.

Sensitivity analyses

We conducted a first sensitivity analyses (**supplemental table 16**) to establish how strong a confounding factor should be in order to explain away (ie, render not statistically significant) the association of each significant in-utero and perinatal factor on outcome. Our analyses were based on E-value, defined as the minimum strength of association, on the risk ratio (RR) scale, that an unmeasured confounder would need to have with both the treatment and the outcome to fully explain away a specific treatment–outcome association.[5] To illustrate, mother's younger age and suicide association (pooled OR 1.80, CI 1.52-2.14) would be explained away by adjusting for a confounding factor associated with both mother's age and suicide with a RR of 3.00. Potential confounding factors for mother's age are those listed in supplementary table 16 and individually analysed in our study. Of those risk factors, none were associated with suicide with an OR of 3.00 (OR can be considered a good approximation of RR due to the low frequency of outcome). This suggests that association between mother's young age and suicide is robust to adjustment for all other in-utero and perinatal factors considered in this meta-analysis. By definition, confounding factors are measured before or at the same time of an exposure (ie, not between the exposure and the outcome, see collider bias).[6] Therefore, factors such as depression in adolescence, stressor(s) in adulthood, adverse childhood experiences (potentially associated with suicide with large ORs) cannot be considered as potential confounding factors here. Similar observations apply to other exposures investigated in our meta-analysis, suggesting the robustness of our results to adjustment of in-utero and perinatal factors included in this meta-analysis.

We conduct a second sensitivity analysis (**supplemental figures 3 and 4**) to establish the contribution of each single study to the pooled estimate and the between-study heterogeneity. In this analysis, we re-estimated the pooled OR removing one study at the time. The supplemental figures 3 and 4 show ORs and CI for each comparison by in-utero and perinatal factor. The removed study is indicated in the x-axis. Heterogeneity (I^2) is indicated by the colour's gradient. The result of this sensitivity analysis shows that the pooled estimates are overall robust to the influence of each single study. In particular, for the studies having high residual heterogeneity ($I^2 > 50\%$) after the meta-regression analysis (ie, birth order 2^{nd}-3^{rd} vs 1^{st} born for suicide and mother's age for suicide and suicide attempt), the following was found:

For birth order 2^{nd}-3^{rd} vs 1^{st}, the study explaining the most heterogeneity was Mittenforfer-Rutz, 2004. The residual heterogeneity after removing this study was 54.7%, with no modification of the pooled OR (1.22,1.12-1.34).

For mother's age, the studies explaining the most heterogeneity was Cnattingus, 2011. The residual heterogeneity after removing this study was 52.7%, with no modification of the pooled OR (1.66, 1.47-1.89).

For mother's age in the association with suicide attempt, the studies explaining the most heterogeneity were Mittenforfer-Rutz, 2004, and Christofferssen, 2003. The residual heterogeneity after removing either studies was 0%, with no modification of the pooled OR (e.g., 1.51, 1.25-1.82 after removing Mittenforfer-Rutz 2004).

Results

Associations between in-utero and perinatal influences and suicide among studies controlling for parental psychopathology

Supplementary tables 17 and 18 summarise findings from studies that adjusted for parental psychopathology, including mental disorders, suicidal behaviours, substance and alcohol abuse. For each risk factor we reported the crude association (or minimally adjusted association) and the fully adjusted association including parental psychopathology in bold (the full list of adjustment variable is provided). Two methods of adjustment were used across identified studies: multiple regression and/or sibling design (ie, calculating association within families, or using fixed-effect models). Overall, adjusting for parental psychopathology did not substantially reduce the estimates, with only one exception (see Class, 2014).[7]

Supplementary Table 1. Literature search strategy

Ovid Medline search

1. Suicidal Ideation/ or Suicide/ or Suicide, Attempted/ or self-injurious behavior/ or self mutilation/
2. (suicide* or suicidal* or self harm* or self mutilation).ti,ab,kf.
3. 1 or 2
4. Birth Order/
5. PARITY/
6. Family Characteristics/
7. SIBLINGS/
8. Birth Weight/
9. exp Infant, Low Birth Weight/
10. maternal age/
11. Paternal Age/
12. exp Fetal Development/ or ASPHYXIA NEONATORUM/
13. exp Perinatal Care/
14. Prenatal Care/
15. Life Change Events/
16. Single Parent/ or Single Parent Family/
17. Smoking/
18. poverty/
19. exp Family Relations/
20. (((neonat* or perinatal or newborn) adj2 asphyxia) or in utero or developmental origin* or (early adj3 (life event? or life experienc*)) or adverse childhood experience* or childhood adversit* or (birth adj2 order) or parity or multiparity or (family adj2 size) or (sibship adj2 size) or (number adj2 siblings) or ((birth adj (weight or length)) or under weight or underweight or maternal age or (mother* adj2 age) or paternal age or (father* adj2 age) or (parent* adj2 age) or foetal growth or fetal growth or early life or perinatal or prenatal or maternal smoking or single parent*)).ti,ab,kf.
21. ((Socioeconomic or income or poverty) and (birth or maternal or paternal or family)).ti,ab,kf.
22. ((family or familial) adj2 (factor? or characteristics or environment* or advers* or relationship*)).ti,ab,kf.
23. or/4-22
24. 3 and 23
25. Epidemiologic studies/
26. exp case control studies/
27. exp cohort studies/
28. Case control.ti,ab,kf.
29. (cohort adj (study or studies)).ti,ab,kf.
30. Cohort analy*.ti,ab,kf.
31. (Follow up adj (study or studies)).ti,ab,kf.
32. (observational adj (study or studies)).ti,ab,kf.
33. Longitudinal.ti,ab,kf.
34. Retrospective.ti,ab,kf.
35. Cross sectional.ti,ab,kf.
36. Cross-sectional studies/
37. "Incidence"/
38. Registries/
39. (registry or register).ti,ab,kf.
40. 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
41. 24 and 40

Supplementary Table 2. Original assessment of birth order in included studies and how birth order was harmonised for the meta-analysis

Study	Original categorisation	Harmonised categorisation
Suicide mortality and/or attempt		
Alaräisänen 2012	1, 2-5, 6+	1, 2+
Bjørngaard 2013	1, 2, 3, 4+	1, 2+
Cnattingius 2011	1, 2+	1, 2+
Mittendorfer-Rutz 2004	1, 2-3, 4+	1, 2+
Geoffroy 2014	1, 2, 3, 4+	1, 2+
Lahti 2014	1, 2, 3, 4+	1, 2+
Riordan 2006	1, 2, 3, 4+	1, 2+
Chen 2013	1, 2, 3, 4+	1, 2+
Danziger 2011	1, 2-3, 4+	1, 2+
Steck 2018	Only child, First, Middle, Last	1, 2+ (1 = only child or first born)
Suicide attempt		
Young 2011	1, 2+	1, 2+
Easey 2019	1, 2, 3+	1, 2+

Supplementary Table 3. Original assessment of birth order in included studies and how birth order was harmonised for the meta-analysis testing dose-response association

Study	Original categorisation	Harmonised categorisation
Suicide mortality and/or attempt		
Bjørngaard 2013	1, 2, 3, 4+	1, 2-3, 4+
Mittendorfer-Rutz 2004	1, 2-3, 4+	1, 2-3, 4+
Geoffroy 2014	1, 2, 3, 4+	1, 2-3, 4+
Lahti 2014	1, 2, 3, 4+	1, 2-3, 4+
Riordan 2006	1, 2, 3, 4+	1, 2-3, 4+
Chen 2013	1, 2, 3, 4+	1, 2-3, 4+
Danziger 2011	1, 2-3, 4+	1, 2-3, 4+

Supplementary Table 4. Original assessment of mother's age in included studies and how mother's age was harmonised for the meta-analysis

Study	Original categorisation	Harmonised categorisation
Suicide mortality and/or attempt		
Alaräisänen 2012	<20, 20-34, 35+	<20, ≥20
Bjørngaard 2013	<20, 20-24, 25-29, 30-34, 35+	<20, ≥20
Cnattingius 2011	<20, 20-24, 25-29, 30-34, 35+	<20, ≥20
Mittendorfer-Rutz 2004	<20, 20-29, 30+	<20, ≥20
Geoffroy 2014	<20, 20-29, 30+	<20, ≥20
Riordan 2006	<20, 20-24, 25-29, 30-34, 35+	<20, ≥20
Chen 2013	<20, 20-24, 25-29, 30-34, 35+	<20, ≥20
Mok 2017	<20, 20-24, 25-29, 30-34, 35-39, 40-45, 45+	<20, ≥20
Suicide attempt		
Young 2011	<20, 20-24, 25-29, 30-34, 35+	<20, ≥20
Fergusson 1999	<20, 20-24, 25-29, 30+	<20, ≥20
Christofferssen 2003	<20, ≥20	<20, ≥20
Suicidal ideation		
Geoffroy 2018	<20, 20-29, 30+	<20, ≥20

Supplementary Table 5. Original assessment of father's age in included studies and how father's age was harmonised for the meta-analysis

Study	Original categorisation	Harmonised categorisation
Suicide mortality and/or attempt		
Miller 2010	<25, 25-29, 30-34, 35-39, 40-45, 45+	<25, 25-35, ≥35
Cnattingius 2011	<20, 20-24, 25-29, 30-34, 35+	<25, 25-35, ≥35
Mok 2017	<20, 20-24, 25-29, 30-34, 35-39, 40-45, 45+	<25, 25-35, ≥35
Steck 2018	<25, 25-34, 35-44, 45+	<25, 25-35, ≥35

Supplementary Table 6. Original assessment of household composition in included studies and how household composition was harmonised for the meta-analysis

Study	Original categorisation	Harmonised categorisation
Suicide mortality and/or attempt		
Alaräisänen 2012	Two-parent family, single-parent family	Single-parent family, not single-parent family (ie, two-parent family)
Bjørngaard 2013	Mother married or cohabitant, other	Single-parent family (ie, other), not single-parent family (ie, married or cohabitant)
Cnattingius 2011	Mother living with infant father, not living with infant father	Single-parent family (ie, not living with infant father), not single-parent family (ie, living with infant father)
Chen 2013	Mother married, not-married (single/divorced/widowed)	Single-parent family (ie, not-married), not single-parent family (ie, single/divorced/widowed)
Danziger 2011	Mother married, other	Single-parent family (ie, other), not single-parent family (ie, mother married)
Osler 2007	Mother married, not-married (single/divorced/widowed)	Single-parent family (ie, not-married), not single-parent family (ie, single/divorced/widowed)
Steck 2018 *	Couple with children, single parent with children, institution	Single-parent family (ie, single parent with children), not single-parent family (ie, couple with children); institution was excluded
Suicide attempt		
Fergusson 2000 *	Single parent family, not single parent family	Single-parent family, not single-parent family

* Did not specified status of the mother

Supplementary Table 7. Original assessment of mother's education in included studies and how mother's education was harmonised for the meta-analysis

Study	Original categorisation	Harmonised categorisation
Suicide mortality and/or attempt		
Bjørngaard 2013	Primary/lower secondary, upper secondary, college/university	Lower (ie, primary/lower education), higher (ie, upper secondary, college/university)
Cnattingius 2011	Years of education: <10, 10-12, 13-14, ≥14	Lower (ie, <10 years), higher (ie, ≥10 years)
Chen 2013	Years of education: <7, 7-9, 10-12, ≥13	Lower (ie, <10 years), higher (ie, ≥10 years)
Suicide attempt		
Fergusson 2000	Lack formal education, at least formal education	Lower (ie, lack formal education), higher (ie, at least formal education)

Supplementary Table 8. Original assessment of father's education in included studies and how father's education was harmonised for the meta-analysis

Study	Original categorisation	Harmonised categorisation
Suicide mortality and/or attempt		
Bjørngaard 2013	Primary/lower secondary, upper secondary, college/university	Lower (ie, primary/lower education), higher (ie, upper secondary, college/university)
Chen 2013	Years of education: <7, 7-9, 10-12, ≥13	Lower (ie, <10 years), higher (ie, ≥10 years)

Supplementary Table 9. Original assessment of socioeconomic status in included studies and how socioeconomic status was harmonised for the meta-analysis

Study	Original categorisation	Harmonised categorisation
Suicide mortality and/or attempt		
Alaräisänen 2012 [a]	Class I and II (high), Class III and IV (low), Class V (farmers)	Low (ie, Class I and II, and Class V), high (ie, Class III and IV)
Geoffroy 2014 [b]	Non-manual, Manual	Low (ie, manual), high (ie, non-manual)
Riordan 2006 [c]	Professional, Skilled, Unskilled	Low (ie, unskilled), high (ie, professional, skilled)
Osler 2007 [d]	Employee, civil servant, Self-employed, Skilled worker, Unskilled worker, Outside/Unknown	Low (ie, Unskilled worker), high (ie, Employee, civil servant & Self-employed & Skilled worker & Self-employed & Outside/Unknown)
Danziger 2011 [e]	Non-manual, Self-employed of farmer, Manual, Other	Low (ie, Manual), high (ie, Non-manual & Self-employed of farmer & Other)
Sorensen 2009 [f]	Parent social status High, Parent social status Low	Low (ie, Parent social status Low), high (ie, Parent social status High)
Suicide attempt		
Barros 2018 [g]	Quintiles	Low (lower quintile), high (second to fifth quantile)
Fergusson 2000 [h]	Professional/Managerial, Clerical/Technical/Skilled, Semi-skilled/Unskilled	Low (ie, Semi-skilled/Unskilled), high (ie, Professional/Managerial & Clerical/Technical/Skilled)
Page 2014 [i]	Class I and II, Class III and IV, Class V and VI	Low (ie, Class IV and V), high (ie, Class I, II, and III)

a. Based on father's occupation (reported by who the mother), assessed in 1966. When the father's occupational status was not known the mother's information on her occupational status was used instead.
b. Based on father's occupation from mother's report of their husband's occupation soon after child's birth (or if missing at 7 years). Occupations were categorized according to the 1951Registrar General's Classification into two categories: non-manual (I/II/IIINM) and manual (IIIM/IV/V).
c. Based on parental occupation
d. Father's occupation at birth of a participant was recorded in 23 strata: non-urban self-employed (four strata) urban self-employed (six strata); employee and civil servants (five strata), skilled and unskilled workers (five strata); pensioners; students and unknown. Preliminary data analyses showed that the strata could be combined, leaving five categories
e. Not further specified
f. The social status classification was based on information about the breadwinner's occupation, breadwinner's education, type of income, and quality of house
g. Derived from principal component analysis of the variables: delivery payment mode, mother's schooling, height, and skin colour
h. Family socio-economic status at the time of the child's birth. This was assessed using the Elley & Irving (1976) scale of socio-economic status for New Zealand. This scale categorizes families into six classes on the basis of paternal occupation. For this analysis, the scale was collapsed into three levels as follows: 1) Levels 1, 2 (professional, managerial); 2) Levels 3, 4 (clerical, technical, skilled); and 3) Levels 5, 6 (semi-skilled, unskilled, unemployed).
i. Professional occupations (class I), managerial and technical occupations (class II), skilled non-manual occupations (class III-NM), skilled manual occupations (class IIIM), partly skilled occupations (class IV), and unskilled occupations (class V). The highest social class of either parent was used to define parental social class.

Supplementary Table 10. Original assessment of birthweight in included studies and how birthweight was harmonised for the meta-analysis

Study	Original categorisation (in grams)	Harmonised categorisation (in grams)
Suicide mortality and/or attempt		
Mittendorfer-Rutz 2004	<2500, 2500-3250, 3250-3750, 3750-4450, >4500	<2500, ≥2500
Geoffroy 2014	<2500, ≥2500	<2500, ≥2500
Li 2003	<2500, ≥2500	<2500, ≥2500
Riordan 2006	<2500, 2500-3250, 3250-3750, 3750-4450, >4500	<2500, ≥2500
Osler 2008	<2500, 2500-3400, >3400	<2500, ≥2500
Suicide ideation		
Geoffroy 2018	<2500, ≥2500	<2500, ≥2500
Nomura 2007	<2500, ≥2500	<2500, ≥2500

Supplementary Table 11. Original assessment of gestational age in included studies and how gestational age was harmonised for the meta-analysis

Study	Original categorisation (in grams)	Harmonised categorisation (in grams)
Suicide mortality and/or attempt		
Risnes 2016	Weeks of gestation: 22-33+6 days, 34-36+6 days, 37-41+6 days, ≥42	Low (ie, <37 weeks), normal (ie, ≥37 weeks)
Cnattingius 2011	Weeks of gestation: <37, ≥37	Low (ie, <37 weeks), normal (ie, ≥37 weeks)
Danziger 2011	Weeks of gestation: <38, 28-41, ≥42	Low (ie, <38 weeks), normal (ie, ≥38 weeks)
D'Onofrio 2013	Weeks of gestation: <37, ≥37	Low (ie, <37 weeks), normal (ie, ≥37 weeks)
Niederkrotenthaler 2012	Weeks of gestation: <34, 34-37, 38-40, ≥41	Low (ie, <37 weeks), normal (ie, ≥37 weeks)

Supplementary Table 12. Original assessment of Small for Gestational Age in included studies and how Small for Gestational Age was harmonised for the meta-analysis

Study	**Original categorisation** (in grams)	**Harmonised categorisation** (in grams)
Suicide mortality and/or attempt		
Cnattingius 2011	< -2 SD, -2 to -1, -1 to +1, +1 to +2, > +2	Small for gestational age (ie, < -2SD), non-small for gestational age (ie, ≥ -2SD)
Niederkrotenthaler 2012	low weight short length, low weight, short length, non-SGA (> -2SD)	Small for gestational age (ie, long, short, both), non-small for gestational age (ie, ≥ -2SD)
Lahti 2015	< -2 SD, -2 to +2, < +2 SD	Small for gestational age (ie, < -2SD), non-small for gestational age (ie, ≥ -2SD)
Danziger 2011	Lowest tertile, Middle tertile, Higher tertile	Small for gestational age (ie, lowest tertile), non-small for gestational age middle tertile, higher tertile)

Supplementary Table 13. Original assessment of mother's smoking during pregnancy in included studies and how mother's smoking during pregnancy was harmonised for the meta-analysis

Study	**Original categorisation** (in grams)	**Harmonised categorisation** (in grams)
Suicide mortality and/or attempt		
Alaräisänen 2012	>1 cigarette/day, no	Yes (ie, >1 cigarette/day), no
Cnattingius 2011	>9 cigarettes/day, 1-9 cigarettes/day, no	Yes (ie, >1 cigarette/day), no
Geoffroy 2014	>1 cigarette/day, no	Yes (ie, >1 cigarette/day), no
Ekblad 2010	>9 cigarettes/day, 1-9 cigarettes/day, no	Yes (ie, >1 cigarette/day), no

Supplementary Table 14. Meta-regression analyses

Risk factor	Heterogeneity - initial model			Meta-regression: moderation analysis for age at follow-up (<30 vs >30 years)					
	Q_H (df)	*p*	I^2 (%)	Test for moderation		Test for residual heterogeneity		Residual I^2 (%)	R^2 (%)
				Q_M (1 df)	*p*	Q_E (df)	*p*		
Suicide									
Birth order 2+ vs 1	29.78 (9)	0.001	69.8	3.03	0.082	15.36 (8)	0.053	47.3	47.0
Birth order 2-3 vs 1	17.67 (6)	0.007	66.1	17.67	0.007	7.87 (5)	0.002	55.8	36.4
Birth order 4+ vs 1	42.45 (6)	0.000	85.9	1.47	0.226	19.44 (5)	0.002	26.3	74.2
Mother's age <20	20.04 (6)	0.027	70.1	1.43	0.231	18.88 (5)	0.002	73.5	0
Father's age <25 vs 25-35	14.55 (3)	0.002	79.4	0.42	0.518	10.29 (2)	0.006	21.6	81.3
Father's age >35 vs 25-35	6.80 (3)	0.079	55.9	4.85	0.028	1.95 (2)	0.377	0	100.0
Single mother	19.31 (6)	0.004	68.9	7.16	0.007	6.38 (5)	0.271	27.7	68.9
Mother smoking in pregnancy	10.75 (3)	0.013	72.1	3.72	0.054	2.89 (2)	0.235	30.9	79.4
Mother low education	2.79 (2)	0.248	28.3	2.40	0.122	0.39 (1)	0.530	0	100
Father low education	2.93 (1)	0.087	65.9	.	.	.	.	.	.
Low socioeconomic status	10.78 (5)	0.056	53.6	.	.	.	.	.	.
Low birthweight	4.12 (4)	0.389	3.0	1.50	0.221	2.63 (3)	0.452	0	100
Low gestational age	4.56 (4)	0.336	11.3	0.18	0.670	4.34 (3)	0.227	30.9	0
Small for gestational age	1.63 (3)	0.653	0	0.01	0.933	1.62 (2)	0.445	0	.
Caesarean section	0.08 (1)	0.776	0	.	.	.	.	.	.
Hypertensive disease	0.10 (1)	0.749	0	.	.	.	.	.	.
Suicide attempt									
Birth order 2+ vs 1	7.58 (4)	0.108	47.3	5.73	0.018	1.86 (3)	0.602	0	100
Mother's age <20	14.65 (3)	0.002	79.5	0.04	0.838	14.11 (2)	0.001	85.8	0
Single mother	1.54 (2)	0.463	0	0.41	0.522	1.13 (1)	0.288	11.5	0
Low socioeconomic status	3.60 (4)	0.463	0	0.50	0.478	3.08 (3)	0.38	.	2.5
Low birthweight	0 (1)	0.986	0	.	.	.	.	.	.
Low gestational age	0.67 (1)	0.413	0	.	.	.	.	.	.
Suicidal ideation									
Mother's age <20	0.28 (1)	0.594	0	.	.	.	.	.	.
Low birthweight	0.03 (1)	0.853	0	.	.	.	.	.	.

I^2 reflects the proportion of heterogeneity
Q_H is the test for heterogeneity in the non-moderated model; Q_M is the test for moderation; QE is the test of heterogeneity after taking into account the moderator in the model. $Q_H \sim Q_M + Q_E$ ($Q_H = Q_M + Q_E$ only in a fixed-effect model)
R^2 is the proportion of heterogeneity explained by the moderator "age at follow-up (≤30 years versus >30 years)" in the meta-regression model.

Supplementary Table 15. Risk of publication bias analysis: Egger test, Timm & Fill, and Funnel plot

	Egger test *p*	Trim & Fill	
		n	*p* pooled estimate
Suicide			
Birth order 2+ vs 1	0.293	.	.
Birth order 2-3 vs 1	0.493	.	.
Birth order 4+ vs 1	0.201	.	.
Mother's age <20	0.034	3	<0.001
Father's age <25 vs 25-35	0.813	.	.
Father's age >35 vs 25-35	0.443	.	.
Single mother	0.895	.	.
Mother smoking in pregnancy	0.002	2	<0.001
Mother low education	0.772	.	.
Father low education	.	.	.
Low socioeconomic status	0.072	.	.
Low birthweight	0.915	.	.
Low gestational age	0.623	.	.
Small for gestational age	0.255	.	.
Caesarean section	.	.	.
Hypertensive disease	.	.	.
Suicide attempt			
Birth order 2+ vs 1	0.463	.	.
Mother's age <20	0.698	.	.
Single mother	0.965	.	.
Low socioeconomic status	0.147	.	.
Low birthweight	.	.	.
Low gestational age	.	.	.
Suicidal ideation			
Mother's age <20	.	.	.
Low birthweight	.	.	.

Supplementary Table 16. Sensitivity analyses using the E-value

	Pooled OR	E-value
Suicide		
Birth order 2+ vs 1	1.22 (1.12-1.34)	1.73
Birth order 2-3 vs 1	1.18 (1.07-1.30)	1.64
Birth order 4+ vs 1	1.51 (1.21-1.88)	2.39
Mother's age	1.80 (1.52-2.14)	3.00
Father's age <25y vs 25-35y	1.24 (0.90-1.71)	.
Father's age >35y vs 25-35y	1.05 (0.88-1.25)	.
Single mother household	1.57 (1.31-1.89)	2.59
Low mother's education	1.36 (1.28-1.46)	2.06
Low father's education	1.38 (1.27-1.51)	2.10
Low socioeconomic status	1.27 (1.00-1.61)	1.86
Caesarean section	1.13 (0.92-1.40)	.
Low birthweight	1.30 (1.09-1.55)	1.92
Low gestational age	1.08 (0.89-1.32)	.
Small for gestational age	1.18 (1.00-1.40)	1.64
Mother's smoking during pregnancy	1.56 (0.99-2.46)	.
Mother's hypertensive disease	1.09 (0.69-1.72)	.
Suicide attempt		
Birth order 2+ vs 1	1.17 (0.97-1.41)	.
Low mother's age	1.81 (1.32-2.50)	3.02
Single mother household	1.78 (1.29-2.45)	2.96
Low socioeconomic status	1.75 (1.47-2.09)	2.90
Low birthweight	1.39 (1.23-1.56)	2.13
Low gestational age	1.09 (1.04-1.15)	1.40
Suicidal ideation		
Low mother's age	1.28 (0.84-1.94)	.
Low birthweight	1.73 (1.04-2.86)	2.85

Supplementary table 17. Crude and adjusted associations between in-utero and perinatal influences and suicide among studies controlling for parental psychopathology (in bold)

In-utero/perinatal factors	Categorisation [a]	Crude association [b,c]	Adjusted association [c]	Method of adjustment for parental psychopathology	Adjustment variables
Birth order					
Alaräisänen 2012 [d]	1 2-5 6+	1.35 (0.74-2.46) Ref 2.39 (1.20-4.78)	1.00 (0.51-1.96) Ref 2.74 (1.19-6.29)	Multiple regression	**Mother's antenatal depressed mood, mother's psychiatric disorder**, mother's age at birth
Bjørngaard 2013	1 2 3 4+	Ref 1.22 (1.12-1.33) 1.28 (1.15-1.42) 1.42 (1.26-1.60)	Ref 1.60 (1.37-1.86) 2.12 (1.62-2.76) 3.05 (2.04-4.58)	Sibling design	Sex, age (time variable), birth period, maternal age, and birth order
Niederkrotenthaler 2012	1 2-3 4+	0.99 (0.88-1.11) Ref 1.34 (1.07-1.69)	0.89 (0.78-1.01) Ref 1.18 (0.92-1.51)	Multiple regression	Maternal age, paternal age, birth weight, gestational age, parental socio-economic and maternal civil status in childhood, **parental death due to suicide and other causes; parental suicide attempt and inpatient care due to mental disorders**
Rostila 2014	1 2 3 4+	NA	Ref 1.17 (1.05-1.30) 1.39 (1.18-1.65) 1.57 (1.23-2.00)	Sibling design	Age, period, sex, and maternal age at child's birth, marital status, socioeconomic status
Saarela 2016	1 2 3 4+	NA	Ref 1.27 (1.09-1.47) 1.35 (1.05-1.73) 1.72 (1.22-2.44)	Sibling design	Age, birth year, sex, and parental age at child birth
Mother's age					
Alaräisänen 2012 [d]	<20 20-34 35+	2.20 (1.02-4.73) Ref 0.80 (0.37-1.70)	2.41 (1.02-5.71) Ref 0.42 (0.17-1.07)	Multiple regression	**Mother's antenatal depressed mood, mother's psychiatric disorder**, birth order
Bjørngaard 2013	<20 20-24 25-29 30-34 35+	Ref 0.72 (0.64-0.81) 0.67 (0.59-0.75) 0.69 (0.60-0.79) 0.71 (0.60-0.84)	Ref 0.87 (0.69-1.09) 0.72 (0.52-0.99) 0.62 (0.40-0.96) 0.53 (0.30-0.94)	Sibling design	Sex, age (time variable), birth period, maternal age, and birth order
Ekeus 2006	<20 20-24 25-29 30-34 35+	2.4 (1.7-3.3) 1.5 (1.1-1.9) Ref 1.7 (1.1-2.6) 2.0 (1.0-3.8)	1.5 (1.0-2.3) 1.3 (0.9-1.7) Ref 1.5 (1.0-2.3) 1.4 (0.7-2.8)	Multiple regression	Age, sex, child welfare intervention, **illicit drug abuse in parents, alcohol addiction in parents, psychiatric illness in parents**, housing, residency, social welfare, ethnicity, SES, single parenthood and paternal age
Mok 2017	<20 20-24 25-29 30-34 35-39 40+	1.46 (1.19-1.79) 1.30 (1.16-1.47) Ref 1.01 (0.87-1.16) 1.15 (0.92-1.42) 0.77 (0.45-1.23)	1.24 (1.00-1.52) 1.22 (1.08-1.38) Ref 1.02 (0.88-1.18) 1.15 (0.91-1.43) 0.84 (0.47-1.40)	Multiple regression	Father's age, offspring age and sex, and calendar year, **parental histories of mental illnesses**, parental socioeconomic status, and urbanicity of birthplace
Niederkrotenthaler 2012	<20 20-29 30+	1.82 (1.41-2.36) Ref 0.99 (0.87-1.13)	1.90 (1.44-2.49) Ref 0.95 (0.81-1.11)	Multiple regression	Birth weight, gestational age and parity, parental socio-economic and maternal civil status in childhood, **parental death due to suicide and other causes; parental suicide attempt and inpatient care due to mental disorders**
Von Borczyskowski 2010	<25 25-34 35+	1.16 (1.11-1.21) Ref 1.11 (1.05-1.17)	1.13 (1.07-1.19) Ref 1.14 (1.07-1.21)	Multiple regression	Age and **parents' morbidity, ie, suicide of parent(s), severe psychiatric disorders of the parent(s), alcohol abuse of the parent(s)**
Single mother					
Von Borczyskowski 2010	Single Two parents	1.46 (1.39-1.54) Ref	1.33 (1.25-1.42) Ref	Multiple regression	Age and **parents' morbidity, ie, suicide of parent(s), severe psychiatric disorders of the parent(s), alcohol abuse of the parent(s)**
Socioeconomic status					
Von Borczyskowski 2010	White collar Blue collar NA/other	Ref 1.15 (1.10-1.21) 1.14 (1.08-1.21)	Ref 1.13 (1.08-1.19) 1.12 (1.06-1.19)	Multiple regression	Age and **parents' morbidity, ie, suicide of parent(s), severe psychiatric disorders of the parent(s), alcohol abuse of the parent(s)**
Birthweight					
Niederkrotenthaler 2012	800-2499 2500-3250 3250-3750 3750-4450 4450-6000	1.82 (1.37-2.43) 1.11 (0.96-1.28) Ref 1.07 (0.93-1.23) 0.77 (0.54-1.11)	1.65 (1.16-2.35) 1.04 (0.89-1.21) Ref 1.07 (0.93-1.24) 0.77 (0.53-1.12)	Multiple regression	Gestational age, parity, maternal and paternal age, parental socio-economic and maternal civil status in childhood, **parental death due to suicide and other causes; parental suicide attempt and inpatient care due to mental disorders**
Birth length					

Niederkrotenthaler 2012	<48 48-49 50-51 52-53 54+	1.40 (1.14-1.71) 1.04 (0.89-1.22) Ref 1.03 (0.89-1.19) 0.80 (0.64-1.00)	1.20 (0.95-1.52) 0.98 (0.83-1.16) Ref 1.03 (0.89-1.19) 0.81 (0.65-1.02)	Multiple regression	Gestational age, parity, maternal and paternal age, parental socio-economic and maternal civil status in childhood, **parental death due to suicide and other causes; parental suicide attempt and inpatient care due to mental disorders**
SGA					
Niederkrotenthaler 2012	Low weight and length Low weight Short length Non-SGA	1.38 (0.94-2.03) 1.39 (0.85-2.28) 1.14 (0.82-1.59) Ref	1.18 (0.79-1.76) 1.25 (0.75-2.08) 0.97 (0.69-1.36) Ref	Multiple regression	Parity, maternal and paternal age, parental socio-economic and maternal civil status in childhood, **parental death due to suicide and other causes; parental suicide attempt and inpatient care due to mental disorder**s

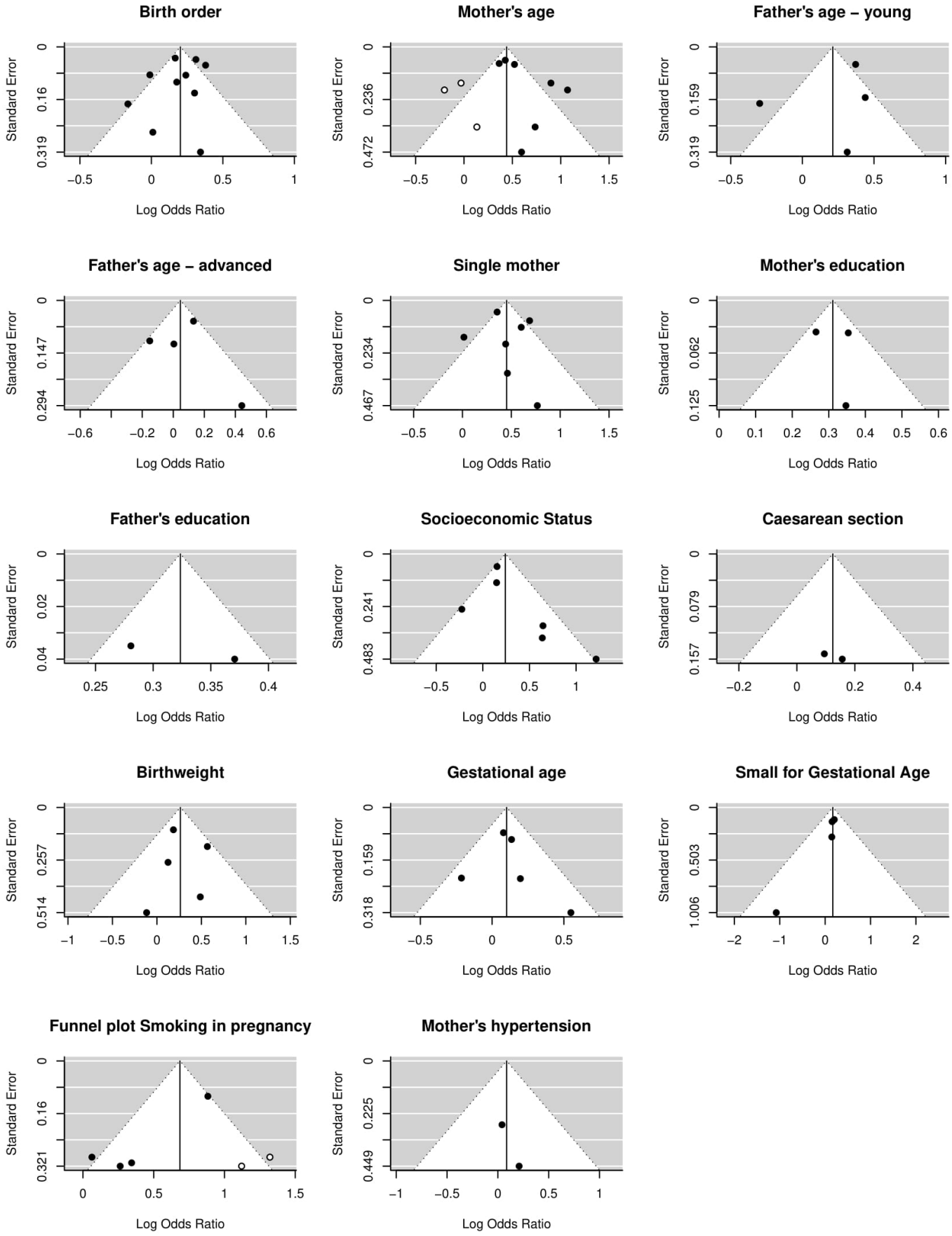
NA, not available; SGA, Small for gestational age; [a] see supplemental material tables S3 to S14 for details about exposure categorisation; [b] minimally adjusted model is reported if the crude association is not available; for sibling design, the association in the entire population is reported, if available; [c] estimates can be odds ratio, risk ratio, hazard ratio, incidence rate ratio; see papers for details. [d] reported only for males

Supplementary table 18. Crude and adjusted association between in-utero and perinatal influences and suicide attempt among studies controlling for parental psychopathology (in bold)

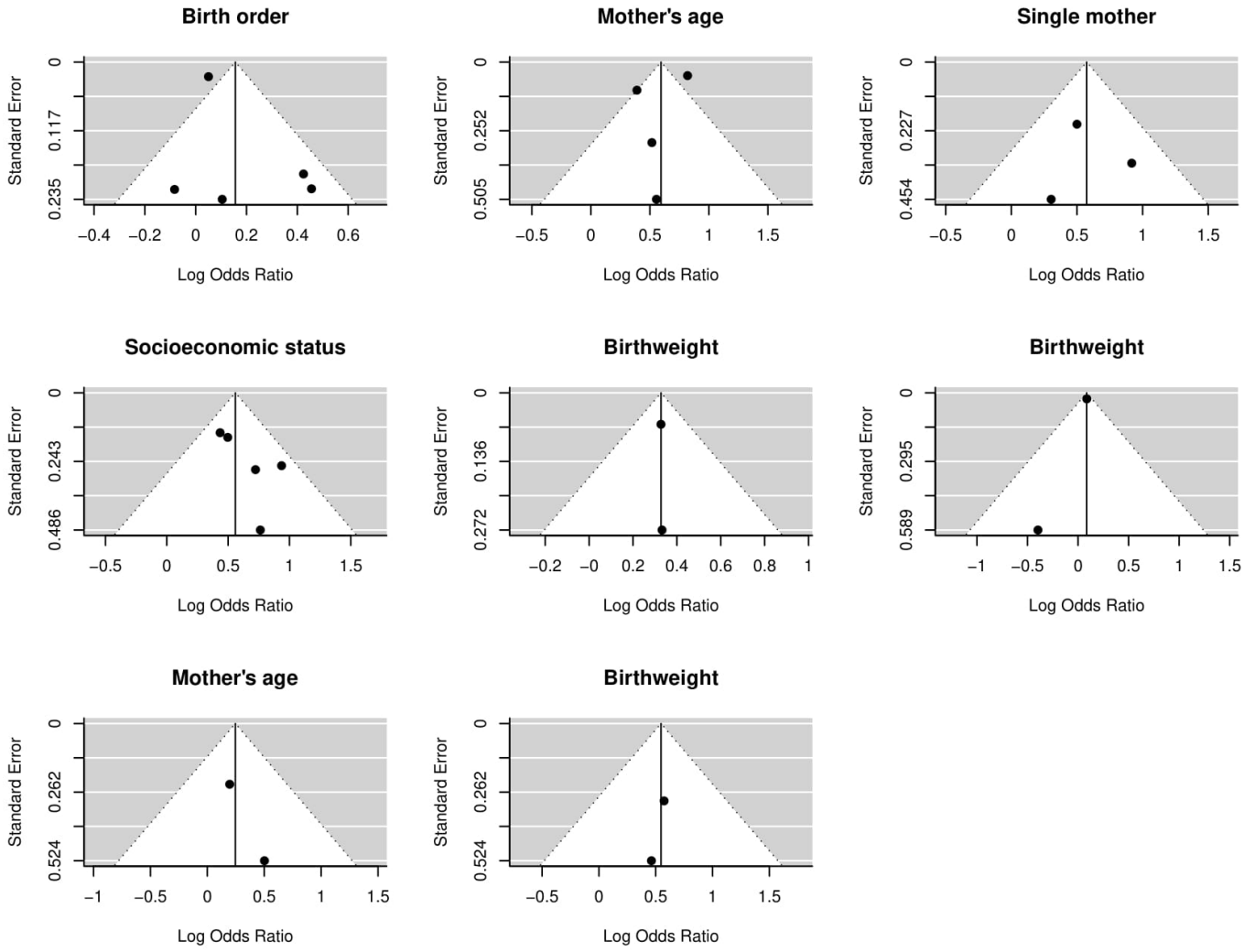
Early-life factor	Categorisation [a]	Crude association [b,c]	Adjusted association [c]	Method of adjustment for parental psychopathology	Adjustment variables
Birth order					
Niederkrotenthaler 2012	1 2-3 4+	0.97 (0.93-1.00) Ref 1.56 (1.46-1.66)	0.80 (0.77-0.84) Ref 1.40 (1.31-1.50)	Multiple regression	Maternal age, paternal age, birth weight, gestational age, parental socio-economic and maternal civil status in childhood, **parental death due to suicide and other causes; parental suicide attempt and inpatient care due to mental disorders**
Mother's age					
Niederkrotenthaler 2012	<20 20-29 30+	2.11 (1.96-2.27) Ref 0.86 (0.83-0.89)	1.66 (1.53-1.80) Ref 0.83 (0.79-0.86)	Multiple regression	Birth weight, gestational age and parity, parental socio-economic and maternal civil status in childhood, **parental death due to suicide and other causes; parental suicide attempt and inpatient care due to mental disorders**
Ekeus 2006	<20 20-24 25-29 30-34 35+	2.0 (1.7-2.3) 1.3 (1.1-1.5) Ref 1.0 (0.8-1.2) 1.3 (0.9-1.8)	1.6 (1.4-1.9) 1.2 (1.1-1.4) Ref 0.9 (0.8-1.2) 1.2 (0.8-1.7)	Multiple regression	Age, sex, child welfare intervention, **illicit drug abuse in parents, alcohol addiction in parents, psychiatric illness in parents**, housing, residency, social welfare, ethnicity, SES, single parenthood and paternal age
Mok 2017	<20 20-24 25-29 30-34 35-39 40+	1.93 (1.85-2.02) 1.33 (1.30-1.37) Ref 0.92 (0.89-0.95) 0.94 (0.89-0.99) 1.03 (0.93-1.14)	1.43 (1.37-1.49) 1.17 (1.14-1.20) Ref 0.96 (0.93-0.99) 0.96 (0.91-1.01) 1.02 (0.91-1.14)	Multiple regression	Father's age, offspring age and sex, and calendar year, **parental histories of mental illnesses**, parental socioeconomic status, and urbanicity of birthplace
Single parent					
Alaräisänen 2012 [d]	No Yes	Ref 5.46 (2.64-11.29)	Ref 4.02 (1.80-08.95)	Multiple regression	Unwanted pregnancy, mothers smoked during pregnancy, single parent family, **father's psychiatric disorder**
Socioeconomic status					
Page 2014	I/II III/IV V/VI	Ref 0.99 (0.81–1.19) 1.10 (0.69–1.77)	Ref 1.00 (0.80–1.25) 1.16 (0.69–1.95)	Multiple regression	Sex, age, substance use, **maternal depression**, other socioeconomic position measures, and depressive symptoms at 10.5, 13 and 16 years
Maternal education					
Page 2014	A level/degree O level CSE/ vocational	Ref 1.16 (0.95–1.40) 0.84 (0.66–1.08)	Ref 1.09 (0.88–1.36) 0.72 (0.53–0.96)	Multiple regression	Sex, age, substance use, **maternal depression**, other socioeconomic position measures, and depressive symptoms at 10.5, 13 and 16 years
Birthweight					
Class 2014	≤2500 2500+	1.19 (1.11-1.28) Ref	0.94 (0.81-1.10) Ref	Sibling design	Gender, birth order, gestational age, year of birth
Niederkrotenthaler 2012	800-2499 2500-3250 3250-3750 3750-4450 4450-6000	1.30 (1.19-1.42) 1.13 (1.08-1.17) Ref 0.93 (0.89-0.97) 0.93 (0.84-1.04)	1.12 (1.01-1.25) 1.06 (1.02-1.11) Ref 0.95 (0.91-0.99) 0.97 (0.87-1.09)	Multiple regression	Gestational age, parity, maternal and paternal age, parental socio-economic and maternal civil status in childhood, **parental death due to suicide and other causes; parental suicide attempt and inpatient care due to mental disorders**
Birth length					
Niederkrotenthaler 2012	<48 48-49 50-51 52-53 54+	1.29 (1.22-1.36) 1.10 (1.05-1.15) Ref 0.90 (0.86-0.94) 0.87 (0.81-0.94)	1.15 (1.08, 1.22) 1.05 (1.00, 1.10) Ref 0.92 (0.88, 0.97) 0.91 (0.84, 0.98)	Multiple regression	Gestational age, parity, maternal and paternal age, parental socio-economic and maternal civil status in childhood, **parental death due to suicide and other causes; parental suicide attempt and inpatient care due to mental disorders**
SGA					
Niederkrotenthaler 2012	Low weight and length Low weight Short length Non-SGA	1.42 (1.27-1.58) 0.95 (0.81-1.12) 1.30 (1.20-1.42) Ref	1.23 (1.10-1.38) 0.91 (0.79-1.08) 1.18 (1.09-1.29) Ref	Multiple regression	Parity, maternal and paternal age, parental socio-economic and maternal civil status in childhood, **parental death due to suicide and other causes; parental suicide attempt and inpatient care due to mental disorders**

NA, not available; SGA, Small for gestational age; [a] see supplemental material tables S3 to S14 for details about exposure categorisation; [b] minimally adjusted model is reported if the crude association is not available; for sibling design, the association in the entire population is reported, if available; [c] estimates can be odds ratio, risk ratio, hazard ratio, incidence rate ratio; see papers for details. [d] reported only for males

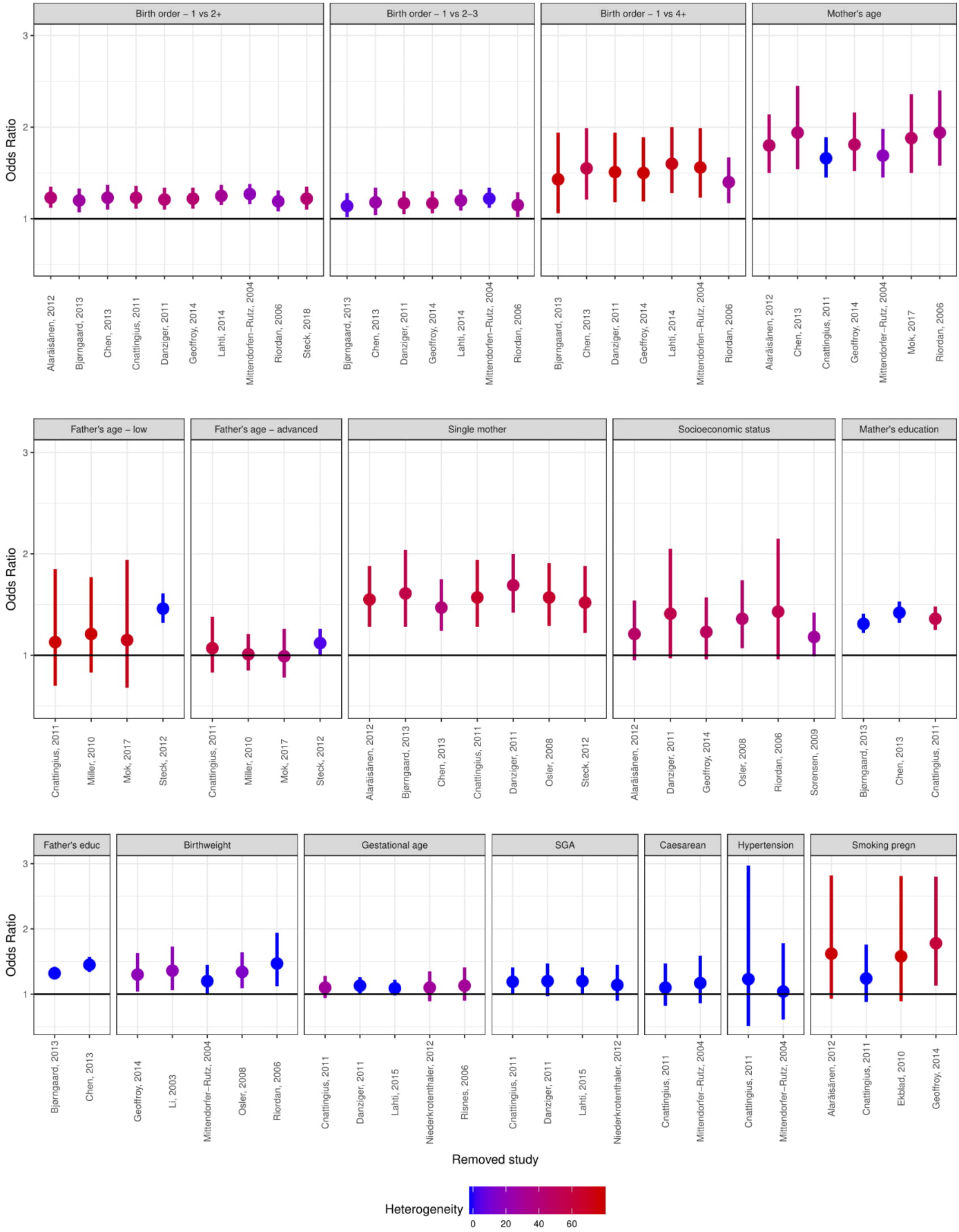
Supplementary Figure 1. Funnel plot for suicide mortality



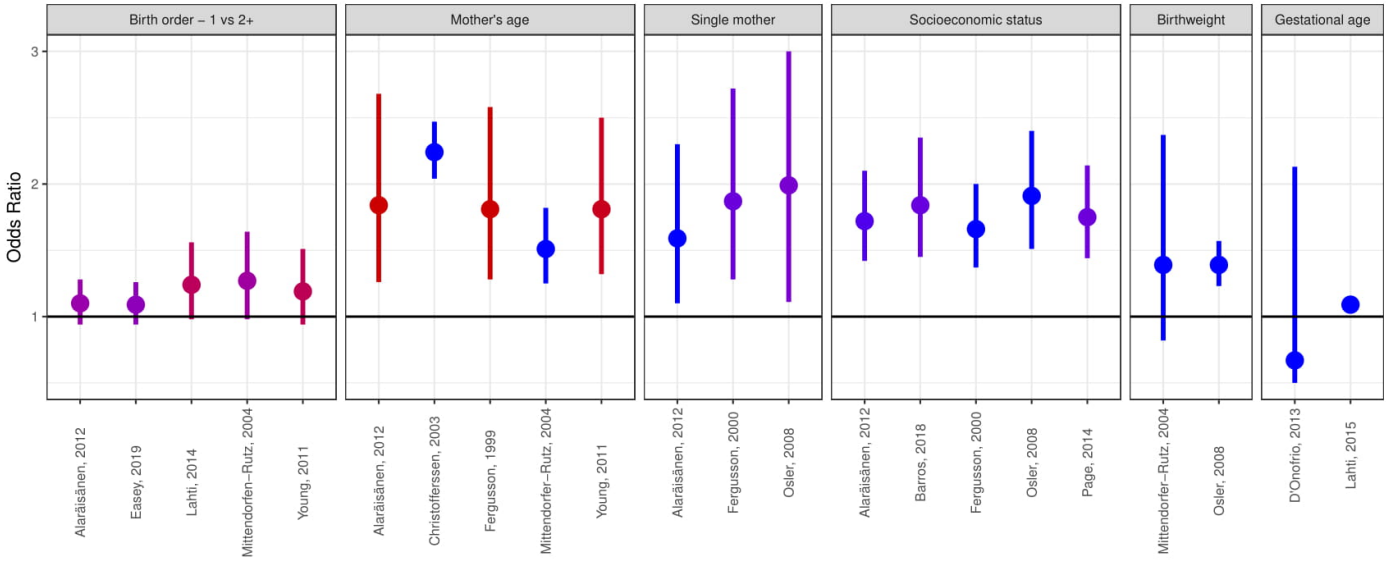
Supplementary Figure 2. Funnel plot for suicide attempt and suicidal ideation



Supplementary Figure 3. Sensitivity analysis using the removing-one-study method for suicide



Supplementary Figure 4. Sensitivity analysis using the removing-one-study method for suicide attempt



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