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Abstract: INTRODUCTION Intrauterine growth restriction (IUGR) is a pregnancy condition, which is associated with poor perinatal outcomes and long-term neurodevelopmental impairment. Several studies also investigated the impact of IUGR on child behaviour (eg, internalising and externalising behaviour, social competencies). However, so far, no systematic review or meta-analysis has been conducted that summarises these effects while considering relevant third variables such as type of IUGR diagnosis and control group, or concurrent cognitive abilities. The objective of this study is to summarise the current evidence regarding the relationship between IUGR and behavioural outcomes from early childhood to young adulthood. Additionally, to explore how third variables such as type of control group, or cognitive abilities, relate to this association. METHODS Search strategy: The following electronic databases will be searched-Web of Science, Medline Ovid, PsycInfo, Cochrane Library, Scopus and Embase. INCLUSION CRITERIA observational (eg, cohort studies and case-control studies) and intervention studies (if standard care is used and norm values are reported for the control group) will be included if they quantitatively compare children with and without IUGR from the age of 2 to 18 years. The main outcomes are internalising and externalising behaviour, and social competencies. ETHICS AND DISSEMINATION No ethics approval was necessary for this protocol. Dissemination of findings will be done by publishing the results in peer-reviewed journals. The results of this systematic review will provide guidance for practice and counselling for clinicians and therapists facing patients affected by IUGR and their families. PROSPERO REGISTRATION NUMBER CRD42022347467.

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Behavioural outcomes of children born with intrauterine growth restriction: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Intrauterine growth restriction (IUGR) is a pregnancy condition, which is associated with poor perinatal outcomes and long-term neurodevelopmental impairment. Several studies also investigated the impact of IUGR on child behaviour (eg, internalising and externalising behaviour, social competencies). However, so far, no systematic review or meta-analysis has been conducted that summarises these effects while considering relevant third variables such as type of IUGR diagnosis and control group, or concurrent cognitive abilities. The objective of this study is to summarise the current evidence regarding the relationship between IUGR and behavioural outcomes from early childhood to young adulthood. Additionally, to explore how third variables such as type of control group, or cognitive abilities, relate to this association.

Methods Search strategy: The following electronic databases will be searched—Web of Science, Medline Ovid, PsycInfo, Cochrane Library, Scopus and Embase. Inclusion criteria: observational (eg, cohort studies and case–control studies) and intervention studies (if standard care is used and norm values are reported for the control group) will be included if they quantitatively compare children with and without IUGR from the age of 2 to 18 years. The main outcomes are internalising and externalising behaviour, and social competencies.

Ethics and dissemination No ethics approval was necessary for this protocol. Dissemination of findings will be done by publishing the results in peer-reviewed journals. The results of this systematic review will provide guidance for practice and counselling for clinicians and therapists facing patients affected by IUGR and their families.

PROSPERO registration number CRD42022347467.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Inclusion of intrauterine growth restriction (IUGR) studies based on consensus definition.
⇒ Examination of different behavioural outcomes of children with IUGR.
⇒ Systematical examination of relevant moderators.
⇒ Broad concept of behavioural outcomes might lead to heterogeneity in effect sizes.

INTRODUCTION

Intrauterine growth restriction (IUGR)

IUGR is a pregnancy condition, in which the fetus does not reach its biological somatic growth potential.[1] The underlying causes of IUGR are manifold but can be broadly categorised into maternal (eg, extreme malnutrition, maladaptive lifestyle, vascular disease), fetal (eg, chromosomal abnormalities, infections, congenital malformations) and placental anomalies[1] (eg, small placenta, circumvallate placenta, chorioangiomata). Most of these conditions result in a compromised placental function, whereby the blood flow to the fetus is reduced. This leads to progressive fetal hypoxia that induces a redistribution of the blood flow to preserve crucial organs like the brain, the heart and the adrenal glands. This adaptive haemodynamic phenomenon is often defined as brain-sparing effect. Brain-sparing has been associated with higher survivability of the fetus[2] but its possible role in preserving the brain and later neurodevelopment is debated. While brain sparing seems to be associated with long-term behavioural impairments,[3] it is not established what dimensions and subdimensions of behaviour specifically are affected by IUGR and to what degree. Furthermore, it has not yet been examined how third variables, such as variations in the criteria used to diagnose IUGR, for example, focusing on growth (morphology) only or also on functional (perfusion) parameters, or cognitive abilities, relate to this association. This systematic review aims to summarise the current evidence regarding the association between IUGR and behaviour considering third variables.

The gold-standard method to diagnose IUGR is by sequential ultrasound measurements focusing on declining growth centiles, functional parameters such as

Doppler waveform analysis of the maternal (uterine arteries) and fetal (umbilical artery (UA), fetal middle cerebral artery and ductus venosus) vessels. The 2016 consensus definition of IUGR is based on one of the following criteria:[4]

1. Estimated fetal weight below the 3rd centile for gestational age by means of ultrasound biometry measurements.
2. Estimated fetal weight or estimated fetal abdominal circumference below the 10th centile for gestational age by means of ultrasound biometry measurements and at least one of the following Doppler measurements:

▶ Pathological Doppler of the UA (pulsatility index >95th centile).
▶ Pathological Doppler of the uterine artery (pulsatility index >95th centile).
▶ Pathological Doppler cerebroplacental ratio (<5th percentile), which is calculated by dividing the MCA pulsatility index by the UA Doppler pulsatility index.

Neurodevelopmental and behavioural consequences of IUGR

Worldwide, IUGR is a leading cause for neonatal death and morbidity with a major impact on the public health system.[5] Next to perinatal complications affecting neonatal adaptation and survival (eg, perinatal asphyxia, pulmonary and gastrointestinal complications, and thermoregulatory and metabolic disturbances), IUGR has also been shown to affect long-term neurodevelopment and health outcomes.[6]

Studies on neurodevelopmental consequences of IUGR focus primarily either on brain imaging data (eg, total brain volume, grey or white matter volume, or connectivity) or on children's performance in cognitive tasks, including tasks on attention, executive functions, processing speed and memory. Other neurodevelopmental domains of children with IUGR have been reported to be language reception and expression, fine and gross motor skills. Results show that children with IUGR, compared with controls, have smaller head size during infancy, decreased total brain and cortical grey matter volumes,[7] discordant cortical gyrification,[8] reduced structural complexity of brain grey and white matter[9–11] and decreased volumes in the hippocampus and the cerebellum.[12] In cognitive tests, children with IUGR show overall lower scores at 5–10 years of age[13 14] and a higher risk for motor developmental delays early in life than children without IUGR.[11 15]

Studies investigating the social–emotional development of children born with IUGR usually assess either internalising or externalising behaviour or competencies:[16]

▶ *Internalising behaviour* can be defined as behaviour that is directed inward or is overcontrolled. Examples of internalising behaviour include anxious behaviour, fearful behaviour and social withdrawal.
▶ *Externalising behaviour* can be defined as behaviour that is directed outward or is undercontrolled. Examples of externalising behaviour include aggressive, hyperactive or impulsive behaviour.

▶ *Competencies* can be defined as the abilities and skills to solve specific problems. This includes the associated motivational, volitional and social readiness to use these abilities and skills successfully and responsibly in variable situations.[17] Competencies in the context of childhood research can be subdivided into social competence, school competence or activity-related competence.

Social–behavioural outcomes are typically measured by parent or teacher reports. There is a wide variety of questionnaires that focus on different dimensions of behaviour (eg, clinical outcomes, social competencies), which leads to heterogeneity in results. In studies examining the social–behavioural consequences of IUGR, children with IUGR compared with controls showed higher emotional reactivity, attentional problems and somatic complaints at 18 months,[18] deficits in communication and problem solving at 2 years of age,[19] higher hyperactivity and social problems between the ages of 5 and 12 years.[20–22]

In the literature on outcomes after IUGR, the concepts of neurodevelopment and behaviour are often not clearly defined and sometimes used interchangeably. This is evident by the multitude of methods used for the measurement of neurodevelopmental and behavioural outcomes. Moreover, behavioural consequences of IUGR might rather be the result of early neurodevelopmental impairments due to an unfavourable intrauterine growth environment.[3 23–25] This would be consistent with the Developmental Origins of Health and Disease hypothesis,[26] which proposes that a suboptimal early developmental environment may influence body structures and functions permanently and thus increase the risk for later disease.[27]

Third variables

Different variables potentially influence the relationship between IUGR and behavioural outcomes and induce heterogeneity between studies. Such variables include the type of control used, differences in cognitive abilities among studies, criteria used to diagnose IUGR, type of outcome measurement and age at follow-up.

In the literature, the type of control group used to compare children with IUGR are very heterogeneous with respect to gestational age at birth. Preterm birth is an important factor to account for when comparing children with IUGR to children without IUGR, since it is associated with similar neurodevelopmental and behavioural outcomes and is co-occurring in children with IUGR.[28 29] Furthermore, the variations in cognitive abilities of participants across studies could partially explain the variability in the association between IUGR and behavioural outcomes, as scoring low on cognitive dimensions has been associated with internalising behaviour and externalising behaviour.[30–32] The multitude of criteria used in the literature to define IUGR may also influence the reported relationship between IUGR and behavioural outcomes. Some studies compared groups according to Doppler parameters defining IUGR based on well-established

cut-off values, while others compared infants with small versus normal birth weight for gestational age. Likewise, there are considerable variations in the measurement of behavioural outcomes even if measures are assumed to assess the same construct[33–35] and therefore it is plausible that variation in the association between IUGR and behavioural outcomes might be explained by the chosen measurement tool.

Finally, the age at follow-up likely moderates the association between IUGR and behavioural outcomes. As has been seen in children with learning difficulties,[36] children with IUGR may experience some behavioural adjustment over time as a result of their social interactions and life events.

Research aims and hypotheses

To date, no meta-analysis has been conducted on the relationship between different behavioural outcomes and IUGR. This systematic review and meta-analysis aims to examine (1) the current evidence regarding the association between IUGR and internalising behaviour, externalising behaviour and competencies and (2) how third variables, such as type of control used, cognitive performance, criteria used to diagnose IUGR, type of outcome measurement and age at follow-up might explain heterogeneity in effect sizes between studies.

METHODS AND ANALYSIS

We used the Preferred Items for Systematic Reviews and Meta-Analysis Protocols checklist when writing our protocol.[37] The protocol has been registered on the International Prospective Register of Systematic Reviews before starting the literature search (registration number: CRD42022347467).

Eligibility criteria

The eligibility criteria for this study have been formulated according to the following Population, Exposure, Comparator & Outcomes (PECO) framework.[38]

Population

The population of interest in this review includes 2- to 18-year-old children and adolescents previously diagnosed with IUGR.

Exposure

Diagnosis of IUGR follows the consensus definition.[4] Studies will be included if they defined IUGR accordingly.

Comparator

Children without IUGR and with a normal intrauterine growth and therefore appropriate for gestational age (10th–90th percentile of estimated fetal size) will be included as comparator. If the study does not include a specific control group but relies on standardised tests, the norm sample will be considered a control group.

Outcomes

The primary outcome of this study will be behavioural outcomes (ie, internalising behaviour, externalising behaviour and competencies).

Study type

All included studies need to be published in a peer-reviewed journal and quantitatively compare children with and without IUGR. This systematic review will include observational studies (eg, cohort studies and case–control studies) and intervention studies. Intervention studies will only be included if they contain a group of children with IUGR that receives standard care (ie, no specific intervention) and if norm values are used as an outcome measure, as in that case the norm sample can approximately serve as a non IUGR sample. Qualitative studies, case studies and case reports as well as conference abstracts will be excluded.

Language

Articles written in German or English will be considered in this systematic review.

Information sources
Database searches

The following electronic databases will be searched for the primary literature search: Web of Science, Medline Ovid, PsycInfo, Cochrane Library, Scopus and Embase. The reference lists of papers identified through the database searches will be scanned to identify further studies of relevance to this systematic review.

Search strategy

The search strategy has been developed in collaboration with a scientific librarian experienced in literature search for systematic reviews. Key papers[19 20 39 40] were used to derive and validate the search strategy. The search strategy only includes terms relating to or describing the population, exposure and outcomes of interest. The search strategy for the study population included terms like 'child*', 'toddler', 'underage', 'minors' and 'adolescent'. For the exposure, terms such as 'intrauterine growth restriction', 'brain sparing', 'cerebral redistribution' have been used. For the outcome of interest, terms such as 'internalising', 'social withdrawal', 'child depression', 'externalising', 'aggression', 'impulsiveness', 'socio emotional competence' or 'academic achievement' have been used. The search terms were adapted for use with the different bibliographic databases in combination with database-specific filters, truncations and Boolean operators. Searches will include all published studies from inception of databases until the date the searches are run and will be carried out by the scientific librarian. The searches will be rerun just before the final analyses and further studies will be screened for inclusion.

Study records

Data management

The citations of the literature search will be first imported to Endnote[41] and duplicates will be removed. For the title and abstract screening process, the list containing all unique citations will be imported to Rayyan[42] to conduct the abstract and full-text screening. After the title and abstract screening, the full-text files for the full-text screening will be uploaded to Rayyan. In case the full text is not accessible, the authors will be contacted with a request to provide the file. For the data collection step, each rater will have a digital coding sheet into which all necessary study information will be collected. An initial pilot phase will be conducted for the study team in order to get familiar with the software, answer questions and resolve any issues. Relevant study materials, such as the literature search strategy for each database, will be uploaded to the Open Science Framework (OSF) platform.[43]

Selection process

A screening procedure guideline for the title and abstract and, in a second separate step, for the full-text screening has been developed and tested by the study team according to the inclusion and exclusion criteria. All studies from the literature search will be independently screened by two authors for inclusion or exclusion while a third reviewer will be consulted for solving discrepancies.

Data extraction and collection process

After all eligible studies have been included, all relevant information of each study will be extracted and collected into a digital coding sheet. Two reviewers will independently collect data from the eligible studies. Disagreements between the two reviewers will be discussed and will be resolved with a third reviewer.

Data items

We will collect general information about the primary studies such as title, authors, publication date, study design, funding sources, conflict of interest and journal name. We will collect sample size, response rate for the relevant outcomes, subgroups, criteria used for describing the exposure and the control group. Furthermore, we will collect baseline demographics of the mothers such as age, socioeconomic status, parental education and ethnicity. Perinatal characteristics of the newborns such as sex, birth weight, gestational age at birth, prematurity, head circumference, height, Apgar Score at 5 min, standardised estimation values (percentile) of fetal growth and perfusion based on ultrasound imaging and Doppler assessment will be also collected. Finally, follow-up variables will be collected, such as age at follow-up, weight, height, psychiatric outcomes, cognitive scores and behavioural outcomes.

Outcomes and prioritisation

The main outcomes of interest are internalising behaviour, externalising behaviour and competencies.

We will collect all reported outcomes of behaviour (total behaviour score), its dimensions (internalising behaviour, externalising behaviour and competencies) and subdimensions (eg, social withdrawal, aggressive behaviour and social competence) from primary studies. Raw scores will be used to determine effect sizes. If raw scores have not been reported, effect sizes will be calculated from test statistics. If a study reports multiple outcomes of the same behavioural (sub)dimension, effect sizes of the (sub)dimension will be averaged. In case of multiple time points of follow-up, the first time point will be chosen for data synthesis.

Psychological disorders will not be counted as behavioural outcomes in this review. Thus, behavioural outcome measures will only be included when they are measured on a symptom level, not on a diagnostic level.

Quality of individual studies

To assess the quality of the included studies, we adapted the Newcastle-Ottawa Scale[44] (NOS) in order to meet the specific needs of this systematic review. It will cover the following domains: sample selection, comparability, exposure/case definition, outcome measurement, incomplete outcome data, selective outcome reporting. The modified NOS will instruct the reviewer to grade the study as low, moderate or high risk of bias for each item. Based on the item ratings, the appraisal of the bias domain will be conducted as follows: If at least one item is appraised as high or moderate risk of bias, the whole domain will be equally appraised as high or moderate risk of bias, respectively. A domain will be appraised as low risk of bias only if all items are appraised as low risk of bias. The quality assessment will be done by two reviewers independently during the data collection process.

Data synthesis

Criteria for synthesis

If at least three studies with the same (sub)dimension of behaviour can be grouped together, a summary estimate for that (sub)dimension will be calculated in the meta-analysis. Meta-regression will be conducted if there is indication for heterogeneity (significant Q statistic or $I^2 > 30\%$).

Synthesis methods

The following measures of effects will be used to determine effect sizes: For dichotomous outcome data (eg, abnormal T-score ≥ 60), relative risk will be determined with 95% CI. For continuous outcome data, standardised mean differences will be determined with 95% CI.

To measure heterogeneity between studies, we will use Higgins' I^2[45 46] and Cochranes Q.[47] The source of heterogeneity will be investigated by means of meta-regression, subgroup or sensitivity analyses.

When there are missing data, the relevant data will be requested by contacting the corresponding author of the study. Relevant data are effect sizes of behavioural outcomes and data used to diagnose IUGR (if IUGR was

stated to be the exposure group). If the authors do not respond, the study will be excluded from the analysis.

Additional analyses

If the collected data allow for it, possible moderators, such as criteria used to define IUGR, gestational age, age at follow-up and cognitive abilities, will be examined with subgroup analyses and meta-regressions. Sensitivity analyses will be conducted for variables that potentially influence the found effect size in the meta-analysis, such as the usage of validated measurement tools, inclusion of children with chromosomal abnormalities, or the inclusion of children with perinatal infections, if enough data points are available. Selective reporting will be inspected visually by funnel plot asymmetry and statistically in all outcomes where quantitative synthesis is possible.

Qualitative synthesis

In case the criteria to conduct a meta-analysis are not met (below three studies per (sub)dimension found), a structured reporting of the evidence will be provided with information presented in text within a table. Characteristics and results of the included studies will be the main content of this table.

Confidence in cumulative evidence

The Grading of Recommendations Assessment[48] will be employed to determine the level of confidence in the resulting body of evidence.

DISCUSSION

The targeted summary of the current literature regarding the association between IUGR and specific dimensions of behaviour from early childhood to adolescence is of both clinical and scientific importance. It improves the scientific basis for clinical counselling of parents of affected children and helps in guiding future research to investigate long-term behaviour outcomes and their underlying mechanisms in children born with IUGR. Furthermore, it investigates certain key variables that might explain between-study heterogeneity in the relationship between IUGR and behaviour, such as type of control used, differences in cognitive abilities between the study arms, criteria used to diagnose IUGR, type of outcome measurement and age at follow-up.

This will be the first meta-analysis on specific behavioural outcomes of children born with IUGR since previous meta-analyses have either not considered specific dimensions of behaviour[49] or did not summarise effect sizes quantitatively.[50] The methods include a comprehensive literature search strategy within multiple major databases that are relevant for the research topic.

Ethics and dissemination

No ethics approval was necessary for this protocol. Dissemination of findings will be done by publishing the results in peer-reviewed journals.

Patient and public involvement

Patients were not involved in the design of the protocol of this systematic review of the literature.

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