The effect of adoption on catch-up in linear growth in children 0 to 59 months of age: a meta-analysis of individual participant data from cohort studies

Statistical analysis plan

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1. Administrative information

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2. Introduction

2.1. Background and rationale

Catch-up growth in individual children was first described in 1963 and characterized as “rapid linear growth that allowed the child to accelerate toward and, in favorable circumstances, resume his/her pre-illness growth curve” (1,2). More recently, catch-up in linear growth has been defined by Boersma and de Wit as “height velocity above the statistical limits of normality for age or maturity during a defined period of time, following a transient period of growth inhibition; the effect of catch-up growth is to take the child towards his/her pre-retardation growth curve” (2). The definition of catch-up growth implies that four criteria must be met to demonstrate catch-up in linear growth:

- Criterion 1: a growth-inhibiting condition is required;
- Criterion 2: the growth-inhibiting condition causes a reduction in linear growth velocity;

- Criterion 3: the period of growth inhibition is followed by alleviation of or compensation for the inhibiting condition;
- Criterion 4: this alleviation subsequently leads to higher-than-normal velocity (3).

Both observational studies and studies assessing the impact of interventions have claimed to assess catch-up growth. Observational studies cannot be used to establish whether catch-up in linear growth is possible since they violate the third criterion, i.e., they do not assess linear growth after the cause of the growth inhibition has been alleviated. Intervention studies assessing the impact of adoption provide an excellent opportunity to study the catch-up in linear growth. Adoption from a resource-poor setting to a high-income setting leads to a dramatic improvement in a child's environment with respect to diet, water, sanitation, hygiene, and opportunities for learning and receiving responsive care in a stable household setting. Accordingly, adoption studies provide evidence of the upper bound for what is possible for linear growth outcomes when environmentally inhibiting conditions are alleviated.

A recent review of the literature showed that adoption or placement in foster can lead to catch-up in linear growth (4). A key limitation of the review, however, was the use of the reported mean values rather than the original individual-level data. This use of the mean values could have affected the precision of the estimates. In addition, the authors did not have access to the growth reference used in many of the studies and thus used the WHO standard to derive absolute height values from the reported Z-scores.

2.2. Objective

The objective is to estimate the effect of adoption (or placement in foster care) before 5 years of age on catch-up in linear growth using individual participant data. In addition, we will identify individual-level factors that may modify the effect of adoption (placement in foster care) on linear growth outcomes.

Adoption is defined as the permanent transfer of a child from a resource-poor setting (e.g., low- or middle-income country) to a setting without the resource constraints that limit linear growth (e.g., high-income country).

Catch-up growth is defined as an absolute linear growth velocity (e.g., cm per month) that is higher than the expected linear growth velocity for age and sex using the WHO growth standard (5). This is mathematically equal to a reduction in the absolute height deficit or height-for-age difference (HAD)(4).

2.3. Review questions

What is the effect on catch-up in linear growth of adoption (or placement in foster care) before 5 years of age from a resource-poor setting (e.g., low- or middle-income country) to a setting without resource constraints that limit linear growth?

How does the effect of adoption on catch-up in linear growth differ by child age at adoption, child sex, and duration of adoption?

3. Study methods

3.1. Eligibility criteria

Eligible studies will be intervention studies of adoption (or foster care placement) of children up to 59 months of age.

Study setting and intervention

- Adoption (or placement in foster care) of children living in low- and middle-income countries (as defined by the World Bank classification) or comparable disadvantaged conditions leading to growth retardation.
- Adoption to (or placement in foster care in) a setting without resource constraints that limit linear growth.
- Adoption before 5 years of age.

Study characteristics

- Intervention studies with longitudinal follow-up data on individual children.
- Baseline data on child length or height collected up to 3 months before (or within 1 month after adoption) adoption and follow-up data on child length or height collected at least 3 months after adoption.

3.2. Identifying studies

The meta-analysis will include studies identified through different mechanisms. First, we will consider studies included in a recently published review of the literature (4). For this review, "we used multiple search strategies to identify articles to include in the review. First, we screened all studies included in the 1994 Martorell et al. seminal review on the reversibility of stunting and screened all studies that have cited this review since it was published using Web of Science. We followed the same backward- and forward-looking strategy using the more recent comprehensive review by van IJzendoorn of studies on plasticity of growth after international adoption published between 1956 and 2006 (26). To identify

additional studies examining the link between linear growth and adoption published after 2006, we searched PubMed using the search string '(catch up OR recovery OR growth OR height) AND (adopt OR orphan) AND (child OR infant)'. We only included studies that assessed height outcomes (absolute height, HAZ, or height percentiles) in children under 5 years of age before and after adoption in order to quantify catch-up growth." All authors included in this review study were contacted and invited to share their data sets.

To conduct the analyses in this published review, we computed children's actual height (i.e., height in absolute terms) using the WHO growth standard and the reported sex, mean age, and mean HAZ. As a consequence, we only included studies that provided information on the proportion of boys and girls and on children's mean age. Studies that did not provide this information were excluded from the published review, but the authors of these excluded studies were contacted to share study data. Studies for which data are shared will be included in the meta-analysis.

3.3. Study selection process

Studies will be assessed against the inclusion criteria detailed in section 3.1.

3.4. Data items

Studies will be identified and selected as described in sections 3.2 and 3.3. Published articles (and statistical analysis plans if available) will be reviewed. We will assess if relevant outcomes were measured.

3.5. Data collection process

Authors of selected studies will be invited to share de-identified individual participant data (IPD) for pre-specified variables (listed below). Individual investigators who cannot share IPD will be asked to produce individual-level estimates of the overall effect of adoption on growth retardation and of the effect stratified by the pre-defined effect modifiers within the trial population. The research team will provide a data dictionary, analytic code, and a data submission table to be completed by the original investigators. The research team will assist the investigators as needed but will not have access to the primary data.

3.6. IPD integrity

The following data integrity checks will be conducted:

- Check for completeness by cross-checking sample sizes with publications.
- Assess missingness in each study by tabulating the percentage of children lost to follow-up between the pre- and post-adoption assessment.

HAD will be calculated using the 2006 WHO child growth standards (6). For reasons of comparison, we will also study height-for-age Z-score (HAZ), using the same WHO standard. Identifying biologically implausible values for HAD will be done indirectly through inspecting HAZ values. These values will be checked for acceptable standard deviations and to be within published WHO acceptable ranges (7). Biologically implausible values (HAZ <-6 or >6) will be inspected for errors and truncated or removed from analysis.

Other variables will be assessed for outliers and low frequency categories. Relevant model assumptions will be assessed. Where necessary, sensitivity analyses will be conducted if model assumption are seriously violated.

3.7. Risk of bias assessment

Risk of bias is typically assessed using the risk-of-bias tool in the Cochrane Handbook for Systematic Reviews of Interventions. Some of the sources of bias in the tool are specific to randomized trials (such as non-random allocation sequence and non-blinding to treatment) and do not apply to most intervention studies available for this review. We will assess the following bias domains:

- Bias arising from the randomization process (for randomized trials only)
- Bias due to deviations from intended interventions (all studies)
- Bias due to missing outcome data (all studies)
- Bias in measurement of the outcome (all studies)
- Bias in selection of the reported result (all studies)

We will summarize the risk of bias for each included study. If necessary, we will conduct sensitivity analyses to assess any impact of bias.

3.8. Outcomes

HAD will be calculated using the 2006 WHO child growth standards. For reasons of comparison, we will also study height-for-age Z-score (HAZ), using the same WHO standard.

3.9. Analysis

The effect of adoption (or placement in foster care) will be assessed by comparing the child's HAD before and after adoption. If studies collected data at more than two time points, then we will restrict the primary analyses to the measurement corresponding to the highest age before adoption and the measurement corresponding to the highest age (but below 5 years of age) after adoption.
We will conduct two types of analyses to separately investigate the full sample intervention effect and effect stratified by individual-level characteristics (child age at the time of adoption, child sex, and duration of exposure to the adoption environment).

The meta-analysis will use a two-stage method.

- **Stage 1**: effect estimates will be estimated within each individual study. The primary parameter of interest will be the mean difference of the continuous outcomes. The impact of adoption will be estimated using a mixed effects model with child -specific random intercepts and a time dummy (before or after adoption), child age and child sex as fixed effects. If available, baseline measurements such as parents' height will be included as covariate to increase efficiency.
- **Stage 2**: The stage 1 estimates will be pooled using inverse-variance study random effects. This reflects our assumption that the effect of adoption could vary from study to study. Sensitivity analyses will be conducted using fixed-effect methods.

Two types of estimates will be produced:

- **Full sample intervention effects:** In the first stage, we will estimate the parameter corresponding to the intervention effect for each study separately. In stage 2, we will combine the study-specific effect estimates, which will generate a point estimate, 95% confidence interval, and corresponding p-value.
- **Stratification by individual level characteristics**: In stage 1, we will estimate the parameter to the intervention within pre-specificed subgroups of children (see section 3.10). The first stage estimates will be combined in stage 2, resulting in combined estimates of the intervention effect within each of the subgroups (8).

I^2 and Tau^2 statistics will be used to assess heterogeneity. In case of substantial heterogeneity (either based on these statistics or based on the forest plots), additional sensitivity analyses will be conducted (9).

We are aware of only one randomized adoption study. For consistency, the primary analyses will only use the data from the intervention arm in the meta-analysis. The randomized intervention design will be used in the additional analyses (see below).

3.10. Exploration of variation in effect

As explained in section 3.9, analyses stratified by individual-level characteristics will be conducted. These characteristics will be dichotomous and include age at adoption, child sex, and the duration of exposure to the adoption environment. Tentatively, categorization of the age variable will be below or above 24 months of age, and the categorization of exposure duration will be below or above 12 months. Studies not contributing at least 5 subjects to each categorical stratum will be excluded from that specific analysis.

The list of potential stratifying variables may be expanded after review of individual studies.

3.11. Sensitivity analyses

As mentioned above, the stage 1 estimates will be pooled using inverse-variance random effects. Sensitivity analyses will be conducted using fixed-effect methods. In addition, sensitivity analyses will conducted as needed (see sections 3.6 and 3.7).

3.12. Additional analyses

Two sets of additional analyses will be carried out.

First, we will conduct a separate analysis with the data from the one randomized adoption study. We will use the randomized intervention design to estimate the effect of adoption on HAD and HAZ, controlling for pre-adoption characteristics.

Second, the analyses stratified by duration of adoption will be repeated including all observations from studies with more than one post-adoption measurement.

4. Modifications to SAP after registration

N/A

5. References

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