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2 **Health impact of catch-up growth in low-birth weight infants: systematic review,**
3 **evidence appraisal, and meta-analysis**

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12 **Abstract**

13 This study aimed to systematically review and appraise evidence on the short-term (e.g.
14 morbidity, mortality) and long-term (obesity and non-communicable diseases, NCDs) health
15 consequences of catch-up growth (versus no catch-up **growth**) in individuals with a history of
16 low birth weight (LBW). We searched MEDLINE, EMBASE, Global Health, CINAHL plus,
17 Cochrane Library, ProQuest Dissertations and Thesis, and reference lists. Study quality was
18 assessed using the risk of bias assessment tool from the Agency for Health Care Research and
19 Quality, and the evidence base was assessed using the GRADE tool. **Eight** studies in **7**
20 cohorts (**2** from **high-income countries**, **5** from **low-middle income countries**) met the
21 inclusion criteria for short-term (mean age: 13.4 months) and/or longer-term (mean age: **11.1**
22 years) health outcomes of catch-up **growth** which had occurred by 24 or 59 months. Of 5
23 studies on short-term health outcomes, 3 found positive associations between weight catch-up
24 **growth** and body mass and/or glucose metabolism; 1 suggested reduced risk of hospitalisation
25 and mortality with catch-up **growth**. **Three** studies on longer-term health outcomes found
26 catch-up **growth** was associated with higher body mass, **BMI**, or cholesterol. GRADE
27 assessment suggested that evidence quantity and quality were low. Catch-up growth
28 following LBW may have benefits for the individual with LBW in the short term, and may
29 have adverse population health impacts in the long-term, but the evidence is limited. Future
30 cohort studies could address the question of the consequences of catch-up **growth following**
31 **LBW** more convincingly, with a view to informing future prevention of obesity and NCDs.

32

33 **Keywords:** obesity; NCDs; infant feeding; catch-up growth; low birthweight.

34 **Key Messages**

- 35 • Some evidence supports the view that early life catch-up growth (compared to no
36 catch-up growth) following LBW is beneficial in the short-term, but harmful in the
37 long-term
- 38 • The evidence base is small (8 eligible studies), relatively low quality, and not entirely
39 consistent
- 40 • Making a strong case for the avoidance of catch-up growth as a target of NCD and
41 obesity prevention strategy would not be evidence-based at present

42

43 INTRODUCTION

44 Low birth weight (LBW), defined by the WHO as a birth weight <2500g (UNICEF, WHO
45 2004), is common, particularly in low-middle income countries (LMICs). It is clear that LBW
46 typically leads to poor health outcomes. Conservative estimates of LBW prevalence made by
47 UNICEF and the WHO in 2004 suggested that at least 16% of births globally were LBW,
48 with around 96% of these in LMICs (UNICEF, WHO 2004).

49 Accelerated postnatal ‘catch-up’ growth (in length, weight, or both) is a common
50 compensatory mechanism for LBW, which occurs typically in the first 24 months of postnatal
51 life (Crowther et al 1998; Jaquet et al 2005). It is believed that catch-up growth is beneficial
52 for the individual in the short-term (Victora et al 2001), but may create public health
53 problems in the long-term because it may be associated with metabolic disturbances which
54 increase the risk of some non-communicable diseases (NCDs) and obesity (Kramer et al
55 2014; Jain et al 2012). It is believed that early catch-up growth, before around the age of two
56 years, is beneficial for long-term health outcomes, but catch-up growth which occurs later
57 [than around 2 years](#) increases risk of later obesity and NCDs (Victora et al 2008), but this
58 evidence has not focused on individuals with LBW and has not been subject to systematic
59 review and evidence appraisal. The extent to which catch-up growth might influence short-
60 term and long-term outcomes following LBW is therefore a major public health nutrition
61 question, of particular importance for obesity and NCD prevention in LMICs.

62 Whether, and to what extent, catch-up growth following LBW in early life should be
63 considered in future policy responses to the obesity and NCD crisis depends on the quantity,
64 quality, and consistency of the evidence relating catch-up growth following LBW to short-
65 term and long-term health outcomes. No previous systematic review has considered
66 differences in health outcomes following LBW in those with catch-up growth versus those
67 without catch-up growth. One review (Nobili et al 2008), generated from a literature search in
68 a single database, compared the effect of catch-up growth in LBW versus non LBW
69 individuals, but did not compare outcomes for individuals born LBW with catch-up growth
70 versus those without catch-up growth. A recent analysis of data from five birth cohorts in
71 LMICs, not focused specifically on those born LBW, suggested that catch-up growth after
72 two years of age would increase later risk of obesity and NCDs (Adair et al 2013).

73 The primary aim of this study was therefore to examine the impact of catch-up growth
74 (versus no catch-up growth) on health outcomes in those born LBW. A secondary aim was to
75 critique the available evidence, identifying gaps and weaknesses, so that future studies might
76 permit a more confident assessment of the impact of catch-up growth following LBW, as part
77 of a more evidence-informed global approach to NCD and obesity prevention in the future.

78

79 **METHODS**

80 **Eligibility criteria: studies; study participants; exposures and outcomes**

81 All study designs were eligible for inclusion in this review so long as they provided data for
82 infants and children where catch-up growth occurred prior to 59 months, with a history of
83 LBW as defined by the WHO (birth weight < 2500g)-only studies with participants who had
84 a history of LBW as defined by WHO were included. Definitions of catch-up growth vary

85 between studies, and no international standard has been established. Study eligibility was
86 therefore not limited by the definition of catch-up [growth](#) used, and studies were included so
87 long as catch up growth was defined (including definitions based on Weight-for-age; Height-
88 for-age; Weight-for-height).

89 The following outcomes were considered: direct measures of adiposity and proxies for
90 adiposity; blood pressure; fasting blood glucose; impaired glucose tolerance; elevated
91 glycosylated haemoglobin (HbA1c); insulin and insulin resistance; total blood cholesterol,
92 triglycerides, lipoprotein levels (low density lipoprotein – LDL, high density lipoprotein –
93 HDL), and cardio-metabolic risk scores which included any or all of the above indicators.
94 Eligible measures of cardiovascular events were angina pectoris, stroke, myocardial infarct,
95 and mortality. Risk of diabetes type 2 was also included.

96 **Search methods for identification of studies**

97 We searched the following electronic databases on 6 August 2014: MEDLINE (1946 to July
98 week 4 2014); EMBASE (1974 to 2014 week 31); Global Health (1910 to 2014 week 30);
99 CINAHL plus (1983 to August 2014); Cochrane Library (up to issue 7 of 12 July 2014);
100 ProQuest Dissertations & Theses (1980 to August 2014). The journal Bulletin of the World
101 Health Organisation was searched in Pubmed Central (1948 to 1st June 2014), and a hand
102 search of the WHO South-East Asian Journal of Public Health and the publication lists of
103 birth cohorts listed at <http://www.birthcohorts.net/> was performed. In addition, we examined
104 reference lists and citations of relevant studies. [A search for new studies which had cited](#)
105 [eligible studies was carried out in November 2015, but produced no additional eligible](#)
106 [studies](#). Keywords were searched as subject headings indexed in databases and as free-text
107 terms. Booleans were used to refine the search. The search strategy for Medline is given
108 below (Figure 1). Controlled vocabulary and search syntax were modified as appropriate
109 when searching other databases. [Only studies in the English language were included.](#)

110

111 **Data collection, management, and analysis**

112 *Selection of studies*

113 AM and AC screened and cross-checked titles and abstracts **independently** to identify
114 potentially relevant studies based on the above criteria. Full text reports of potentially
115 relevant studies were assessed for eligibility independently by two reviewers (AM, JJR).
116 Discrepancies were resolved by discussion and where needed, RMB arbitrated. A list of
117 excluded studies was generated and reasons for exclusion recorded.

118 *Data extraction and management*

119 We used a standardised protocol for extracting relevant information from the studies. Data
120 extraction was performed **independently** by two reviewers (AM and JJR) who resolved any
121 differences by discussion.

122 *Quality assessment of included studies*

123 Quality of included studies was assessed independently by AM and JJR, cross-checked and
124 discussed to resolve disagreement where required. We used the 10-item risk of bias
125 assessment tool from the Agency for HealthCare Research and Quality (Viswanathan et al
126 2013) to assess study quality formally.

127 *Assessment of publication bias*

128 If the number of included studies allowed (≥ 10 studies), we aimed to assess reporting bias by
129 using a funnel plot.

130 *Data synthesis and quality assessment of evidence*

131 Available data were not suitable for meta-analysis, with the exception of two studies which
132 examined weight-for-age and height-for-age catch-up associations with fasting insulin (see

133 below). Weighted mean differences of insulin levels between children with and without
134 catch-up growth were combined using random effect models to account for unobserved
135 variables. Review manager 5.3 was used for data synthesis (RevMan 2014). Where studies
136 were considered insufficiently similar to each other to be combined in a meta-analysis, results
137 were described by timing of outcome (short-term-up to the age of 5 years; longer-term after 5
138 years). Estimates of effects were summarised in the GRADE Evidence Profile (Brozek 2008)
139 along with the quality rating of the evidence.

140 Where studies did not report the statistical significance of the group difference (between
141 those with a history of LBW with catch-up growth vs. those with a history of LBW without
142 catch-up growth), and where data were available, data were re-analysed to determine
143 significance of a group difference using inverse variance and random effect models.

144

145 **RESULTS**

146 **Search outcomes**

147 The searching and screening process is summarised in Figure 2. The literature search yielded
148 881 records, of which 283 were duplicates. Titles and abstracts of 598 records were screened,
149 resulting in 98 records for full-text screening (86 papers and 12 abstracts). Independent
150 screening and cross-checking (AM, JJR) identified eight eligible studies for inclusion; 90
151 records did not meet the inclusion criteria and thus were excluded. Reasons for exclusion are
152 listed in Figure 2.

153 **Characteristics of included studies**

154 Included studies are summarised in Table 1a and 1b for short-term and longer-term outcomes,
155 respectively.

156 *General study characteristics.* Of the **eight** studies (**7** cohorts), **five** were prospective and
157 three were cross-sectional. Evidence was available from **two** studies in high income countries
158 and six (**from five cohorts**) from LMICs.

159 *Population.* The total number of children studied was **535** (**short-term health outcomes**; Table
160 **1a**) and **553** (**longer-term health outcomes**; Table 1b). LBW was defined by individual studies
161 as: birth weight or length < 10th percentile of a sex and gestational age specific reference
162 (Horta et al 2003; Han et al 2010; Rustogi et al 2013; Victora et al 2001); weight < 5th
163 percentile for gestational age (Soto et al 2003; Rustogi et al 2013); weight and/or length <
164 2SD below means for gestational age (Tenhola et al 2000); birthweight<2500g (**Khandelwal**
165 **et al 2014; Mai et al 2005**). **In all of the eligible studies participants met the WHO definition**
166 **of LBW**. Attrition rates of participants ranged from 16% to 86% with a median of 27%. Two
167 studies did not report how many children were lost to follow-up (Han et al 2010; Rustogi et al
168 2013).

169 *Exposure.* Dichotomous definitions of catch-up **growth** (comparing those who ‘caught-up’
170 with those who did not) were used, but with **different cut-offs to distinguish between those**
171 **who caught up and those who did not**: weight and/or height gain of ≥ 0.67 z-scores
172 (Khandelwal et al 2014; Rustogi et al 2013; Soto et al 2003; Victora et al 2001; Horta et al
173 2003), or weight or height z-score increase from birth-follow-up of ≥ 2 (Tenhola et al 2000) or
174 >0 (Han et al 2010). All included studies reported outcomes related to weight catch-up
175 **growth**, while three also reported on height/length catch-up **growth** (Han et al 2010; Rustogi
176 et al 2013; Soto et al 2013) and one provided additional data on weight-for-height catch-up
177 **growth** (Rustogi et al 2013). **Seven** studies reported on catch-up growth up to the age of 24
178 months and three studies included children who caught up after 24 months.

179 *Comparison.* All but three studies reported the impact of catch-up growth on markers of
180 obesity or NCD risk compared to children who did not catch-up. Three studies provided data
181 on the impact of change in weight z-scores between two time points on obesity, NCD risk, or
182 risk or markers of NCDs (Horta et al 2003; Khandelwal et al 2014; Mai et al 2005).

183 *Outcomes.* Of the nine eligible studies, 5 tested for associations between catch-up growth and
184 early health outcomes (Han et al 2010; Khandelwal et al 2014; Rustogi et al 2013; Soto et al
185 2003; Victora et al 2001; early outcomes defined here [and pre-specified](#) as aged < 5 years),
186 while 4 tested for associations between catch-up growth and later health outcomes (Horta et
187 al 2003; Mai et al 2005; Tenhola et al 2000; Victora et al 2001; later defined [here and pre-](#)
188 [specified](#) as aged \geq 5 years); one of the eligible studies included both short-term and longer-
189 term outcomes (Victora et al 2001). The following NCD risk factors were assessed: BMI
190 (Mai et al 2005; Soto et al 2003; [percentage fat](#) (Khandelwal et al 2014); [glucose metabolism](#)
191 (Han et al 2010; Rustogi et al 2013; Soto et al 2013); [blood pressure](#) (Horta et al 2003);
192 [plasma cholesterol](#) (Tenhola et al 2000); [hospital admissions and mortality](#) (Victora et al
193 2001).

194 **Quality appraisal of included studies**

195 Overall, the quality across all included studies was low. Only two studies met five (i.e. low
196 risk of bias) out of the 10 quality criteria; the remaining studies met less than five quality
197 criteria. Attrition bias (applicable for cohort studies only) and selective reporting bias, were
198 not addressed by included studies, and bias due to confounding was only rarely addressed.

199 *Selection bias.* None of the included studies were at risk of selection bias. Children with or
200 without catch-up growth were from the same cohort and thus quality item 2 was not
201 applicable (differing recruitment strategy for individuals).

202 *Detection bias.* All studies failed to provide adequate details on whether the assessor was
203 blinded to the exposure or outcome and thus the studies were judged to be of ‘unclear’ risk of
204 bias. Six out of nine studies used valid and reliable measures of exposure and outcome and
205 thus were of low risk of bias. However, three studies were judged as ‘unclear’ as insufficient
206 information was reported (Horta et al 2003; Rustogi et al 2013; Victora et al 2001).

207 *Attrition bias.* Attrition bias was not applicable in the longitudinal studies which used cross-
208 sectional analyses (Han et al 2010; Rustogi et al 2013; Soto et al 2003). The remaining
209 prospective studies showed no differences in follow-up time between comparison groups.
210 However, **three** of the prospective studies did not assess the impact of attrition which was
211 high (>20%), **with potential** to bias the outcome (Horta et al 2003; Khandelwal et al 2014;
212 Tenhola et al, 2000). Thus these studies were at high risk of attrition bias. A further two
213 studies did not assess the impact of attrition; however, their attrition rates were low and so
214 less likely to bias the results (Mai et al 2005; Victora et al 2001). Therefore, the risk of
215 attrition bias was low.

216 *Selective reporting bias.* The majority of studies did not refer to a published study protocol
217 which would allow assessment of whether all predetermined outcome measures were
218 reported. Thus for these studies the risk of selection bias was judged to be ‘unclear’ (Han et al
219 2010; Horta et al 2003; Mai et al 2005; Rustogi et al 2013; Victora et al 2001). For **three**
220 studies it was possible to determine that relevant outcomes were not reported (Khandelwal et
221 al 2014; Soto et al 2003; Tenhola et al 2000) thus the risk of selective reporting was judged to
222 be high. Assessment of missing adverse events or harms was not applicable to all included
223 studies.

224 *Bias due to confounding.* **One** study took known confounding factors into account when
225 analysing the association between catch-up growth and non-communicable disease risk

226 factors and so was judged to be of low risk of confounding bias (Horta et al 2003). The
227 remaining studies did not account for confounders and were therefore considered to be at
228 high risk of bias.

229 **Synthesis of evidence**

230 Most studies showed a high level of heterogeneity in terms of study design, length of follow-
231 up, definition of the catch-up growth, timing of catch-up growth, and outcomes assessed.
232 Therefore, a quantitative synthesis of the evidence in a meta-analysis was not suitable except
233 for one outcome measure. The evidence is described largely narratively by timing of outcome
234 assessment below.

235 *Short-term outcomes of catch-up growth in LBW children*

236 Of the studies that provided data on short-term outcomes, all referred to weight catch-up
237 growth; only two studies (Rustogi et al 2013; Soto et al 2003) assessed the association of
238 length/height catch-up growth on short-term health. Findings for weight and/or length catch-
239 up growth can be found in Table 1a (by study) and 2a (by outcome). Reported short-term
240 outcomes were hospital admission, body mass and glucose metabolism up to the age of 30
241 months, the mean age at outcome measurement was 13.4 months.

242 One study suggested that catch-up growth was associated with reduced risk of hospitalisation:
243 hospitalisation (all-cause) was significantly lower in children with catch-up growth (n=304)
244 compared to children without (n=25; Victora et al 2001). Two studies found significantly
245 higher fat mass by 5.7% (95%CI 0.0 to 11.4%; n=27; Khandelwal et al 2014) and BMI by
246 1.30 kg/m² (95%CI 1.20 to 1.40 kg/m², n=85; Soto et al 2003) in children with catch-up
247 growth compared to children without catch-up growth at 3 and 12 months, respectively.
248 Three studies assessed the association between catch-up growth and glucose metabolism

249 (fasting glucose or insulin or insulin sensitivity; Han et al 2010; Rustogi et al 2013; Soto et al
250 2003). One study found no association between catch-up **growth** and fasting glucose (Han et
251 al 2010). Meta-analysis of the other two studies indicated higher fasting insulin levels of 2.54
252 uIU/ml (95% CI 2.33 to 2.76 uIU/ml, $p < 0.001$, $I^2 = 0\%$) in children with weight catch-up
253 growth (n=50) compared to the no weight catch-up **growth** group (n=54). Individual study
254 findings on the association between height catch-up **growth** and fasting insulin were
255 inconclusive. However, pooled mean differences showed higher fasting insulin levels of 2.00
256 uIU/ml (95%CI 1.70 to 2.29 uIU/ml, $p < 0.001$, $I^2 = 0\%$) in children with height/length catch-up
257 growth. Insulin sensitivity was more impaired in children without weight and/or height catch-
258 up **growth** compared to children that showed weight and/or height catch-up growth at 3
259 months (Rustogi et al 2013) and 12 months (Soto et al 2003, Table. 2a).

260 ***Longer-term outcomes of catch-up growth in LBW children***

261 Longer-term outcomes were available for weight catch-up growth from all studies and for
262 height catch-up growth by one study (Tenhola et al 2000). Reported longer-term outcomes
263 between 5-15 years (mean age 10.2 years) were mortality, body mass index, blood pressure,
264 and cholesterol levels. Findings are summarized for each study in Table 1b and by outcome
265 in Table 2b.

266 Based on one single study (Victora et al 2001), mortality by the age of 5 years was (non-
267 significantly) lower in children with catch-up growth compared to those with no catch-up
268 **growth**. BMI at age 12 years was significantly correlated with changes in weight z-scores
269 between birth and 6 months and between birth and 18 months (n=74). The correlation
270 coefficients were 0.34 and 0.24, respectively (Mai et al 2005). There was no evidence of a
271 significant association between catch-up growth and diastolic blood pressure at 15 years in
272 one study (n=101; Horta et al 2003). Children with height (not weight) catch-up growth

273 (n=21) had a 13.8 fold (95%CI 2.0 to 97.5) increased risk of high total cholesterol levels of >
274 4.8 mM/L at 12 years compared to children without catch-up growth (n=35; Tenhola et al
275 2000).

276 **Quality and consistency of evidence**

277 The GRADE evidence profiles for short- and long-term outcomes are summarised in Table
278 2a and b, respectively. The quality of evidence was very low for the outcomes [percent body](#)
279 [fat](#), BMI, glucose levels, insulin levels, insulin sensitivity, systolic and diastolic blood
280 pressure, [risk of high cholesterol levels for height catch-up growth](#) and low for hospital
281 admissions and mortality. The reason for the grades of very low to low quality was because
282 evidence was available from predominantly low quality observational studies only. Evidence
283 inconsistency could not be adequately assessed because for [almost all](#) outcomes only one or
284 two studies were eligible.

285

286 **DISCUSSION**

287 **Main study findings and implications**

288 The present study found a relatively small body of evidence of low to very low quality
289 according to AHRQ and GRADE methodology which addressed the question of the impact of
290 catch-up growth (versus no catch-up [growth](#)) in LBW infants on short-term and longer-term
291 health outcomes. No previous systematic review addressed this research question. [For some](#)
292 [of the studies the main research questions were not the same as the research questions](#)
293 [addressed by the present review. In addition, for studies conceived, conducted, and/or](#)
294 [reported prior to the recent widespread use of AHRQ and GRADE methodology, low study](#)

295 quality was likely due in part to the age of the studies and lack of awareness of the
296 methodology.

297 Consistency of the evidence is hard to assess because, for almost all of the outcomes, only
298 single studies were available. With limited quantity and quality of evidence, and uncertainty
299 over the consistency of the evidence, it cannot be concluded that catch-up growth following
300 LBW increases risk of adverse cardio-metabolic health in later life. Long-term outcome data,
301 in adults, were missing.

302 **Limitations of the review**

303 Meta-analysis of the studies identified in the present review was limited to one outcome and
304 only two studies because of substantial heterogeneity between studies and lack of data on the
305 same outcome measure. Publication bias could not be assessed formally because the number
306 of eligible studies was too small. It may be of note that included studies reported both
307 significant and non-significant associations of catch-up growth versus no catch-up growth on
308 health outcomes of relatively small participant number. Thus the presence of publication bias
309 on the grounds of effect sizes and study impact is less likely. We had planned subgroup-
310 analyses, e.g. examining differences by age, exposure characteristics such as being LBW as a
311 result of being born too small for gestational age or appropriate for gestational age, gender,
312 setting, study design, and sensitivity analyses (synthesizing all of the available evidence and
313 then only those studies deemed to have low risk of bias), but the small number of eligible
314 studies, and their heterogeneity, precluded such analyses. This review focused solely on
315 research published in English language, and thus potentially relevant studies published in
316 other languages might have been missed. Translating records into English language was not
317 feasible for this review.

318 **Limitations of the evidence base and implications for future research**

319 The research question asked by the present review is an important one for global public
320 health nutrition, regardless of whether or not it can be answered with any great confidence at
321 present. In order to answer it with evidence of higher quality, future research should address
322 [the issues summarised in table 3](#). Namely, (i) many of the eligible studies made no reference
323 to study power; (ii) many failed to take into account confounders, despite potentially
324 important differences between those with catch-up [growth](#) versus no catch up [growth](#) (e.g.
325 greater prevalence or severity of morbidity in the latter); (iii) many studies did not account
326 for attrition; (iv) substantial heterogeneity in the definitions of catch-up make it difficult to
327 understand what exposure actually matters (iv) there was substantial heterogeneity inherent in
328 the exposure. The LBW definition included individuals of widely varying birth weight,
329 timing of catch-up [growth](#) will have varied, [and includes both those born too early and those](#)
330 [born too small- an important distinction \(Lapillone and Griffin 2013\)](#) which was made by
331 [some studies \(Table 1\) but not all](#).

332 A large number of ineligible studies compared catch-up growth of LBW children with growth
333 of children born at or above 2500g (Figure 2). Studies which were excluded because they did
334 not meet the comparison group criterion might have suitable data available to answer the
335 research question asked by the present study. [Some studies which did not meet our inclusion](#)
336 [criteria for other reasons can also provide useful evidence](#). Kramer et al (2014) did not
337 compare formally between those who showed catch-up growth versus those who did not, but
338 [noted that those who caught-up had slightly higher adiposity than those who did not](#). In one
339 [large study from the USA Hemachandra et al \(2007\) treated catch-up growth as a continuous](#)
340 [exposure variable, with no comparison between those who showed catch-up growth versus](#)
341 [those who did not \(so was ineligible here\), but reported that those with higher gains in weight](#)
342 [z score in infancy and early childhood had significantly increased risk of high blood pressure](#)
343 [at age 7 years](#).

344

345 There is a need for a clearer understanding of the nature and timing of the exposure of catch-
346 up, more evidence on the short-term and long-term impacts of catch-up [growth](#) versus no
347 catch-up growth in LBW infants, and whether the consequences of catch-up vary between
348 children with a history of LBW versus those without. Researchers with access to existing (or
349 planned cohorts) might consider this research question in future in order to address the
350 evidence gaps identified by this review. Specific questions, such as the importance of the
351 precise timing or rate of catch-up [growth](#), the relative importance of length versus weight
352 catch-up [growth](#) , whether health outcomes of catch-up [growth](#) differ for those born too early
353 versus those born too small, and the mechanisms which relate catch-up [growth](#) to later health
354 outcomes, could not be answered.

355

356 **Conclusions**

357 In summary, the present study has found some evidence that catch-up growth in those born
358 LBW is beneficial relative to no catch-up in the short-term. The longer-term population
359 health impact of catch up [growth](#) (versus no catch up [growth](#)) in those born LBW is less
360 clear. Major weaknesses and gaps in the evidence, combined with the importance of the issue
361 of catch-up [growth](#) to global population health, demonstrate that further studies, or
362 secondary analyses of available data, are required urgently.

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366

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442 **Figure Legends**

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444 **Figure 1**

445 Search Strategy in Medline (ovid)

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447 **Figure 2**

448 Literature Search: Study Flow Diagram

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Table 1a: Characteristics and short-term health outcomes of included studies

Study ID	Study characteristics					Participant characteristics			Exposure- catch-up growth			Outcome							
	Study design	Study location	Recruitment setting	Exclusion criteria	Attrition rates	Low BW/SGA definition	Mean BW	Term / preterm	Definition	Type	Timing	Outcome measure	Time point	No catch-up group		Catch-up group		p-value of difference	Confounders
Han 2010	Cross-sectional	Peking, China	Third Hospital, Peking University	not singletons, gestational age <33wks, non SGA, 1-min Apgar score <7, 5 min Apgar score <10, intrauterine infections, congenital malformations, major neonatal problems, breastfed <3 months, mothers with diabetes, gestational diabetes, chronic hypertension	29%	below <10th percentile of the sex specific distribution for gestational age using birth weight standards of Chinese	1996.59g (353.15)	gestational age of >33 weeks (mean 36.46 SD:2.38wk)	The change of weight Z-score during the 3 months > 0 Z-score was defined as catch-up growth	weight	3 mo	Fasting glucose (mmol/L)	3mo	n=12	Mean (SD): 4.18 (0.58)	n=32	Mean (SD): 4.32 (0.64)	0.528	none
												Insulin sensitivity (HOMA)	3mo	n=12	4.15 (2.96)	n=32	2.11 (1.06)	0.356	
Khandelwal 2014	Prospective cohort study	India	not reported	birth weight <1500 g, breast feeding not possible, requirement of intravenous fluids, antibiotics, oxygen or NICU stay for more than 24 h at birth, major congenital malformations, stigmata of intrauterine infections, genetic syndromes or chromosomal anomalies and residence more than 40 km from the study site	50%	BW <2500g	2175 ± 180g, z-score -2.67 ± 0.49	term: gestational age between 37 and 42 weeks	Changes in weight z score between birth and the follow up visits	Weight	1.4 mo	FM%	7.2 mo	n=33	β= -2.91, 95%CI -0.88 to 6.70		0.13	gender, current age and current length	
											3 mo		7.2 mo	n=33	β=5.00, 95%CI 0.67 to 9.33		0.03		
											7.2mo		7.2 mo	n=33	β=5.42, 95%CI 1.43 to 9.43		0.01		
											1.4 mo		7.2 mo	n=14	Mean (SD) = 12.8 (7.6)	n=6	Mean (SD)= 21.4 (7.5)		0.06
											3 mo		7.2 mo	n=14	Mean (SD)= 12.8 (7.6)	n=13	Mean (SD)= 18.5(7.5)		Not reported
Rustogi 2013	Cross-sectional study	India	not reported	not reported	not reported	weight or length < 10th percentile	not reported	term	gain in weight/ length SDS or both of >0.67	weight	12-18 mo	fasting insulin (uIU/ml)	12-18mo	n=32	Mean (SD)= 3.0 (2.5)	n=18	Mean (SD)= 7.3 (9.2)	0.01	none
										length	12-18 mo	fasting insulin (uIU/ml)	12-18mo	n=25	Mean (SD) = 3.2 (2.2)	n=25	Mean (SD)= 5.9(8.3)	0.2	none
										weight / height	12-18 mo	fasting insulin (uIU/ml)	12-18mo	n=20	Mean (SD)= 2.8 (1.9)	n=30	Mean (SD)= 5.8 (7.6)	0.06	none
Soto 2003	Cross-sectional	Chile	neonatal units of Hospital San Borja Arriaran and Hospital So'tero del Rí'o	significant medical, neurological, or genetic conditions, on unusual diets or were taking any medication that could interfere with growth or appetite	Not reported	birth weight <5th percentile for gestational age, using Chilean birth weight standards	2.1 SDS ± 0.1	term: Gestational age 37-41wks	weight/lengths gain, between zero and 1 yr, greater than 0.67 SDS	weight	1y	BMI (kg/m ²)	1y	n=22	Mean (SD)= 15.9 (0.2)	n=63	Mean (SD)= 17.2(0.2)	<0.001	none
												fasting insulin (pmol/L)		n=22	Mean (SD): 14.9 (2.3)	n=63	Mean (SD)= 32.6 (4.6)	<0.001	
												Insulin sensitivity AUC (pmol/minxL)		n=22	Mean (SD)= 2215.4(461.6)	n=63	Mean (SD)= 2302.6	0.4	
												Insulin sensitivity (1 st phase insulin release - pmol/L)		n=22	Mean (SD)= 303.5 (91.2)	n=63	Mean (SD) = 298.8 (46.4)	0.82	
												BMI (kg/m ²)		n=41	Mean (SD)= 16.8(0.2)	n=44	Mean (SD)= 16.8(0.2)	1	
												fasting insulin (pmol/L)		n=41	Mean (SD)= 20.9 (2.1)	n=44	Mean (SD)= 34.6(6.5)	<0.001	
												Insulin sensitivity AUC (pmol/minxL)		n=41	Mean (SD)= 1767.6(199)	n=44	Mean (SD)= 2790.8 (400.9)	<0.001	
Victoria 2001	Prospective cohort study	Pelotas, Brazil	households	not reported	15%	BW <10th centile of weight for gestational age of the Williams curve	not reported	not reported for SGA	weight change in z-scores >=0.66 from birth to 20 months	weight	20 mo	All-cause Hospital admissions	30 mo	n=25	Proportion of children 16.00%	n=304	5.60%	Not reported	family income, maternal schooling, age
												Diarrhoea - hospital admissions		n=25	0.00%	n=304	0.00%	Not reported	
												Lower respiratory infections - hospital admissions		n=25	4.00%	n=304	2.30%	Not reported	none

BW: birth weight, SGA: small-for-gestational age, mo: months, y: year, B: unstandardized regression coefficient, β: standardized regression coefficient, OR: odds ratio, SD: standard deviation, CI: Confidence interval

454 Table 1b: Characteristics and long-term health outcomes of included studies

Study ID	Study characteristics					Participant characteristics			Exposure- catch-up growth			Outcome						
	Study design	Study location	Recruitment setting	Exclusion criteria	Attrition rates	Low BW/SGA definition	Mean BW	Term / preterm	Definition	Type	Timing	Outcome measure	Time point	No catch-up group	Catch-up group	p-value of difference	Confounders	
Horta 2003	prospective cohort study	Pelotas, Brazil	5 maternity hospitals	not reported	86%	< 10th centile for gestational age and sex, according to the reference developed by Williams et al	not reported	not reported for SGA	Changes in weight z score between birth and the follow up visits	weight	20 mo	systolic blood pressure	15y	total n= 101	B= -0.49; 95% CI -4.80 to 3.82		not reported	family income, duration of breast feeding, gender, maternal height, and maternal smoking during pregnancy
											42 mo				B= 1.86, 95%CI -2.91 to 6.64			
											20 mo				B= -0.01; 95% CI - 4.21 to 4.20			
											42 mo				B=-0.32, 95% CI -4.98 to 4.34			
Mai 2005	prospective cohort	Sweden	hospitals	not reported	16%	VLBW <1500g	not reported	not reported	changes of SDS in weight between postmenstrual age of 40 wk and follow up time points (6 months, 18 months)	weight	6 mo	12y	n=74	correlation: $\rho = 0.34$		<0.01	None	
											18mo			12y	n=74			correlation: $\rho = 0.24$
Tenhola 2000	Prospective cohort study	Finland	Kuopio University Hospital	Metabolic Disease	25%	birth weight and/or length and/or ponderal index <2 SD score below the respective mean for the gestational age	median 2452g (2367, 2537)	term	weight or height increase ≥ 2 SD score between birth and 5y	weight	5y	high cholesterol levels (> 4.8 mM)	12y	total n=34	OR 0.3, 95% CI 0.1 to 1.9	OR 1.0	0.3	none
										height	5y							
Victora 2001	Prospective cohort study	Pelotas, Brazil	households	not reported	15%	BW <10th centile of weight for gestational age of the Williams curve	not reported	not reported for SGA	Weight change in z-scores ≥ 0.66 from birth to 20 months	weight	20 mo	mortality	5y	Total n=329	75% lower in catch-up group		Not significant	none

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456 BW: birth weight, SGA: small-for-gestational age, mo: months, y: year, B: unstandardized regression coefficient, β : standardized regression coefficient, OR: odds ratio, SD: standard deviation,
 457 CI: Confidence interval

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465 Table 2a: GRADE evidence profile for short-term outcomes of catch-up growth

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Catch-up growth	No catch-up growth	Relative (95% CI)	Absolute	
Percentage fat mass – weight catch-up at 3 months (follow-up 5.8 months)											
1	observational study	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	13	14	-	MD 5.7% higher	⊕○○○ VERY LOW
Body Mass Index - weight catch-up at 12 months											
1	observational study	serious ³	no serious inconsistency	no serious indirectness	no serious imprecision	none	63	22	-	MD 1.30 kg/m ² higher (1.20 to 1.40 higher)	⊕○○○ VERY LOW
Body Mass Index - height catch-up at 12 months											
1	observational study	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	44	41	-	MD 0.00 kg/m ² higher (-0.09 to 0.09)	⊕○○○ VERY LOW
Fasting glucose - weight catch-up at 3 months											
1	observational study	serious ⁴	no serious inconsistency	no serious indirectness	no serious imprecision	none	32	12	-	MD 0.14 mmol/L higher	⊕○○○ VERY LOW
Insulin sensitivity levels - weight catch-up 3 months (HOMA) and 12 months (AUC)											
2	observational studies	serious ¹	no serious inconsistency	no serious indirectness	serious ⁵	none	95	34	-	HOMA: MD 2.04 higher AUC: MD 87.2 pmol/minL lower	⊕○○○ VERY LOW

Fasting insulin levels - weight catch-up at 12 – 18 months											
2	observational studies (cross-sectional)	serious ³	no serious inconsistency	no serious indirectness	no serious imprecision	none	50	54	-	Not pooled: mean ranged from 2.6 to 4.3 uIU/ml higher	⊕○○○ VERY LOW
Hospital admission - weight catch-up at 20 months (follow-up mean 10 months)											
1	observational study	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	304	25	-	10.4 % lower	⊕⊕○○ LOW

466 ¹ Studies did not account for attrition and confounding variables, there was evidence of selective outcome reporting. ² Wide confidence intervals indicate imprecision, The sample size was low. ³ Study did not account
467 for confounders and selective reporting of outcomes was evident. ⁴ Study did not account for confounding variables. ⁵ Low sample size in the comparison group is likely to add imprecision to the overall effect.

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480 Table 2b: GRADE evidence profile for long-term outcomes of catch-up growth

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Catch-up growth	No catch-up growth	Relative (95% CI)	Absolute	
Body Mass Index - weight catch-up at 6 and 18 months (follow-up 10.5-11.5 years)											
1	observational study	serious ¹	no serious inconsistency	serious ²	no serious imprecision	none	74		-	Correlation 0.34 to 0.24 higher	⊕○○○ VERY LOW
Systolic blood pressure - weight catch-up at 20 months (study 2) (follow-up mean 13.3 years)											
1	observational study	serious ³	no serious inconsistency	serious ²	serious ⁵	none	101		-	B=0.49 mmHG lower (-4.80 to 3.82)	⊕○○○ VERY LOW
Diastolic blood pressure - weight catch-up at 20 months (follow-up mean 13.3 years)											
1	observational study	serious ³	no serious inconsistency	serious ²	serious ⁵	none	101		-	B=0.01 mmHG lower (-4.21 to 4.2)	⊕○○○ VERY LOW
Systolic blood pressure - weight catch-up at 42 months (study 2)											
1	observational study	serious ³	no serious inconsistency	serious ²	serious ⁵	none	101		-	B=1.86 mmHG higher (-2.91 to 6.64)	⊕○○○ VERY LOW
Diastolic blood pressure - weight catch-up at 42 months (follow-up mean 12.5 years)											
1	observational studies	serious ³	no serious inconsistency	serious ²	serious ⁵	none	101		-	0.32 lower (4.98 lower to 4.34 higher)	⊕○○○ VERY LOW
Cholesterol levels - weight catch-up at 59 months (follow-up mean 7 years)											
1	observational studies	serious ³	no serious inconsistency	no serious indirectness	no serious imprecision	none	21/55 (38.2%)	34/55 (61.8%)	OR 0.3 (0.1 to 1.9)	291 fewer per 1000 (from 479 more to 136 more)	⊕○○○ VERY LOW

Cholesterol levels - height catch-up at 59 months (follow-up mean 7 years)											
1	observational studies	serious ³	no serious inconsistency	no serious indirectness	serious ⁵	strong association ⁶ reduced effect for RR >> 1 or RR << 1	20/55 (36.4%)	35/55 (63.6%)	OR 13.8 (2 to 97.5)	324 more per 1000 (from 141 more to 358 more)	⊕○○○ VERY LOW
Mortality – weight catch-up at 59 months (follow-up mean 3.3 years)											
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	304	25	-	75% lower (3 vs 13 less per 1000)	⊕⊕○○ LOW

481 ¹ Study did not account for confounding variables. ² Study assessed effect of change in weight z-score over time rather than effect of catch-up vs no catch-up. ³ Studies did not account for confounding and attrition. ⁴
482 Study assessed the effect of change in weight z-score rather than effect of weight catch-up vs no weight catch-up. ⁵ Wide confidence intervals indicate imprecision, the sample size was small. ⁶ Study reported a large
483 effect size.

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495 Table 3: Summary of research suggestions for population, exposure, comparison, outcomes and data analysis

Population	Exposure	Comparison	Outcomes	Data analysis
<p>More research on low birth weight infants needed</p> <p>More focus on subgroups within the low birth weight population (e.g. SGA and AGA)</p> <p>Increased sample size to increase statistical power</p> <p>Reporting of reasons of attrition (e.g. mortality, drop out, moving away)</p>	<p>Standardised definitions of length catch-up growth and weight catch up growth;</p> <p>More emphasis on trajectories of catch up;</p> <p>More emphasis on growth and anthropometric end points (e.g catch up growth to height or length within the healthy range vs. stunting)</p>	<p>Need for more research specifically comparing those with low birth weight and catch up growth vs LBW with no catch up growth</p>	<p>Need for more evidence on a range of outcomes, but particularly adult health outcomes</p>	<p>Multivariate regression analysis taking potential confounding variables into account</p> <p>Consideration of attrition and missing outcome data in data analysis</p>

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