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Low birthweight or rapid catch-up growth: which is more associated with cardiovascular disease and its risk factors in later life? A systematic review and cryptanalysis

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Background: The effects of birthweight (the Barker hypothesis) and growth trajectory in early life on the incidence of cardiovascular disease (CVD) and its risk factors in later life have been investigated in a number of studies.

Objective: To undertake a systematic review and cryptanalysis of the association of low birthweight (LBW) and the postnatal growth trajectory with CVD and its risk factors.

Methods: English-language publications in PubMed, ISI Web of Science and Scopus were searched. Initially, two independent reviewers identified relevant papers in several steps and the quality of papers was then determined by a validated quality-appraisal checklist.

Results: By applying maximum sensitivity, 7259 papers were identified, 382 of which were duplicates and 1273 were considered to be relevant to the topic. Then, after title and abstract review, 628 irrelevant papers were excluded; 26 papers were added after reference-checking. Then, 250 other papers were deleted after full text review. Finally, 39 relevant papers remained and were entered into the systematic review. Overall, 79.6% of all CVD risk factors reported in primary studies of the rapid catch-up growth hypothesis were statistically significant, whereas the corresponding figure was 58.5% for the effects of LBW (Barker hypothesis).

Conclusions: This systematic review highlights the importance of low birthweight in increasing the risk of CVD and its risk factors in later life. The results support rapid postnatal catch-up growth of LBW neonates as a more important factor than LBW alone in CVD and its risk factors.

Keywords: Low birthweight, Cardiovascular disease, Metabolic syndrome, Systematic review

Abbreviations

ACM	all-cause mortality;	HDL-C	high-density lipoprotein-cholesterol;
AGA	appropriate for gestational age;	HR	hazard ratio;
AIR	acute insulin response;	IR	insulin resistance;
β	regression co-efficient;	IUGR	intra-uterine growth retardation;
BMI	body mass index;	LBW	low birthweight;
BW	birthweight;	LDL-C	low density lipoprotein-cholesterol;
CDM	circulatory disease mortality;	MetS	metabolic syndrome;
CHD	coronary heart disease;	MS-R	metabolic syndrome risk factors;
CM	cardiovascular mortality;	NAFLD	non-alcoholic fatty liver disease;
CVD	cardiovascular disease;	NCD	non-communicable disease;
DBP	diastolic blood pressure;	OB	obesity;
FHD	family history of diabetes;	OR	odds ratio;
HBW	high birthweight;	OW	overweight;
		r	correlation co-efficient;
		SBP	systolic blood pressure;
		SDS	standard deviation score;
		SGA	small for gestational age;
		SW	stable weight;

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TC	total cholesterol;
TG	triglycerides;
WBWR	current weight (kg)/birthweight (kg);
WG	weight gain;
WF	weight fluctuation;
WHR	waist-hip ratio;
WL	weight loss;
Wt	weight

Introduction

Various factors such as lifestyle changes and longer life expectancy have led to a global increase of non-communicable diseases (NCDs) as the main causes of mortality and disease burden.^{1,2} It has been documented that the development of some chronic diseases originate in early life, and that these might be influenced by early life exposure to various risk factors.³ According to the fetal origin hypothesis, most NCDs are affected by growth retardation during sensitive periods of life, such as fetal life and infancy.^{4,5}

There is growing evidence of a strong relationship between low birthweight (LBW) and chronic disease in later life.^{6–11} The usual definition of LBW, i.e. ≤ 2 standard deviations (SD) of weight for gestational age, might not be applicable to all ethnic groups and races, and some prefer to define LBW as birthweight less than the tenth percentile for gestational age and gender.¹² While some concepts emphasise intra-uterine under-nutrition as the main factor, other studies postulate the role of postnatal growth trajectory as the important factor in the development of NCDs, mainly cardiovascular disease (CVD).^{13,14}

There are two hypotheses regarding the long-term health consequences of LBW, the 'Barker hypothesis' and the 'rapid catch-up growth hypothesis'. The Barker hypothesis suggests that intrauterine growth retardation (IUGR) is closely related to NCDs and their underlying factors such as the metabolic syndrome (MetS).^{13,14} The latter is defined as the co-existence of three of the five following components: elevated blood pressure, disturbed glucose metabolism, hypotriglyceridaemia, low high-density lipoprotein-cholesterol, and obesity; disturbed insulin metabolism is considered to be the underlying factor.⁷ The second hypothesis suggests that LBW *per se* does not increase the risk of NCDs, but only in small-for-gestational age (SGA) newborns who experience a rapid catch-up growth during the first years of life.^{15–21}

Given the importance of primordial/primary prevention of NCDs and conflicting ideas on early life origins of NCDs and their prenatal and postnatal determinants, this study aimed to systematically review evidence of the association of LBW and postnatal growth trajectory with CVD and cardiometabolic risk factors.

Methods

This was a systematic review and cryptanalysis of the association of LBW and rapid postnatal catch-up

growth of LBW newborns with CVDs and cardio-metabolic risk factors in later life.

Search strategy

The search was undertaken during March–May 2013 and included primary studies published electronically up to April 2013. PubMed, ISI Web of Science and Scopus were searched and only articles in English were retrieved. Main keywords and probable combinations of important words used for the search included: 'small for gestational age' OR 'intrauterine growth retardation' OR 'low birthweight' OR 'infant size' OR 'fetal under-nutrition' OR 'growth trajectory' OR 'growth velocity' OR 'growth spurt' OR 'catch up growth' OR 'rebound adiposity' OR 'fetal programming', AND 'cardiovascular disease' OR 'coronary artery disease' OR 'atherosclerosis' OR 'insulin resistance' OR 'metabolic syndrome X' OR 'dysmetabolic syndrome' OR 'Reaven syndrome'. In addition, reference lists of published studies were evaluated to increase the search sensitivity and select more studies. Search evaluation was undertaken randomly by two independent researchers and it was confirmed that no studies were excluded.

Studies selection

Titles and abstracts of papers were screened and relevant papers selected. The full texts of relevant papers were then read and their findings re-screened. Two independent reviewers (MM and FJ) screened the titles and abstracts of the papers identified by the literature search for potential relevance or assessed the full text for inclusion in the review. In the case of disagreement, the discrepancy was resolved in consultation with a third arbitrating investigator (RK). Entire texts or a summary of all searched articles, documents and reports were extracted. After reviewing and studying the titles, author(s), journal names and publication years, any duplications were excluded. To avoid cross-publication bias, the findings were reviewed to identify and eliminate duplicates. The full texts of the articles were then carefully studied by the researchers and relevant articles were selected and irrelevant ones excluded.

Quality evaluation

Having identified relevant studies in terms of title and content, a checklist (Appendix 1) was used to evaluate the quality of the documents. This included the study objective, study methods, sample size, sampling method, data collection tool, variables evaluation status, studied target group, and analysis status. These were examined using 12 questions (one score for every question), the maximum score being 12, and the minimum acceptable score being eight.²² Finally, articles with a score of eight or higher were selected and the relevant information extracted and analysed.

Inclusion eligibility

All studies of acceptable quality examining the association of either LBW or post-natal catch-up growth with CVD or cardiometabolic risk factors were included.

Exclusion eligibility

After reviewing and examining articles or abstracts of articles and resolving disagreements, the following studies were excluded: papers, documents and reports with unclear results, and studies reporting qualitative results. It was also decided to exclude abstracts with unavailable full texts, and thus the abstracts of dissertations, congresses and meetings were excluded.

Data extraction

Data were extracted in terms of article title, first author, publication year, total sample size, sample size according to gender, study setting, data source, data availability, follow-up duration, birth year, age at follow-up, adjustment of variables regarding BW, LBW and high BW (HBW). The following cardiometabolic risk factors or diseases were identified: body mass index (BMI), waist circumference (WC), overweight (OW), obesity (OB), blood pressure (BP), systolic BP (SBP), diastolic BP (DBP), total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), triglycerides (TG), insulin resistance (IR), insulin, glucose, impaired glucose tolerance, diabetes, hypertension, MetS, coronary heart disease (CHD), CVD, and type 2 diabetes. Data were entered into an Excel spreadsheet. Indicators were extracted from the output of results of the full model, adjusted or multivariate of primary studies. Reported indicators were percentage, mean, correlation coefficient (r), regression coefficient (β), hazards ratio (HR), odds ratio (OR), and standard deviation (SD) with significance level or confidence interval according to the type of data, study design or researchers' interest (Tables 1–6).

Results

Using relevant keywords and applying maximum sensitivity, 7259 papers were identified, 5986 of which were removed after limiting the search and 382 because of repetition. Then, after reviewing titles and abstracts, 628 other irrelevant papers were excluded. We also entered 26 papers after reference checking. Thereafter, 250 other papers were deleted after full text review by applying the inclusion and exclusion criteria and the quality appraisal checklist. Finally, the 39 remaining relevant papers were selected for systematic review^{3,21,23–59} (Appendix 2, Tables 1–6).

Twenty-one of the articles selected for review investigated the Barker hypothesis, and the other 18 the rapid catch-up hypothesis.

The study design of the articles reviewed comprised 31 cohorts (16 birth cohorts), one nested case–control,

one longitudinal, four cross-sectional, one case-control and one health survey. There were control groups in 15 studies (nine on the Barker hypothesis, six on rapid catch-up growth). In all these studies, small-for-gestational age (SGA) infants whose weight was less than the tenth percentile for sex and gestational age according to local growth standard curves were compared with appropriate-for-gestational-age (AGA) infants (Tables 1 and 2). The exceptions were studies by Nobili *et al.*,²⁶ Wang *et al.*,²⁸ Huang *et al.*,²⁹ Reinher *et al.*³⁰ and Efstathiou *et al.*³⁶ which included cases of non-alcoholic fatty liver disease (NAFLD), MetS, overweight, MetS and high-risk clusters (BMI, SBP, TC and glucose at 8 years of age were used as clustering variables), respectively, and control groups which included NAFLD, non-MetS, overweight, non-MetS and low-risk clusters, respectively. Both genders were included in the studies reviewed, except in the four following studies: Mericq *et al.*,²⁵ Ibanez *et al.*,³⁴ Fagerberg *et al.*³⁹ and Mori *et al.*⁵⁷

Findings related to the Barker hypothesis

Results of the primary studies on the Barker hypothesis are summarised as follows (Tables 3, 5 and 7):

1. BMI during adolescence or later life was reported in five papers,^{24,26,31,32,35} two of which reported that BMI was higher in the SGA than in the AGA group,^{24,31} in one of which²⁴ the difference was significant. However, three papers reported that BMI was lower in later life in SGA newborns than in AGA ones,^{26,32,35} and the difference was statistically significant in one of them.³² Moreover, one study indicated that the odds of OW and OB at older ages was significantly higher in SGA than in AGA newborns.⁵⁶
2. Mean SBP was related to BW in six studies,^{31,32,35,43,49,57} mean SBP of the SGA group was higher than in the AGA group in three studies,^{31,32,35} whereas, in three other studies,^{43,49,57} it was inversely related to BW. Five of these studies reported statistically significant results.^{31,32,43,49,57}
3. In five studies,^{31,32,35,49,57} mean DBP was related to BW; in three of them, it was higher in the SGA group than in the AGA group,^{31,32,35} and in the two others it was reversely related to BW.^{49,57} The differences were statistically significant in four of the studies.^{32,35,49,57}
4. In eight studies,^{24,26,27,28,31,35,49,57} serum insulin levels in older subjects were related to BW; six of them^{24,26,27,28,31,35} reported higher mean serum insulin in the SGA than in the AGA group, and two studies^{49,57} reported an inverse relationship between insulin and BW. Except for two studies,^{35,49} the differences documented were all statistically significant.
5. In five studies,^{24,26,31,32,43} glucose levels in older age were related to BW; four of them^{24,26,31,32} reported higher mean glucose levels in the SGA than in the AGA groups, and in one study⁴³ it was inversely related to BW; this difference was statistically significant in one of the studies.³² Moreover, in one study,³⁵ the glucose level was higher in the

Table 1 Primary studies included in the review (with control groups)

First author, year	Study objective	Setting	No. samples			Gender	Age, y
			Total	SGA	AGA		
Veening, 2004 ²³	To study the components of Syndrome X* in pre-pubertal children born SGA	Cohort	53	29	24	M/F	9
Arends, 2005 ²⁴	To investigate insulin sensitivity and risk factors for CVD in short pre-pubertal children born SGA	Cohort	40	28	12	M/F	5–12 (range)
Jaquet, 2005 ²¹	To establish the role of insulin resistance with restricted fetal growth and characterise the fetal and postnatal determinants of long-term metabolic outcome	Birth cohort	1620	734	886	M/F	22
Mericq, 2005 ²⁵	To explore the early development of insulin resistance and secretion as markers of future risk of type II diabetes	Cohort	68	55	13	–	3
Nobili, 2007 ²⁶	To study IUGR, IR and NAFLD in children	Cohort	88	35	55	M/F	12
Abe, 2007 ²⁷	To clarify the relationship between lower birth weight and current overweight status and to examine the involvement of these factors in the development of the MetS in obese	Cohort	97	44	53	M/F	11.3 (mean)
Wang, 2007 ²⁸	To determine the association between the components of the insulin resistance syndrome & reduced fetal growth	Case-control	175	39	136	M/F	72 h
Huang, 2007 ²⁹	To identify early life influences on development of obesity, hypertension & dyslipidaemia in children	Birth cohort	406	102	304	M/F	8
Reinehr, 2009 ³⁰	To assess the association between SGA status and components of MetS	Cohort	761	35	726	M/F	11 (mean)
Meas, 2010 ³¹	To determine the respective impact of fetal growth and weight gain in the progression over time of MetS & IR in young adults	Nested case-control	1308	593	715	M/F	22–30 (range)
Euser, 2010 ³²	To study the association between IUGR and MetS	Cohort	6749	750	5999	M/F	24.7 (mean)
Brufani, 2011 ³³	To evaluate the association of body fat distribution, birth weight and FHD with MetS in children & adolescents	Cohort	371	98	273	M/F	5–18 (range)
Ibanez, 2011 ³⁴	To study across childhood the features of SGA girls with spontaneous catch-up growth	Longitudinal study	31	18	13	F	2–8 (range)
Eyzaguirre, 2012 ³⁵	To study the prevalence of metabolic risks markers in obese and overweight subjects according to BW	Cohort	870	107	763	M/F	2–18 (range)
Efstathiou, 2012 ³⁶	To construct a classification score to detect children at high risk of MetS in adolescence	Cohort	1270	105	1165	M/F	13–15 (range)

* Syndrome X, clustering of insulin resistance, dyslipidaemia and hypertension

Table 2 Primary studies included in the review

First author, year	Study objective	Setting	No. samples	Gender	Age, y
Vanhala, 1999 ³⁷	To study relative weight gain and obesity in childhood as a predictor of adult metabolic syndrome	Birth cohort	428	M/F	36,41, 46
Dwyer, 2002 ³⁸	To investigate clustering of Syndrome X* factors in a sample of 8-year-olds	Birth cohort	298	M/F	7.4–8.9 (range)
Fagerberg, 2004 ³⁹	To study the combined effects of LBW and pronounced weight increase up to early adulthood on the presence of cardiovascular risk factors	Birth cohort	396	M	58
Wadsworth, 2005 ⁴⁰	To study the relationship between early growth and type II diabetes	Birth cohort	3934	M/F	31–53 (range)
Diaz, 2005 ⁴¹	To evaluate the association between weight fluctuation and mortality	Birth cohort	68,200,905	M/F	25–74(range)
Ezzahar, 2005 ⁴²	To characterise the dynamic changes in adiposity during childhood in SGA and their consequences in adulthood	Birth cohort	127	M/F	20
Tamakoshi, 2006 ³	To investigate the association between LBW and adult hypertension	Cross-sectional	3107	M/F	35–66 (range)
Ramadhani, 2006 ⁴³	To study the relationship between intrauterine growth and MeTS, particularly fasting serum lipids in young adulthood	Birth cohort	749	M/F	28 (mean)
Tian, 2006 ⁴⁴	To investigate the association between birth weight and risk of type II diabetes, abdominal obesity and hypertension	Cross-sectional	973	M/F	46.2 (mean)
Ekelund, 2007 ⁴⁵	To study the association between weight gain in infancy and early childhood with metabolic risk in young adults	Prospective cohort	128	M/F	17
Baker, 2008 ⁴⁶	To study the association between BW with ACM	Birth cohort	216,464	M/F	25–68 (range)
Hirschler, 2008 ⁴⁷	To explore the relationship between BW and childhood overweight and obesity and MeTS	Cross-sectional	1027	M/F	9.4 (mean)
Hui, 2008 ⁴⁸	To investigate the association between BW, infant growth rate and childhood adiposity as a proxy for adult metabolic or cardiovascular risk	Birth cohort	6075	M/F	7
Sayers, 2009 ⁴⁹	To study the relationships between BW and biomarkers of chronic disease in childhood	Birth cohort	571	M/F	11.4 (mean)
Guerrero-Romero, 2010 ⁵⁰	To investigate the relation between cluster of FHD and either LBW or HBW with increased risk of MeTS in childhood	Cross-sectional	1262	M/F	7–15 (range)
Xiao, 2010 ⁵¹	To investigate the association between BW and number of MeTS components	Birth cohort	2019	M/F	59.3 (mean)
Lemos, 2010 ⁵²	To study the relationship between BW and insulin resistance in childhood	Cohort	506	M/F	5–8 (range)
Barker, 2010 ⁵³	To study the association between body and placental size at birth and later chronic heart failure	Birth cohort	187	M/F	After 25
Andersen, 2010 ⁵⁴	To study associations between BW and childhood BMI with the risk of CHD in adulthood	Birth cohort	216,771	M/F	25–74 (range)
Boyne, 2010 ⁵⁵	To study the determinants of cardiovascular risk in a cohort of Afro-Jamaican children	Cohort	296	M/F	15–40 (range)
Li, 2012 ⁵⁶	To identify the differential impact of aberrant birth categories related disease on development of childhood overweight and obesity	Cohort	1282	M/F	9–15 (range)
Mori, 2012 ⁵⁷	To examine the relationships between BW and MeTS risk factors	Health Survey	243	F	16.4 (mean)
Kerhof, 2012 ⁵⁸	To study the relationship between low BW and increased risk of MeTS in later life	Cohort	280	M/F	18–24 (range)
Jones-Smith, 2013 ⁵⁹	To study the association between growth velocity, independent of current size and overweight	Birth cohort	586	M/F	8

* Syndrome X, clustering of insulin resistance, dyslipidaemia and hypertension

Table 3 Results of primary studies with control groups which investigated the association between low birthweight and cardiovascular diseases and their risk factors

Components of MetS and CVD				Components of MetS and CVD					
First author, year	Index	SGA	AGA	P	First author, year	Index	SGA	AGA	P
Meas, 2010 ³¹	MetS, %	8.8	4.9	0.05	Veening, 2004 ²³	BW, g, mean	2442	3471	0.01
	BMI, kg/m ²	24.2	24	NS		Diabetes, %	17.2	41.7	NS
	SBP, mmHg	121	119	0.04		Hypertension, %	46.3	66.7	NS
	DBP, mmHg	72.5	71.9	NS		CHD, %	44.8	54.2	NS
	Fasting glucose, mmol/L, mean	4.9	4.87	NS		Total cholesterol, mmol/L, mean	4.1	4.1	NS
	Fasting insulin, µU/L, mean	38.5	34.9	0.02		HDL-cholesterol, mmol/L, mean	1.4	1.5	NS
	Total cholesterol, mmol/L, mean	4.84	4.81	NS		LDL, mmol/L, mean	2.3	2.3	NS
	HDL-cholesterol, mmol/L, mean	1.32	1.36	0.03		TG, mmol/L, mean	0.7	0.6	NS
	Triacylglycerol, mmol/L, mean	1.12	1.04	NS		BW, g, mean	2583	3327	0.01
	IR, mean	1.41	1.27	0.04		BMI, kg/m ² , mean	23.7	23.9	NS
	BW, kg, mean	2.41	3.57	<0.05		Glucose, mmol/L, mean	4.7	4.8	NS
	BMI, kg/m ² , mean	26	26.5	NS		Fasting insulin, µU/L	13.1	12.4	NS
	Cholesterol, mg/dl	164	148	<0.05		TG, mmol/L, mean	1.2	1.1	NS
Triglycerides, mg/dl	99	93	<0.05	Total cholesterol, mmol/L, mean	4.6	4.5	NS		
Fasting glucose, mg/dl	85	81	NS	HDL cholesterol, mmol/L, mean	1.3	1.3	NS		
Fasting insulin, µU/L	13.5	10.5	<0.05	LDL, mmol/L, mean	2.8	2.7	NS		
IR, mean	2.85	1.99	<0.05	IR, mean	2.7	2.7	NS		
BW, g, mean	3260	3508	<0.05	SBP, mmHg, mean	110	109.6	NS		
Weight, kg, mean	64.2	62.7	NS	DBP, mmHg, mean	64.3	64.2	NS		
Hip circumference, cm, mean	93.1	92	NS	Hypertension, %	9.3	9.2	NS		
T-cholesterol, mg/dl, mean	189.6	185.8	NS	MetS, %	7.5	5.6	NS		
LDL, mg/dl, mean	120.4	116.6	NS	MetS, %	25.7	14.5	0.01		
Serum insulin, µU/ml, mean	25.3	16.5	<0.05						
WBWR, mean	21.9	18.2	<0.01						
BW, g, mean	2733	3506	-	TG, mmol/L, mean	2.29	1.57	<0.01		
BMI, kg/m ² , mean	24.4	24.7	<0.01	Total cholesterol, mmol/L, mean	2.35	1.82	<0.04		
Diabetes, %	0.9	0.5	NS	LDL, mmol/L, mean	2.11	1.24	0.01		
TG, mmol/L, mean	1.5	1.4	NS	Insulin concentration, µU/ml, mean	17.11	6.7	<0.01		
HDL cholesterol, mmol/L, mean	1.33	1.35	NS	Fasting glucose, mmol/L, mean	4.8	4.5	NS		
SBP, mmHg, mean	127.8	126.2	0.02	Fasting insulin, mU/L, mean	6	4.4	0.01		
DBP, mmHg, mean	72.1	71.2	0.03	AIR, mU/L, mean	241	90	0.01		
Serum glucose, mmol/L	5	4.9	0.01	BMI SDS	-1.3	-0.6	0.02		

* Both SGA and AGA were NAFLD; † SGA, MetS and AGA, non-MetS.

Table 4 Results of primary studies with control groups which investigated the association of rapid catch-up growth with cardiovascular diseases and their risk factors

Components of MetS and CHD				Components of MetS and CHD					
First author, year	Index	SGA	AGA	P	First author, year	Index	SGA	AGA	P
Ibanez, 2011 ³⁴	BW, kg, mean	2.2	3.3	-	Mericq, 2005 ²⁵	Birthweight, SDS	-2.07	0.76	<0.01
	Catch-up in weight at 2 yrs, kg/m ² , mean	12	12.5	NS		Weight catch-up at 1 yrs, SDS	-0.72	0.2	<0.01
	Weight at 8 yrs, kg/m ² , mean	30	28.4	<0.01		Weight catch-up at 3 yrs, SDS	-0.03	0.39	NS
	Glucose, mg/dl, 8 yrs, mean	89	84	<0.01		Weight catch-up change from 1 to 3 yrs, SDS	0.71	0.2	<0.05
	Insulin, mU/L, 8 yrs, mean	7.7	3.5	<0.01		BMI, kg/m ² , 3 yrs, mean	16.2	16.7	NS
	IR, 8 yrs, mean	1.7	0.7	<0.01		Fasting insulin, 3 yrs, pmol/L	38.9	23.8	<0.01
	TG, 8 yrs, mg/dl, mean	65	54	<0.05		IR, 3 yrs, mean	8.5	4.9	<0.01
	LDL cholesterol, 8 yrs, mg/dl, mean	106	81	<0.01		Fasting glucose, 3 yrs, mmol/L	4.8	4.4	NS
	HDL cholesterol, 8 yrs, mg/dl, mean	52	57	<0.05		BW, g, mean	2474	3489	<0.01
	BW, g, mean	2700	3400	<0.01		BMI, kg/m ² , mean	26.4	27.3	NS
Jaquet, 2005 ²¹	BMI at birth, kg/m ² , mean	11.5	13.3	<0.01	WHR, mean	0.96	0.97	NS	
	Catch-up in BMI at 22 yrs, kg/m ² , mean	22.4	22.6	NS	SBP, mmHg, mean	120	115	0.01	
	Fasting serum insulin, pmol/L, mean	33.7	30.1	0.01	DBP, mmHg, mean	70	64	<0.01	
	WHR, mean	0.81	0.8	NS	Fasting glucose, mmol/L, mean	4.7	4.7	NS	
	SBP, mmHg, mean	121	120	NS	HDL cholesterol, mmol/L, mean	1.27	1.31	NS	
	DBP, mmHg, mean	63	63	NS	TG, mmol/L, mean	1.35	1.2	0.03	
	HDL cholesterol, mmol/L, mean	1.4	1.43	0.05	Insulin, mU/L, mean	19.7	16.8	0.03	
	TG, mmol/L, mean	1.1	1.03	0.002	IR, mean	4.1	3.6	NS	
	Impaired glucose tolerance, %	27	14	0.01	Hypertension, %	8.4	1.6	0.03	
	Fasting plasma glucose, mmol/L, mean	4.76	4.74	0.03	MetS, %	8.3	3.1	0.02	
*Efstathiou, 2012 ³⁶	BW, g, mean	2941	3447	<0.01	Impaired glucose tolerance, %	8.4	3.2	<0.01	
	Catch-up in BMI at 6-8 yrs, kg/m ² , mean	17.4	16.7	0.01	BW, g, mean	3474	3510	NS	
	SBP, mmHg, mean	130	110	<0.01	Mean for weight gain at birth to <1 yr	7	6.8	NS	
	DBP, mmHg, mean	85	69	<0.01	Mean for weight gain at 1-3 yrs	5.7	4.6	<0.01	
	LDL, mg/dl, mean	106	90	0.02	Mean for weight gain at 3-5 yrs	8.2	6	<0.01	
	HDL, mg/dl, mean	39	54	<0.01	Mean for weight gain at 5-8 yrs	9.2	6	<0.01	
	TG, mg/dl, mean	152	88	<0.01					

† SGA and AGA groups were overweight, * SGA, MetS and AGA, non-MetS

Table 5 Results of primary studies which investigated the association of low birthweight with cardiovascular diseases and their risk factors

First author, year	Components of MetS and CVD			Components of MetS and CVD		
	Index	Figure	P or CI	Index	Figure	P or CI
Baker, 2008 ⁴⁶	*HR for ACM for LBW (2000–2750 g)	1.17	1.11–1.22	OR for MetS for BW 1250–3209 g, 28 yrs	1.8	1–3.5
	*HR for ACM for BW 2751–3250 g	1.01	NS	OR for MetS for BW 3210–3649 g, 28 yrs	1.4	NS
	*HR for ACM for BW 3751–4250 g	0.96	NS	β between BW and glucose, mmol/L, 28 yrs	-0.027	NS
	*HR for ACM for BW 4251–5500 g	1.07	1.01–1.15	β between BW and SBP, mmHg, 28 yrs	-1.868	<0.05
	*HR for CDM for LBW(2000–2750 g)	1.21	1.09–1.35	β between BW and TG, mmol/L, 28 yrs	-0.032	<0.05
	*HR for CDM for BW 2751–3250 g	1.09	1.01–1.18	β between BW and TC, mmol/L, 28 yr	-0.067	NS
	*HR for CDM for BW 3751–4250 g	0.92	NS	β between BW and LDL, mmol/L, 11 yrs	-0.03	NS
	*HR for CDM for BW 4251–5500 g	1.09	NS	β between BW and HDL, mmol/L, 11 yrs	0.015	NS
**Tamakoshi, 2006 ³	OR for hypertension for BW <2500 g, 46 yrs	1.26	NS	β between BW and SBP, mmHg, 11 yrs	-0.3	<0.01
	OR for hypertension for BW 3000–3499 g, 46 yr	0.89	NS	β between BW and DBP, mmHg, 11 yrs	-1.7	<0.01
	OR for hypertension for BW ≥3500 g, 46 yrs	0.7	0.49–1	β between BW and TC, mmol/L, 11 yrs	-0.001	NS
Li, 2012 ⁵⁶	OR for OW and OB in SGA at 9–15 yrs	1.45	1.09–1.94	β between BW and TG, mmol/L, 11 yrs	0.17	NS
Dwyer, 2002 ³⁸	r for IR with BW	0.1	NS	β between BW and fasting insulin, mU/L, 11 yrs	-0.16	NS
	r for IR with weight at 8 yrs	0.23	<0.01	OR for MetS components for BW <2500 g	1.66	1.18–2.34
	r for dyslipidaemia with BW	-0.03	NS	OR for MetS components for BW 2500–3000 g	1.33	1.09–1.63
	r for dyslipidaemia with weight(at 8 yrs)	0.05	NS	OR for MetS components for BW >3500 g	0.97	NS
*Guerrero-Romero, 2010 ⁵⁰	OR MetS for high BW (4041 g)	1.4	1.2–10.9	OR for type II diabetes for BW <2500 g, 46 yrs	3.97	1.71–9.22
	OR MetS for low BW (2067 g)	0.97	NS	OR for type II diabetes for BW 2500–2999 g, 46 yrs	1.35	NS
	OR MetS in high BW at FHD (4041 g)	2.7	1.4–15.1	OR for type II diabetes for BW 3000–3499 g, 46 yrs	1.24	NS
	OR MetS in low BW at FHD (2067 g)	3.3	1.3–30.6	OR for MetS in LBW (<2500 g)	3.16	1.4–7.2
Mori, 2012 ⁵⁷	r for IR with BW, 16 yrs	-0.123	0.05	OR for MetS in HBW (≥ 4000 g)	1.06	NS
	r for MS-R with BW, 16 yrs	-0.15	0.02	β between BW with IR at 5–8 yrs	-0.027	<0.01
	r for SBP with BW, 16 yrs	-0.184	0.07			
	r for DBP with BW, 16 yrs	-0.137	0.03			
	r for insulin with BW, 16 yrs	-0.125	0.04			
	r for TG with BW, 16 yrs	-0.177	0.09			

Reference group: * BW 3251–3750 g; ** BW 2500–2999 g; † BW 2500–3999 g; ‡ BW 3650–5500 g; †† BW >3500 g

Table 6 Results of primary studies which investigated the association of rapid catch-up growth with cardiovascular diseases and their risk factors

Components of MetS and CVD		Components of MetS and CVD	
First author, year	Index	Figure P or CI	Index
*Diaz, 2005 ⁴¹	HR for ACM with SW (obese)	1.35 NS	***HR for type II diabetes at 31–53 yrs with BW ≤3 kg
	HR for ACM with WG	1.1 NS	†HR for type II diabetes at 31–53 yrs with catch-up at 2 yrs
	HR for ACM with WL	3.36 2.47–4.5	†HR for type II diabetes at 31–53 yrs with catch-up at 4 yrs
	HR for ACM with WF	1.83 1.25–2.7	†HR for type II diabetes at 31–53 yrs with catch-up at 7 yrs
	HR for CM with SW (obese)	2.37 NS	OR for MS at 21 yrs with BW
	HR for CM with WG	1.24 NS	OR for MS at 21 yrs with catch-up W at 0–3 mths
	HR for CM with WL	4.22 2.6–6.8	OR for no. of components MetS at 21 yrs with BW (SGA)
	HR for CM with WF	1.86 1.1–3.15	OR for no. of components MetS at 21 yrs with catch-up W at 0–3 mths
Ekelund, 2007 ⁴⁵	β for association between BW with cluster MetS risk at 17 yrs	0.1 NS	OR for no. of components MetS at 21 yrs with catch-up W at 3–6 mths
	β for association between rapid weight gain at 0–6 mths with cluster MetS risk at 17 yrs	0.16 <0.01	OR for no. of components MetS at 21 yrs with catch-up W at 6–9 mths
	β for association between rapid weight gain at 3–6 yrs with cluster MetS risk at 17 yrs	0.1 NS	OR for no. of components of MetS at 21 yrs with catch-up wt at 9–12 mths
Ezzahir, 2005 ⁴²	r for SGA and catch-up at 1 yr with BMI in adulthood (20 yrs)	-0.02 NS	HR for CHD at 24 yrs with BW <3.4
	r for SGA and catch-up at 2 yrs with BMI in adulthood (20 yrs)	0.34 0.04	% risk CHD at 24 yrs with BW 2.5 kg and catch-up BMI 17.7 kg/m ² at 7 yrs (compared with median BW 3.4 kg)
	r for SGA and catch-up at 4–6 yrs with BMI in adulthood (20 yrs)	0.43 0.03	β for WC at 11 yrs with BW
Fagerberg, 2004 ³⁹	r for BW with BMI at 58 yrs	<0.1 NS	β for WC at 11 yrs with catch-up BMI at 0–6 mths
	r for BW with W/H at 58 yr	<0.1 NS	β for WC at 11 yrs with catch-up BMI at 6–24 mths
	r for BW with SBP at 58 yrs	<0.1 NS	β for IR at 11 yrs with BW
	r for BW with DBP at 58 yrs	<0.1 NS	β for IR at 11 yrs with catch-up BMI at 0–6 mths
	r for BW with HDL at 58 yrs	<0.1 NS	β for IR at 11 yrs with catch-up BMI at 6–24 mths
	r for BW with LDL at 58 yrs	<0.1 NS	β for fasting insulin at 11 yrs with BW
	r for ratio of wt at 18 yrs/BW with BMI at 58 yrs	0.24 0.01	β for fasting insulin at 11 yrs with catch-up BMI at 0–6 mths
	r for ratio of wt at 18 yrs/BW with W/H at 58 yrs	0.24 0.01	β for fasting insulin at 11 yrs with catch-up BMI at 6–24 mths
	r for ratio of wt at 18 yrs/BW with SBP at 58 yrs	<0.1 NS	β for SBP at 11 yrs with BW
	r for ratio of wt at 18 yr/BW with DBP at 58 yrs	0.13 <0.05	β for SBP at 11 yr with catch-up BMI at 0–6 month
	r for ratio of wt at 18 yr/BW with serum insulin at 58 yrs	0.14 <0.01	β for SBP at 11 yrs with catch-up BMI at 6–24 mths
	r for ratio of wt at 18 yr/BW with TG at 58 yrs	0.1 <0.05	β for HDL at 11 yrs with BW
	r for ratio of wt at 18 yr/BW with HDL at 58 yrs	-0.13 <0.01	β for HDL at 11 yrs with catch-up BMI at 0–6 mths
	r for ratio of wt at 18 yr/BW with LDL at 58 yr	-0.17 <0.05	β for HDL at 11 yrs with catch-up BMI at 6–24 mths
†Vanhala, 1999 ³⁷	OR for MetS at 36, 41 or 46 yrs with catch-up W at 7 yrs	1.6 NS	OR for overweight at 8 yrs with weight velocity at 0–24 mths
Barker, 2010 ⁵³	††OR for chronic heart failure with BW -2.5 kg	1 NS	OR for overweight at 8 yrs with timing of peak weight velocity at 0–24 mths
	††OR for chronic heart failure with BW -3 kg	1.2 NS	OR for overweight at 8 yrs with timing of peak weight velocity at 0–24 mths
	††OR for chronic heart failure with BW -3.5 kg	1.1 0.7–1.8	Z-score for BMI at 7 yrs with catch-up W at 0–3 mths
	††OR for chronic heart failure with BW -4 kg	0.9 NS	Z-score for BMI at 7 yrs with catch-up W at 3–12 mths

Reference group: * Stable weight, non-obese; † those whose relative weight was the same or had been reduced from birth to age 7 yrs; †† catch-up at 11 yrs; ** median BW 3.4 kg; †† BW >4 kg; *** BW ≥4 kg.

- AGA than in the SGA group, but it was not statistically significant.
6. In seven studies,^{23,26,27,28,35,43,49} TC level was related to BW with two of them^{26,28} finding statistically significant differences, and in one study²³ TC was equal in both the SGA and AGA groups.
 7. In eight studies,^{23,26,28,31,32,35,43,57} TG at older ages was related to BW, and was statistically significantly in four of them.^{26,28,43,57}
 8. HDL-C in older age was reported in three^{23,31,49} of five studies,^{23,31,32,35,49} and its level was related to BW, with one of them showing significant difference;³¹ in two studies^{32,35} this relationship was not documented.
 9. LDL-C level was reported in five studies.^{23,27,28,35,49} In four studies,^{27,28,35,49} LDL-C was related to BW with significant differences in one of them.²⁸ In one study, it was equal in the SGA and AGA groups.²³
 10. In four^{26,31,52,57} of six studies which reported IR,^{26,31,35,38,52,57} IR at older ages was related to BW and there were statistically significant associations. IR in the other two studies^{35,38} was not related to BW.
 11. Of three papers^{23,32,44} reporting the prevalence of diabetes, two^{32,44} found a higher prevalence at older ages in the SGA than in the AGA group, which was statistically significant in one of them,⁴⁴ and the other²³ reported that diabetes was more prevalent in the AGA than in the SGA group, although this was not statistically significant.
 12. Of three papers^{3,23,35} which reported the prevalence of hypertension, two^{3,35} indicated that its prevalence was higher in the SGA group than in the other weight groups; however, none was statistically significant. The other study²³ reported a non-significant greater prevalence of hypertension in older age in the AGA than in the SGA group.
 13. All seven papers which studied MetS^{33,35,43,47,50,51,57} indicated that the risk of its incidence was higher in those born with LBW than in those of normal BW, and findings in four of them^{33,43,51,57} were statistically significant.
 14. The only paper which studied the relationship between all-cause mortality and BW demonstrated statistically significant results, and found that the risk of death in those with a BW of 2000–2750 g was 1.17 times higher than in those of normal BW.⁴⁶
 15. A study⁴⁶ which investigated the relationship between circulatory disease mortality (CDM) and BW indicated that the risk of death in those with BWs of 2000–2750 g was 1.21 times higher than in those of normal BW, and this was statistically significant.

Summary of the main findings of the Barker hypothesis

Twenty-one studies fulfilled the inclusion criteria. Five confirmed the association between LBW and BMI, and one was statistically significant; with OB or OW in one study (significant association), with SBP in six studies (five of them showing significant association), with DBP in five studies (four of them significant), with serum insulin in eight studies (six of them significant), with glucose in six studies (one

significant), with TC in seven studies (two of them significant), with TG in eight studies (four of them significant), with HDL in five studies (one of them significant), with LDL in five studies (one of them significant), with IR in six studies (four of them significant), and with MetS in seven studies (four of them significant). The association of LBW with other variables is presented in Table 7.

Findings related to the rapid catch-up growth hypothesis

Results of the primary studies of the hypothesis regarding rapid weight gain by LBW neonates are summarised as follows (Tables 4, 6 & 7):

1. All four studies^{25,29,34,59} which investigated BW and weight in later life indicated that later weight gain was higher in the SGA than in the AGA group, and in three of them^{29,34,59} the findings were significant. Moreover, of eight studies^{21,25,30,36,39,42,48,55} investigating the relationship between BW and BMI in adolescence, five^{25,36,42,48,55} reported that mean BMI was higher in the SGA than in the AGA group, and the findings were significant in four of them.^{36,42,48,55} In three other studies^{21,30,39} in which mean BMI was non-significantly lower in the SGA than in the AGA group, the increase in BMI was more prevalent in the SGA group.
2. Mean SBP was related to rapid postnatal catch-up growth in five studies,^{21,30,36,39,55} significantly so in three of them.^{30,36,55}
3. Mean DBP was related to BW and rapid catch-up growth in four studies,^{30,36,39,55} three of which^{30,36,39} had statistically significant findings. In one other study,²¹ it was equal in cases and controls.
4. Serum insulin was related to rapid catch-up weight in six studies,^{21,25,30,34,39,55} with statistically significant findings in five of them.^{21,25,30,34,39}
5. In five studies,^{21,30,34,36,39} a statistically significant association was documented between TG and BW and postnatal catch-up growth.
6. Two studies^{21,30} reported a relationship between impaired glucose tolerance and catch-up growth, both of them were statistically significant.
7. HDL-C level was reported in six studies,^{21,30,34,36,39,55} and five of them showed an inverse association with postnatal catch-up growth.^{21,34,36,39,55}
8. LDL-C level was reported in three studies,^{34,36,39} all of which demonstrated a statistically significant relationship with rapid catch-up growth.
9. All four studies^{25,30,34,55} which investigated IR status in later life indicated that IR was higher in the SGA than in the AGA group, and three of them^{25,34,55} reported a statistically significant relationship with rapid catch-up growth.
10. In the only study reporting diabetes prevalence,⁴⁰ it was higher in those with rapid catch-up growth, but it was not statistically significant.
11. In the only study which reported the prevalence of hypertension,³⁰ it was significantly higher in those with rapid catch-up growth than in others.
12. In all four studies^{30,37,45,58} which reported on MetS, the odds of its incidence was statistically higher in LBW individuals with rapid catch-up growth. Moreover, one study⁵⁸ showed that the number of

Table 7 Results of primary studies reporting the existing relationship and level of significance of low birthweight or rapid catch-up growth with cardiovascular diseases and their risk factors

Components of MetS and CHD	Association of LBW with components of MetS and CHD			Association of LBW and rapid catch-up growth with components of MetS and CHD		
	No. of studies which reported this variable	No. of studies that confirmed the relationship	No. of studies with significant results	No. of studies which reported this variable	No. of studies that confirmed the relationship	No. of studies with significant results
BMI	5	2	1	8	5	4
OW or OB	1	1	1	4	4	3
SBP	6	6	5	5	5	3
DBP	5	5	4	5	4	3
Serum insulin	8	8	6	6	6	5
Glucose	6	5	1	–	–	–
TC	7	6	2	–	–	–
TG	8	8	4	5	5	5
HDL	5	3	1	6	6	5
LDL	5	4	1	3	3	3
IR	6	4	4	4	4	3
Type II diabetes	3	2	1	1	1	0
Hypertension	3	2	1	1	1	1
MetS	7	7	4	4	4	4
ACM	1	1	1	1	1	0
CDM or CM	1	1	1	1	1	0
Impaired glucose tolerance	–	–	–	2	2	2
CHD	–	–	–	2	2	2
Total (%)	77	65 (84.4)	38 (58.5)	58	54 (93.1)	43 (79.6)

MetS components was statistically higher in children with rapid catch-up growth than in their counterparts.

- Two studies^{53,54} indicated that the risk of CHD and heart failure in older age was higher in those of LBW who experienced rapid postnatal catch-up growth, and the findings were significant. In a simultaneous regression, chronic heart failure was associated with low BMI at 2 years of age and high BMI at 11 years of age ($P = 0.01$ and 0.01 , respectively).⁵³
- The only study⁴¹ of the relationship between all-cause mortality and catch-up growth showed that the risk of death was higher in those with rapid weight gain than in the non-obese with normal catch-up growth, but it was not statistically significant.

In a study by Ibanez *et al.*,³⁴ weight catch-up by the age of 2 years was higher in the SGA group but this was not significantly different from that of the AGA group. But mean weight, glucose, insulin, IR, LDL and TG at the age of 8 years in the SGA group was significantly higher than in the AGA group, and mean HDL in the SGA group was significantly lower than in the AGA group. Another study³⁶ demonstrated that mean catch-up in BMI at 6–8 years in the SGA group was significantly higher than in the AGA group. Also, a study by Huang *et al.*²⁹ indicated that mean weight gain from birth to 1 year in the SGA group was higher than in the AGA group, although the difference was not statistically significant. However, mean weight gain in the age groups 1–3, 3–5 and 5–8 years in the SGA group was significantly greater than in the AGA group (Table 4).

Summary of the main findings of the rapid catch-up growth hypothesis

Eighteen studies met the inclusion criteria. Rapid catch-up growth and LBW were associated with BMI in eight studies (four of them with a statistically significant association), with OB or OW in four studies (three of them significant), with SBP in five studies (three of them significant), with DBP in five studies (three of them significant), with serum insulin in six studies (five of them significant), with TG in five studies (all of them significant), with HDL in six studies (five of them significant), with IR in four studies (three of them significant), and with MetS in four studies (all of them significant). Table 7 presents the association of rapid catch-up growth and LBW with other variables.

Summary of the main findings of both hypotheses

Of the 18 primary studies related to the catch-up growth hypothesis, 15 reported a significant difference for at least one risk factor. On the other hand, 18 of the 21 primary studies of the Barker hypothesis indicated at least one risk factor with a significant difference.

The cumulative number of studies of 18 risk factors for CVDs according to the Barker hypothesis was 77. The reason for the difference between the cumulative sum of studies which investigated risk factors and the number of primary studies is that each of the primary studies included more than one risk factor. Of 65 (84.4%) studies which reported a relationship with risk factors, only 38 (58.5%) were statistically significant. The cumulative number of studies of 18 risk factors for

CVDs according to the catch-up growth hypothesis was 58, and 54 (93.1%) of them reported an association, 43 (79.6%) of which demonstrated a statistically significant difference (Table 7).

Discussion

Results of this systematic review demonstrate that 79.6% of risk factors for CVDs and other risk factors were statistically significant for the catch-up hypothesis, and 58.5% for the Barker hypothesis. Postnatal rapid catch-up growth is more prevalent in LBW newborns, which makes them more susceptible later to chronic diseases. Also, studies conducted at different stages of life demonstrate that LBW increases the risk of CVDs and their risk factors in later life. These findings underscore the importance of regular growth monitoring of LBW infants, and of counselling parents on feeding and growth of their children in the first months of life.

A systematic review⁶⁰ of the association of LBW and catch-up-growth with MetS showed that in the majority of studies of SGA children, adolescents and adults, insulin resistance might be a prelude to other metabolic disorders; in later life, both LBW and catch-up-growth correlated with some aspects of MetS in later life. However, it was not clear whether LBW or catch-up growth played the more important role in the development of MetS. Another systematic review⁶¹ found that a number of studies reported an inverse relationship between BW and fasting plasma glucose and insulin concentrations, 2-hour post-load plasma glucose, the prevalence of type 2 diabetes mellitus, and levels of insulin resistance and secretion. Yet another systematic review⁶² and meta-analysis on BW, early weight gain and subsequent risk of type I diabetes analysed 12 studies which included 2,398,150 subjects, and found that 7491 had type I diabetes associated with BW. LBW *per se* was associated with a non-significantly decreased risk of type 1 diabetes (OR 0.82, 95% CI 0.54–1.23). Each 1000-g increase in BW was associated with a 7% increase in the risk of type II diabetes. In all the studies, however, patients with type II diabetes showed increased weight gain during the first year of life compared with controls. The authors concluded that high BW and accelerated early weight gain were important risk factors for type II diabetes.

A growing body of evidence suggests that early-life environment is probably the most important causal component in the aetiology of many chronic adult diseases.^{63,64} It has been proposed that epigenetic rearrangements might play an equally essential role in disease development, particularly at key developmental stages. Evidence suggests that interaction between genetic, intra-uterine and environmental factors might lead to NCDs and related metabolic disorders.^{63,64}

NCDs and their risk factors are a major global health threat. Given the tracking of cardiometabolic risk factors from childhood to adulthood, more attention needs to be directed to primordial and primary prevention of NCDs and their risk factors.⁶⁵

The change in the global pattern of diseases from infectious diseases towards NCDs is of special concern for developing countries facing an epidemiologic transition along with rapid lifestyle change and an emerging epidemic of NCDs in the near future.⁶⁶

Atherosclerosis, the underlying pathology of CVDs, originates in early life, even during the fetal period. It has been well documented that adverse intra-uterine environment and impaired fetal growth contribute to the early development of atherosclerosis, with a long latency period between these and other exposures and adult CVDs.⁶⁶

LBW, notably when accompanied by rapid postnatal catch-up growth, can be considered to be a modifiable risk factor for CVDs and their risk factors in later life. BW is not determined only by genetic variation, but also by the prenatal environment.^{67–69} Likewise, postnatal growth velocity is strongly dependent on modifiable factors.^{70–72}

It seems that adaptation to prenatal and postnatal environments establishes patterns of interaction between various factors which control diverse cellular and organic functions and enable the survival of early prenatal and postnatal life, but then have adverse outcomes much later in life. Furthermore, adaptation to an inappropriate prenatal environment might put infants at risk of adult-onset diseases if the postnatal environment is not matched to that *in utero*.^{73,74}

Therefore, more attention should be paid to a healthy lifestyle and environment for women of reproductive age, particularly during pregnancy. Likewise, growth monitoring of all children should be emphasised, especially those of LBW who have a high risk of childhood obesity, which is an emerging health problem, even in low- and middle-income countries in which the risk is increased by LBW and stunting.^{75–77}

We could not conduct a meta-analysis because of the large degree of heterogeneity of variables used in primary studies, variations in the age at which outcomes have been studied, and large differences in the design of various studies. A limitation of the study was that the types of primary studies that were included in our review were dissimilar and their causal relationships had large variations. In addition, the sample size of primary studies ranged from 100 to 70,000 cases and thus the weight of many studies was not the same, with higher weight for studies with larger sample sizes. Moreover, because meta-analysis was not possible, we were unable to determine any publication bias by statistical tests (e.g. Egger or Begg) or graphically (e.g. funnel plot).

In general, this systematic review highlights the importance of LBW in increasing the risk of CVDs and their risk factors in later life. It suggests that rapid postnatal catch-up growth of LBW neonates plays an important role in this regard. The study's findings provide important pointers for health policy-makers to pay more attention to improvement of fetal growth and close monitoring of the growth trajectory of LBW infants in planning cost-effective primordial preventive strategies to reduce the burden of NCDs. Further long-term follow-up studies of birth cohorts should be conducted to examine outcome of LBW newborns with a rapid growth trajectory and risk factors in later life.

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