Nutrition, Metabolism and Cardiovascular Diseases xxx (xxxx) xxx

Contents lists available at ScienceDirect

Nutrition, Metabolism and Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

Early life factors and later metabolic syndrome in European children and adolescents

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ARTICLE INFO

Handling Editor: Prof. F. Galletti

Keywords:
Pre-
Peri-
Postnatal factors
Metabolic syndrome
Waist circumference
Blood pressure
Insulin resistance
Dyslipidemia
IDEFICS/I.Family study

ABSTRACT

Background and aims: Early life factors have been suggested to be associated with later cardiometabolic risk in children, adolescents and adults. Our study aimed to investigate the associations between early life factors and metabolic syndrome (MetS) in children and adolescents.

Methods and results: Our analysis sample comprised of 8852 children aged 2–9 years at baseline that participated in up to three examination waves of the pan-European IDEFICS/I.Family cohort (baseline: 2007/08, 1st follow-up 2009/10, 2nd follow-up 2013/14). Mixed-effects models were used to estimate the associations between early life factors and MetS score and z-scores of waist circumference (WC), systolic (SBP) and diastolic blood pressure (DBP), Homeostasis Model Assessment for Insulin Resistance, high density lipoprotein cholesterol (HDL) and triglycerides.

Being born large for gestational age (LGA) showed a positive association with MetS score (β = 0.67; 99%CI 0.44, 0.90) and with WC z-score (β = 0.51; 99%CI 0.39, 0.63) and was weakly inversely associated with HDL z-score. Being born small for gestational age (SGA) was associated with lower WC z-score (ß = −0.26; 99%CI -0.37, −0.16), with a lower MetS score (ß = −0.13; 99%CI −0.33, 0.08) and slightly higher z-scores of SBP and DBP. Weight gain during pregnancy was positively associated with MetS score and WC z-score while premature birth was positively associated with SBP.

Conclusions: Children born LGA, SGA or preterm may warrant closer monitoring to prevent MetS later on.

Abbreviations: AGA, appropriate for gestational age; BMI, body mass index; DBP, diastolic blood pressure; HDL, high density lipoprotein cholesterol; HOMA-IR, Homeostasis Model Assessment for Insulin Resistance; IOTF, International Obesity Task Force; ISCED, International Standard Classification of Education; LGA, large for gestational age; MetS, metabolic synrome; NCD, Non-Communicable Diseases; SD, standard deviation; SGA, small for gestational age; SBP, systolic blood pressure; TG, triglycerides; Wave 0, baseline examination; Wave 1, follow-up after 2 years; Wave 2, follow-up after 6 years; WC, waist circumference.

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https://doi.org/10.1016/j.numecd.2024.103808
Received 15 July 2024; Received in revised form 12 November 2024; Accepted 21 November 2024
Available online 30 November 2024

1. Introduction

Cardiovascular diseases are among the most prevalent non-communicable diseases (NCD) in adulthood and the leading cause for death worldwide. Metabolic disturbances such as hypertension, obesity, hyperglycemia and dyslipidemia, known as components of the Metabolic Syndrome (MetS), increase the risk of developing NCD [1,2]. Several studies showed that the interplay of different modifiable and non-modifiable risk factors including behaviour-related and genetic factors promote the development of metabolic disturbances in adolescence [3] and cardiometabolic diseases in mid-to late adulthood [4,5]. These classical risk factors have been widely investigated but there is also evidence that exposures during foetal and early development, namely pre-, peri- and postnatal early life factors, influence the manifestation of cardiovascular diseases in adulthood [6]. Barker and colleagues formulated the "foetal origins of adult disease" hypothesis in the 1990's and showed that unfavourable factors during gestation, such as maternal undernutrition and a resulting low birth weight, are associated with higher blood pressure, elevated triglycerides (TG), decreased high-density lipoprotein cholesterol (HDL), and insulin resistance in adulthood [7,8]. They hypothesized that adverse exposures during gestation lead to adaptations and cardiometabolic changes which persist over time and increase the risk for cardiovascular diseases in adulthood [8].

While many studies investigated associations between early life factors and childhood overweight or elevated blood pressure, only few studies [9–11] focused on potential associations with MetS and its components [12] despite its increasing prevalence in children and adolescents. In addition, evidence from these studies is inconsistent [9–11, 13,14]. One reason for the discrepancies might be that many studies assessing associations between early life factors and later cardiometabolic risk adjust for body mass index (BMI) or other measures of weight status while these variables are not confounders but potential mediators lying on the causal pathway from early life factors to cardiometabolic risk. Furthermore, most previous results were based on small study samples, as large studies in children and adolescents, particularly with blood sampling, are scarce. The high number of children and adolescents with overweight and obesity [15] and abnormal cardiometabolic profiles in industrial countries makes further research desirable [12,16,17]. Therefore, this study investigates the long-term effects of prenatal (smoking and weight gain during pregnancy, maternal age), perinatal (mode of delivery, premature birth, birth weight for gestational age) as well as postnatal (exclusive breastfeeding duration, age at introduction of solid food) factors on the risk of MetS in children and adolescents in a large pan-European cohort. We further study associations between early life factors and the single components of the MetS to show the comprehensive picture. Our results provide evidence on the impact of unfavourable early life factors on the risk of MetS and can help to develop prevention strategies which address the most promising targets.

2. Methods

2.1. Study sample

The present analysis is based on the population-based IDEFICS/I.Family cohort study (https://www.ifamilystudy.eu/), registered under https://www.isrctn.com/ISRCTN62310987. This large European cohort of children and adolescents investigates associations of dietary, behavioural and socio-economic factors with non-communicable chronic diseases and disorders, focusing on overweight and obesity. The IDEFICS study started recruitment of children from 8 European countries (Belgium, Cyprus, Estonia, Germany, Hungary, Italy, Spain, Sweden) in 2007. A total of 16230 children aged 2.0–9.9 years were examined at baseline (Wave W0). After W0, half of the children participated in a setting-based community-oriented intervention programme for primary prevention of obesity [18]. The first follow-up (W1) was conducted 2 years later and included 11044 children from baseline and 2540 newly recruited children. The next follow-up examination was conducted in 2013/2014 within the I.Family study (W2) and included 7123 children between 8.0 and 17.0 years who already participated at W0 and/or W1. The children underwent an intensive phenotyping with physical examinations, collection of biological samples and questionnaires addressing social, behavioural and environmental factors, individual characteristics, health behaviours and health outcomes, as previously described in detail [19,20]. Written informed consent was obtained from the parents and from children aged 12 years and older while younger children gave oral consent. Both the IDEFICS and I.Family studies were approved by the Institutional Review Boards of each survey centre.

The current analysis includes 8852 children with at least one examination at either W0 and/or W1 and information on all considered pre-, peri- and postnatal variables (weight gain of mother during pregnancy, smoking of mother during pregnancy, age of mother, mode of delivery, preterm delivery, birth weight for gestational age, exclusive breastfeeding duration, age at introduction of solid food) and all of the MetS health outcomes [(waist circumference (WC), systolic (SBP) and diastolic blood pressure (DBP), Homeostasis Model Assessment for Insulin Resistance (HOMA-IR), HDL, TG, MetS score)]. Children with non-fasting state at the time of blood collection or those born as twins were excluded from the analysis. The number of physical examinations per child varied from one to three. The age interval of children at measurements ranged from 2.0 to 15.4 years. Fig. 1 shows the flow chart of children included in the analyses.

2.2. Information on factors during gestation and early life

Detailed information on pre-, perinatal and early life factors was collected based on maternity cards, records of routine child visits or parental questionnaires collected at W0 or W1.

2.2.1. Prenatal factors

Information on mothers' age at delivery (years) and weight gain during pregnancy (kg) were collected from maternity cards. In case this information was not available from maternity cards it was taken from the parental questionnaire at W0 or W1 which further included questions on maternal smoking behaviour during pregnancy (never, < daily smoking, daily smoking).

2.2.2. Perinatal factors

From the records of routine child visits, information about birth weight (g), gestational age in weeks (dichotomized; delivered $<$ 37 weeks of gestation considered as pre-term vs. $\geq$ 37 weeks as term) and mode of delivery (Caesarean section vs vaginal birth) was taken. These records were completed by trained nurses or paediatricians at delivery. If records of routine child visits were missing, the information was obtained from the parental questionnaire. Birth weight was related to gestational age using the percentiles according to WHO [21]. Children with a birth weight $<$ 10th percentile for gestational age were defined as small for gestational age (SGA), those $>$ 90th percentile for gestational age as large for gestational age (LGA) and children with a birth weight $\geq$ 10th and $\leq$ 90th percentile were defined as appropriate for gestational age (AGA). Children with missing gestational age were classified as AGA if their birth weight was between the 10th and 90th sex–specific percentile at week 40 (P10: males: 3142 g, females: 3010 g; P90: males: 4149 g, females: 4131 g) and as LGA if it was above the 90th sex–specific percentile at week 40. For children with missing gestational age and birth weight below the 10th sex-specific birth weight percentile, no classification was made (i.e. handled as missing value).

2.2.3. Postnatal factors

The duration of exclusive breastfeeding (months) and the age at introduction of solid food into the child's diet (months) were reported by

parents in the parental questionnaire. The age at introduction of solid food was defined as the time when the child had received fruits, vegetables, cereals, or meat for the first time. Exclusive breastfeeding means that the child only receives breast milk without any other complementary food, formula or other milk.

2.3. Cardiometabolic health outcome measures

The main outcome of interest was a continuous MetS score derived based on the definition of Ahrens et al. [12]. The MetS score is calculated as the sum of z-scores reflecting the four MetS components. The z-scores of the included components were calculated based on previously published age- and sex-specific reference curves for the single components: WC z-score [22] for abdominal obesity, HOMA-IR z-score [23] for insulin resistance, the mean of TG and inverse HDL z-scores [24] for dyslipidemia, and means of age-, sex- and height-specific z-scores of SBP and DBP [25] for hypertension. Based on the same methods, extended reference percentiles up to the age of 15 years were derived to calculate the MetS score in children above the age of 11. A higher MetS score indicates a less favorable metabolic profile. Children were categorized as having MetS if at least three of the following conditions were met [12]:

- Central adiposity: waist circumference $\geq$ 90th age- and sex-specific percentile
- Hypertension: SBP and DBP $\geq$ 90th age-, sex- and height-specific percentile
- Insulin resistance: HOMA-IR $\geq$ 90th age- and sex-specific percentile
- Dyslipidemia: TG $\geq$ 90th sex-specific percentile or HDL $\leq$ 10th age- and sex-specific percentile

The measurement of WC was performed by trained nurses with an inelastic tape (Seca 200) in a standing position of the child with relaxed abdomen and feet together, midway between the lowest rib margin and the iliac crest to the nearest 0.1 cm.

SBP and DBP were measured twice at the right arm after at least 5 min of rest in seated position according to a standardised protocol with an automated oscillometric device (Welch Allyn, Inc., 4200B-E2, Skaneateles Falls, NY, USA). A third measurement was taken if the first and second measurement differed by >5 %. The mean value of the two measurements with the smallest difference was used as outcome measure.

In W0 and W1, fasting venous blood samples or capillary blood from children who refused the venous blood draw were used to assess blood lipids and blood glucose with the point-of-care analyser Cholestech LDX (Cholestech Corp.) based on enzymatic methods [26]. In W2, blood lipids and blood glucose were measured in venous blood by an enzymatic colorimetric test (cobas 701; Roche Diagnostics GmbH, Mannheim, Germany) in a central laboratory. Serum insulin concentrations were measured in venous blood by luminescence immunoassay (Immulite 2000, Siemens, Eschborn, Germany) at W0 and W1 and by a protein multiplex analyses with electrochemiluminescence technology (Sector Imager 2400, Meso Scale Diagnostics, Rockville, MD, USA) at W3 in a central laboratory and were used to determine insulin resistance with HOMA-IR. This was calculated as fasting insulin (µIU/ml) × FG (mg/dl)/405 [27].

2.4. Covariable information

Data on age (years), sex, country of residence (8 categories), parental education, and living in the intervention or control region were considered as potential covariables in the main analysis. Additionally, pubertal stage and body mass index (BMI) at the time of examination were considered in a sensitivity analysis.

The highest educational level of parents was classified according to the ISCED level (International Standard Classification of Education 2011) [28] in three categories (ISCED level 0–2: low; ISCED level 3, 4: medium; ISCED level 5, 6: high). A binary variable indicating control versus intervention regions was used to adjust for potential differences resulting from the IDEFICS intervention. Pubertal stage was classified in three categories (pre-pubertal, pubertal and not determined) based on voice mutation in boys and first menstrual period in girls. Boys and girls reported their pubertal stage using a one-page self-completion

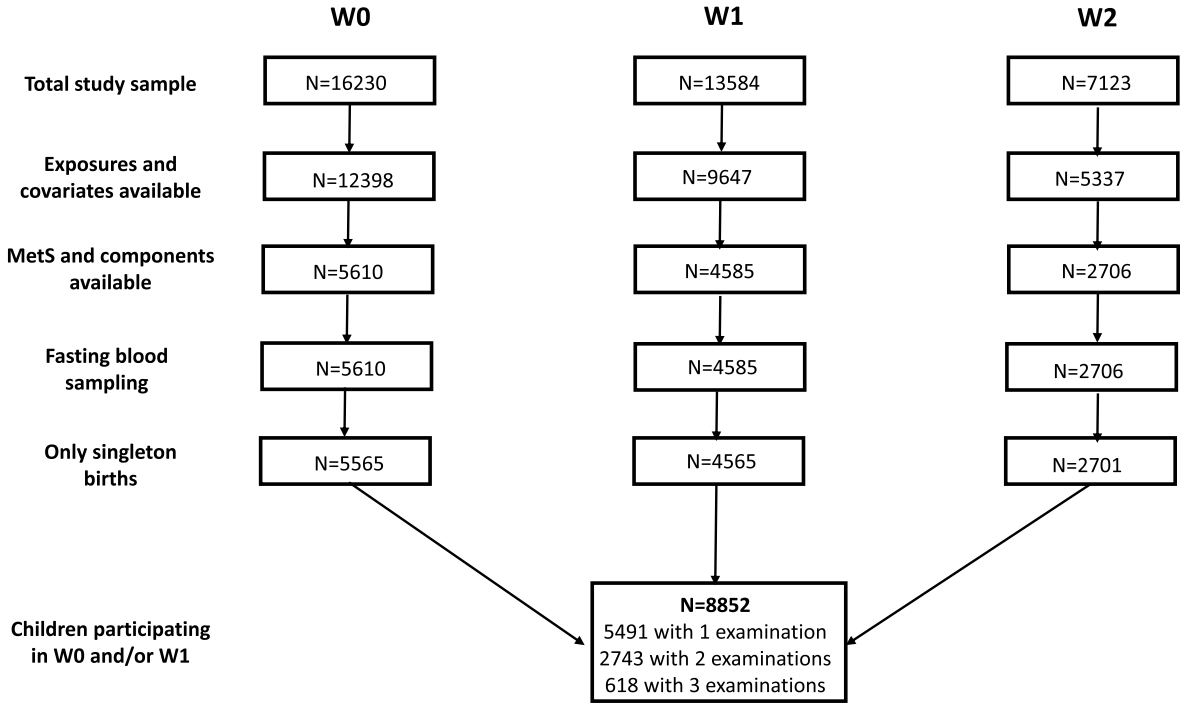

Fig. 1. Flow chart of the study population
MetS, Metabolic syndrome score; W0, Wave 0: baseline examination; W1, Wave 1: Follow-up examination after 2 years; W2, Wave 2: Follow-up examination after 6 years.

questionnaire from the age of 8 years onwards in W3 only. BMI z-scores were calculated according to the extended IOTF (International Obesity Task Force) criteria [29].

2.5. Statistical analysis

Mixed-effects models were used to analyse the associations between pre-, peri- and postnatal factors and the MetS score as well as z-scores of its components (WC, SBP, DBP, TG and HDL or HOMA-IR) over time. Mixed-effects models were chosen because they can flexibly handle unbalanced, clustered data as we have here (repeated measurements nested within children, children nested within families). Separate models were estimated for each exposure in order not to adjust for variables lying on the causal pathway between the exposure of interest and the metabolic outcomes [30]. Fig. 2 displays the (temporal) relationships among exposures that were assumed here (only arrows relevant to visualize the temporal order are shown). This means, the first model included maternal age at delivery as exposure and a basic adjustment for age, sex of the child, country, parental education and participation in the intervention (yes vs. no). When maternal smoking during pregnancy was the exposure of interest, the model was additionally adjusted for maternal age and so forth. Finally, in a sensitivity analysis, BMI z-score and pubertal stage were added to the models in order to check whether the potential associations between early life exposures and metabolic outcomes were mainly mediated by the BMI and puberty. As BMI z-score is highly correlated with the MetS score and WC z-score, only pubertal stage was added to the models with MetS and WC z-score as the outcome.

All models included random effects for family affiliation and age and the models accounted for correlations among repeated measurements taken from the same child. Continuous variables were centred to the mean before model fit to enhance interpretability (age of mother at delivery to 29.2 years, weight gain during pregnancy to 14.1 kg, exclusive breastfeeding duration to 4.4 months and introduction of solid food to 5.6 months). All models were estimated for the whole study population as well as stratified by three age groups: pre-school children 2-<6 years, primary school children 6-<10 years and teens 10-<16 years of age. Before model building, variance inflation factors (VIF) were calculated to check for multicollinearity between variables. VIF ranged from 1.01 to 1.07 i.e. collinearity between variables was negligible. All models were run using SAS Proc Mixed. We used a significance level of 0.01 to adjust at least partially for multiple testing. Results are mainly interpreted in terms of plausibility (comparing to previous literature) and clinical relevance. All analyses were performed using SAS® statistical software version 9.3 (SAS Institute, Inc., Cary, NC).

3. Results

3.1. Descriptive statistics

The analysis is based on 8852 children with 12831 measurements. 62.0 % of all children were examined only once at W0 or at W1, 31.0 % participated in one baseline (W0 or W1) and one follow-up (W1 or W2) examination and 7.0 % provided three observations. Characteristics of the study sample at the first examination are described in Table 1. The mean age of the children at the first examination was 7 years. In our sample, 15.3 % of the children were small and 11.0 % were large for gestational age. One quarter of the children were born prematurely.

Mean MetS score and z-scores of WC, SBP, DBP, HOMA-IR, TG, HDL are presented for pre-school children (2-<6 years), primary school children (6-<10 years) and teens (10-<16 years) in Table S1. MetS score and WC z-score were higher in teens as compared to pre-school and primary school children. SBP, DBP and HOMA z-scores were similar in primary school children and teens but higher as compared to pre-school children. Primary school children showed the most favorable TG z-scores.

Fig. 3 shows the percentage of children fulfilling the above described criteria for adiposity, hypertension, insulin resistance, dyslipidemia and

Table 1
Characteristics of the study sample.

	N	% or mean (SD)
Sex, % (male/female)	4506/4346	50.9/49.1
Age in years at first examination, mean (SD)	8852	7.27 (2.40)
Country, %		
- Belgium	735	8.30
- Cyprus	598	6.76
- Estonia	1166	13.2
- Germany	1113	12.6
- Hungary	2052	23.2
- Italy	1277	14.4
- Spain	972	11.0
- Sweden	939	10.6
Educational level of parents, %		
- Low	505	5.70
- Medium	4054	45.8
- High	4293	48.5
Birth weight in g, mean (SD), total sample	8852	3364 (547)
- Small for gestational age (SGA), %	1352	15.3
- Appropriate for gestational age (AGA), %	6524	73.7
- Large for gestational age (LGA), %	976	11.0
Age of mother at birth in years, mean (SD)	8852	29.2 (4.96)
Premature birth <37 week of gestation, %		
- Yes	2244	25.4
- No	5816	65.7
- Not specified	792	8.95
Delivery, %		
- Spontaneous birth	6730	76.0
- Caesarean section	2122	24.0
Smoking during pregnancy, %		
- Never	7644	86.4
- < Daily	690	7.79
- ≥ Daily	518	5.85
Weight gain during pregnancy in kg, mean (SD)	8852	14.2 (5.57)
Breastfeeding		
- Yes, %	6563	74.1
- No, %	2289	25.9
Exclusive breastfeeding duration[a], mean (SD)	6563	4.39 (1.95)
Age at introduction of solid food in months, mean (SD)	8852	5.59 (2.32)

SD=Standard deviation.
[a] Mean exclusive breastfeeding duration excluding children which were never breast feeding.

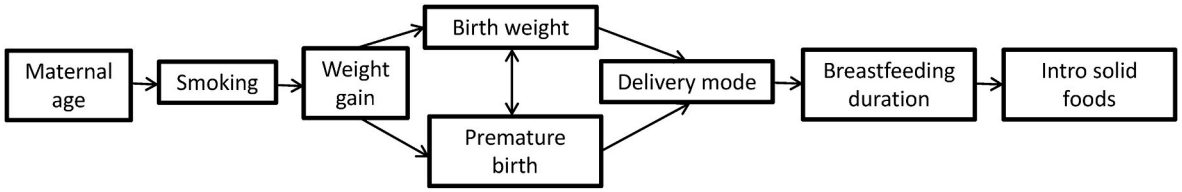

Fig. 2. Pre-, peri- and postnatal exposures in chronological order.

MetS, respectively, based on the 90 % reference percentiles. Adiposity was observed in 23.4 %, hypertension in 17.9 %, insulin resistance in 21.6 %, dyslipidemia in 17.2 % and MetS in 5.5 % of all children. Except for dyslipidemia, prevalences increased continuously across the age groups.

3.2. Associations of early life factors with MetS and its components

Tables 2a and 2b presents the associations between pre-, peri- and postnatal factors and MetS score as well as z-scores of WC, SBP, DBP, HOMA-IR, HDL and TG for the total study population. Being born LGA was positively associated with the MetS score (β = 0.67; 99 % CI 0.44, 0.90) and the WC z-score (β = 0.51; 99 % CI 0.39, 0.63) (Table 2a). Additionally, there was a weak negative association of LGA status with HDL z-score (Table 2b)). SGA status was associated with lower z-scores of WC (ß = −0.26; 99 % CI −0.37, −0.16), slightly higher z-scores of SBP and DBP (Table 2a). Weight gain during pregnancy was positively associated with the MetS score and the WC z-score (Table 2a) and showed a weak negative association with HDL z-score (Table 2b). Premature birth showed a positive association with SBP. The exclusive breastfeeding duration and age at introduction of solid food were negatively associated with HDL z-scores (Table 2b). Smoking during pregnancy points to a positive association with MetS score and WC z-score (though the confidence interval includes zero) whereas age of mother and Caesarean section delivery did not show associations with any of our outcomes.

3.3. Associations of early life factors with MetS and its components by age group

In the stratified analysis by age group, many of the associations observed for the whole study group were confirmed (Tables S2–S8). For some exposures, effect sizes changed from infancy to adolescence. For instance, effect sizes for the positive associations between born LGA and MetS as well as WC z-score decreased from the lowest to the highest age group (Tables S2 and S3). The weak association between weight gain during pregnancy and MetS observed in the total population was also strongest in the youngest age group (Table S2). In primary school aged children, a weak positive association between the age at introduction of solid food and MetS (Table S2) as well as HOMA-IR (Table S6) was observed which was not found in the total population. Also, a negative association between daily smoking during pregnancy and HDL z-score was only found in teens (Table S8), but not for the total study group.

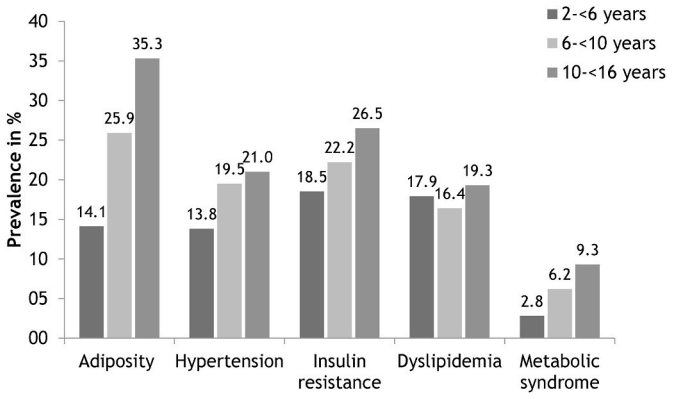

Fig. 3. Mets and MetS components exceeding the 90th reference percentiles* by age group at baseline

*Metabolic syndrome and its components are classified by percentiles derived from healthy children of the IDEFICS/I.Family cohort: adiposity: waist circumference ≥90th age- and sex-specific percentile; hypertension: SBP and DBP ≥90th age-, sex- and height-specific percentile; insulin resistance: HOMA-IR or fasting glucose values ≥ 90th age- and sex-specific percentile; dyslipidemia: triglycerides ≥90th sex-specific percentile or HDL ≤10th age- and sex-specific percentile; MetS: threshold exceeded for three or more of the cardiometabolic markers.

3.4. Associations of early life factors with MetS and its components adjusted for BMI z-score and pubertal stage

The sensitivity analysis with additional adjustment for BMI z-score and pubertal stage was conducted for all outcomes except for MetS and WC, which were only adjusted for pubertal stage, as they are strongly associated with BMI. Most results remained similar as compared to the main analysis. After adjustment for BMI and pubertal stage, the strength of associations between SGA status and our cardiometabolic outcomes increased, in particular for HOMA-IR and TG. LGA status was negatively associated with SBP only after adjustment (Table S9).

4. Discussion

We studied the associations between selected pre-, peri- and postnatal factors and cardiometabolic risk markers including the MetS in children and adolescents. LGA status was strongly associated with a higher MetS score and higher WC z-score and less strongly with lower HDL while SGA status was negatively associated with WC z-score and positively with BP. Preterm birth was positively associated with SBP. Our results partially support previous studies indicating that unfavourable early life factors, particularly high birth weight for gestational age is associated with an increased cardiometabolic risk mainly in terms of higher MetS score and adiposity [31,32]. Being born SGA showed a negative association with WC z-score in children below the age of ten which became smaller in teens. Interestingly, daily smoking during pregnancy was associated with a lower HDL z-score only in teens, i.e. the effect was seen only several years after initial exposure.

4.1. Metabolic syndrome and waist circumference

Our results indicated a 0.67 units higher MetS score in children born LGA compared to those born AGA which represents a relatively strong increase considering the means of the observed MetS score of e.g. 0.84 in primary school children and 0.11 in pre-school children. The finding of an increased risk of MetS in children born LGA is in line with that of a meta-analysis which reported a higher odds ratio of MetS (OR = 1.43, 99 % CI 1.05–1.96, I^2 = 68 %) in individuals born LGA [32]. Also, a small longitudinal cohort study evaluating outcomes at 6, 7, 9, and 11 years of age showed a higher prevalence of MetS (defined based on at least two components) in children born LGA compared to those born AGA. LGA status increased the risk of MetS approximately twofold [33]. Another study in children with obesity found a MetS prevalence of 65.0 % in children born LGA compared to 42.3 % in children born AGA and accordingly an increased risk of MetS with a hazard ratio of 2.53 [34]. In a Chinese study, the risk of MetS increased with increasing BMI but was similar in children and adolescents born LGA and AGA. In contrast to our results, adolescents born SGA had an elevated risk of MetS compared to those born AGA, but this applied mainly for adolescents with overweight or obesity [35] and is in line with a study conducted in children with overweight and obesity [11]. In an Australian population, a U-shaped relationship was observed between expected birth weight and metabolic risk where both low and high quintiles of expected birth weight (indicating SGA and LGA status) were associated with an increased metabolic risk in children [10]. Age at outcome assessment may play an important role for the association of SGA and MetS and may explain some discrepancies; while the effect estimates in our study were negative in pre-school and primary school children, they turned positive with older age. Additionally, we observed weak positive associations of gestational weight gain with MetS and WC which are in line with previous results in younger IDEFICS children [36] and results of a systematic review [37, 38].

Table 2a
Effect estimates and 99 % confidence intervals for associations of pre-, peri- and postnatal factors with metabolic syndrome score and z-scores of waist circumference, systolic and diastolic blood pressure in the total study population*.

	Metabolic Syndrome score		Waist circumference		Systolic blood pressure		Diastolic blood pressure	
	Beta	99 % CI	Beta	99 % CI	Beta	99 % CI	Beta	99 % CI
Age of mother[a] (1 unit = 1 year)	−0,01	(−0.02, 0.01)	−0.002	(−0.010, 0.006)	−0.0002	(−0.0056, 0.0105)	−0.001	(−0.006, 0.004)
Smoking during pregnancy[b]								
- Never	Ref		Ref		Ref		Ref	
- < Daily	0.22	(−0.05, 0.48)	0.10	(−0.03, 0.24)	−0.005	(−0.098, 0.088)	−0.002	(−0.094, 0.089)
- Daily	0.26	(−0.05, 0.57)	0.160	(−0.002, 0.321)	0.003	(−0.105, 0.112)	−0.01	(−0.11, 0.10)
Weight gain during pregnancy[c] (1 unit = 1 kg)	**0.03**	**(0.01, 0.04)**	**0.02**	**(0.01, 0.03)**	0.001	(−0.003, 0.006)	0.001	(−0.004, 0.005)
Birth weight[d]								
- Small for gestational age (SGA)	−0.13	(−0.33, 0.08)	**−0.26**	**(−0.37, -0.16)**	**0.08**	**(0.01, 0.15)**	**0.076**	**(0.001, 0.140)**
- Appropriate for gestational age (AGA)	Ref		Ref		Ref		Ref	
- Large for gestational age (LGA)	**0.67**	**(0.44, 0.90)**	**0.51**	**(0.39, 0.63)**	−0.01	(−0.09, 0.07)	0.03	(−0.05, 0.11)
Premature birth[e] < 37 week of gestation								
- Yes	−0.006	(−0.176, 0.164)	−0.06	(−0.14, 0.03)	**0.08**	**(0.19, 0.14)**	0.04	(−0.02, 0.10)
- No	Ref		Ref		Ref		Ref	
- Not specified	0.18	(−0.18, 0.54)	0.18	(−0.01, 0.36)	0.04	(−0.08, 0.16)	−0.03	(−0.15, 0.09)
Delivery[f]								
- Caesarean section	−0.04	(−0.21, 0.14)	0.02	(−0.07, 0.11)	−0.01	(−0.07, 0.05)	−0.03	(−0.09, 0.03)
- Spontaneous birth	Ref		Ref		Ref		Ref	
Exclusive breastfeeding duration[g] (1 unit = 1 month)	−0.001	(−0.030, 0.028)	−0.01	(−0.02, 0.01)	−0.002	(−0.01, 0.01)	−0.005	(−0.015, 0.005)
Age at introduction of solid food[h] (1 unit = 1 month)	0.031	(−0.003, 0.066)	0.005	(−0.013, 0.023)	0.010	(−0.002, 0.022)	0.004	(−0.008, 0.016)

All models are adjusted for age, sex, country, control vs. intervention region, educational level of parents and include a random effect for age and family affiliation, accounting for collinearity among repeated measurements.
Effect estimates are shown in bold if the 99 % confidence interval does not include the zero. Ref, Reference category.
[a] Centred to mean of 29.3 years.
[b] Additionally adjusted for maternal age.
[c] Additionally adjusted for maternal age and smoking; centred to mean of 14.2 kg.
[d] Additionally adjusted for maternal age, smoking, weight gain and premature birth.
[e] Additionally adjusted for maternal age, smoking, weight gain and birth weight.
[f] Additionally adjusted for maternal age, smoking, weight gain, premature birth and birth weight.
[g] Additionally adjusted for maternal age, smoking, weight gain, premature birth, birth weight and delivery mode; centred to mean of 4.4 months.
[h] Additionally adjusted for maternal age, smoking, weight gain, premature birth, birth weight, delivery mode and breast feeding; centred to mean of 5.6 months.

An elevated WC probably plays a major role for the association of LGA and MetS as we also observed that born LGA was strongly positively associated with WC. This finding supports previous study results in children with adiposity or overweight/obesity [31,39,40], including an earlier analysis in IDEFICS children (W0 and W1) [41]. Another study in children with overweight or obesity revealed that those born LGA had an increased risk of severe obesity compared to those born AGA or SGA [42]. In agreement with our results, the meta-analysis by Zhang et al. [32] found higher ORs of overweight and obesity in children born LGA with a decreasing effect size from toddler age to puberty. This is in line with the slightly decreasing effect sizes for WC from pre-school children to teens in our study. Other studies reported a positive association, according to the hypothesis that rapid catch-up growth of children with low birth weight, which usually includes SGA status, seems to determine the association with adiposity and cardiometabolic risk factors in later life [43,44].

After additional adjustment for pubertal status, we observed a positive association between daily smoking and WC, which did not appear in the main analysis. Previous studies reported that maternal smoking during pregnancy is associated with increased offspring adiposity [45] and with earlier puberty [46,47]. Additionally, overweight and obesity are strongly associated with earlier puberty in girls whereas this association is less clear in boys [48]. Further, it has been suggested that the prenatal exposure of nicotine and carbon monoxide leads to foetal growth restriction and low birth weight, which results in a stronger weight gain compared to infants of non-smoking mothers and then in an increased risk for overweight in later life [49]. Birth weight and puberty status are hence likely to lie on the causal pathway from pregnancy smoking to WC which may explain the differing results when adjusting e.g. for puberty status.

4.2. Blood pressure

We observed a positive association between being born SGA and SBP and DBP as well as between preterm birth and SBP. There is also some evidence from previous studies for an association between born SGA and increased BP in childhood, adolescence and adulthood [50]. In a Finnish cohort, mean SBP at the age of 31 was higher in those born preterm SGA compared to those born preterm AGA after adjustment for age and sex [51]. A Chinese study in 2-year-old children reported increased SBP levels only in boys born SGA, adjusted for age and weight-for-length z-score [52]. In a Brazilian cohort study, born SGA was associated with higher SBP and DBP in adolescents aged 14–15 years only after adjustment for BMI and height [53]. In the same cohort, an inverse association between born SGA and SBP at age 11 was reported which was attenuated and no longer statistically significant after adjustment for current BMI [54]. A study including participants from an Australian and a Finnish cohort observed at age 11, 18 and 25 to 26 reported no longitudinal associations between born SGA and SBP or DBP [55]. Low birth weight for gestational age can result from intrauterine growth restriction. Some studies indicate that a positive association between born SGA and BP are particularly found when children show high catch-up growth in weight [50,56,57].

Our result of a positive association of preterm birth and SBP in

Table 2b
Effect estimates and 99 % confidence intervals for associations of pre-, peri- and postnatal factors with z-scores of insulin resistance (HOMA-IR), triglycerides and HDL in the total study population*.

	HOMA-IR		Triglycerides		HDL	
	Beta	99 % CI	Beta	99 % CI	Beta	99 % CI
Age of mother[a] (1 unit = 1 year)	−0.0002	(−0.0060, 0.0056)	−0.002	(−0.007, 0.002)	0.001	(−0.004, 0.007)
Smoking during pregnancy[b]						
- Never	Ref		Ref		Ref	
- < Daily	0.09	(−0.01, 0.19)	0.03	(−0.05, 0.12)	−0.01	(−0.11, 0.09)
- Daily	0.09	(−0.03, 0.21)	0.02	(−0.07, 0.11)	0.01	(−0.10, 0.13)
Weight gain during pregnancy[c] (1 unit = 1 kg)	0.004	(−0.001, 0.009)	0.001	(−0.003, 0.005)	**−0.0052**	**(−0.0100, −0.0004)**
Birth weight[d]						
- Small for gestational age (SGA)	0.04	(−0.04, 0.12)	0.03	(−0.03, 0.09)	−0.02	(−0.09, 0.06)
- Appropriate for gestational age (AGA)	Ref		Ref		Ref	
- Large for gestational age (LGA)	0.07	(−0.01, 0.16)	0.03	(−0.04, 0.10)	**−0.092**	**(−0.177, −0.007)**
Premature birth[e] < 37 week of gestation						
- Yes	0.01	(−0.06, 0.07)	0.02	(−0.03, 0.07)	0.03	(−0.04, 0.09)
- No	Ref		Ref		Ref	
- Not specified	0.07	(-0.07, 0.20)	−0.003	(−0.109, 0.103)	0.11	(−0.02, 0.24)
Delivery[f]						
- Caesarean section	−0.02	(−0.08, 0.05)	−0.02	(−0.07, 0.03)	−0.004	(−0.067, 0.059)
- Spontaneous birth	Ref		Ref		Ref	
Exclusive breastfeeding duration[g] (1 unit = 1 month)	0.002	(−0.009, 0.013)	0.001	(−0.008, 0.010)	**−0.012**	**(−0.022, -0.001)**
Age at introduction of solid food[h] (1 unit = 1 month)	0.011	(−0.002, 0.025)	0.008	(−0.003, 0.018)	**−0.004**	**(−0.017, 0.009)**

All models are adjusted for age, sex, country, control vs. intervention region, educational level of parents and include a random effect for age and family affiliation, accounting for collinearity among repeated measurements.
Effect estimates are shown in bold if the 99 % confidence interval does not include the zero. Ref, Reference category.
[a] Centred to mean of 29.3 years.
[b] Additionally adjusted for maternal age.
[c] Additionally adjusted for maternal age and smoking, centred to mean of 14.2 kg.
[d] Additionally adjusted for maternal age, smoking, weight gain and premature birth.
[e] Additionally adjusted for maternal age, smoking, weight gain and birth weight.
[f] Additionally adjusted for maternal age, smoking, weight gain, premature birth and birth weight.
[g] Additionally adjusted for maternal age, smoking, weight gain, premature birth, birth weight and delivery mode; centred to mean of 4.4 months.
[h] Additionally adjusted for maternal age, smoking, weight gain, premature birth, birth weight, delivery mode and breast feeding; centred to mean of 5.6 months.

children and adolescents supports findings from earlier systematic reviews and meta-analyses in adult populations unadjusted for BMI [58, 59]. For 16-year-old adolescents, Sipola-Leppanen et al. reported a positive association of early preterm birth (<34 weeks of gestation) with SBP and DBP in girls with and without adjustment for BMI, but not in girls born late preterm (34–36 weeks of gestations) or in boys [60]. A positive association with SBP adjusted for BMI was also found in UK children aged 10.8 years [61] and in Chinese children aged 5–17 years [62].

We found LGA status to be negatively associated with SBP only after adjustment for BMI and pubertal status. Contradictory findings of the associations between early life exposures and blood pressure – as also reported above from other studies - might result from the 'reversal paradox' which describes an artefactual statistical effect due to inappropriate statistical adjustment for variables lying on the causal pathway between exposure and outcome [63] such as the current BMI z-score of the child.

4.3. Blood lipids and insulin resistance

In our study, weak inverse associations of being born LGA and gestational weight gain with HDL was observed. Participants born LGA had lower HDL concentrations, particularly at primary school age, compared to those born AGA. This was also shown in a meta-analysis without adjustment for BMI among the subgroup of children of mothers without gestational diabetes [32] and in a study in children with obesity [64]. In line with our study, results of a meta-analysis indicated an inverse association of gestational weight gain and the child's HDL concentration which was also rendered non-significant or attenuated after adjustment for the child's BMI [65].

Additionally, we observed a positive association of SGA with TG only after adjustment for BMI and pubertal status. Similarly, in a study including 20-40-year-old adults, a trend toward higher TG was observed in men born SGA adjusting for current overweight/obesity [66].

We did not observe associations of early life factors and HOMA-IR in our main analysis, while others reported a positive association of LGA status and HOMA-IR, even in participants with normal weight status [32]. Our study indicated a positive association between SGA status and HOMA-IR only after adjustment for BMI and pubertal stage. This is in line with several studies included in a systematic review which reported that born SGA and low birth weight were associated with higher mean HOMA-IR in children and adolescents after adjusting for age, sex, BMI and pubertal status [67]. Increased insulin resistance may result from higher liver fat in children born SGA who were shown to have a higher likelihood of severe steatosis [68].

4.4. Strengths and limitations

The large number of study participants and the fact that birth weight and gestational age were mainly obtained from maternity cards and records of routine child visits are major strengths of our study. Blood pressure and all other parameters were assessed according to highly standardised examination protocols. In addition, we individually selected covariates and confounders for the different early life exposures in order to prevent adjustment for factors lying on the causal pathway (such as BMI which should typically not be adjusted for). We conducted a sensitivity analysis with additional adjustment for current BMI z-score to enhance comparison with previous literature, and further compared associations across different age groups, as the age at outcome assessment is likely to affect the strengths of associations.

Mixed effects models are a flexible tool to handle unbalanced data, i.e. they do not require all participants to have the same number of observations. Our analyse hence did not require participation in all assessment waves such that selection effects induced by drop-outs are less likely to affect our results.

Our study also had some limitations. Misreporting of smoking behaviour cannot be precluded because smoking during pregnancy is a social taboo which may lead to social desirability bias. Additionally, breastfeeding duration and time of introduction of solid food were recalled by parents many years after weaning which may have resulted in random misclassification that could have attenuated observed associations. As the information on parity and ethnicity was not available in our population, both could not be considered in our analyses.

5. Conclusions

In conclusion, our findings provide evidence that birth weight for gestational age is strongly associated with MetS and WC and weaker with BP and HDL in children and adolescents. Further, preterm birth was found to be associated with SBP. Pubertal status seems to influence the association of maternal smoking during pregnancy with MetS and WC.

Based on our findings, we encourage monitoring the growth development of the foetus. Additionally, children born LGA, SGA or preterm warrant closer monitoring and early intervention to prevent adverse health outcomes later on.

Author contributions

Kathrin Günther and Maren Pflüger were responsible for the conceptualisation and contributed to data interpretation and writing of the manuscript. Claudia Börnhorst conducted the statistical analyses, contributed to the writing of the manuscript and critically reviewed the manuscript. Maike Wolters contributed to the data interpretation and writing of the manuscript. All authors were involved in the acquisition of the data, reviewed the manuscript and approved the submitted and published versions.

Data availability

Due to the sensitive nature of data collected, ethical restrictions prohibit the authors from making the minimal data set publicly available. Each cohort center received approval of the corresponding local Ethical Commission. Data are available on request and all requests need approval by the study's Steering Committee. Interested researchers can contact the study coordinator (i.family@leibniz-bips.de) to request data access. All requests for accessing data of the IDEFICS/I.Family cohort are discussed on a case-by-case basis by the Steering Committee.

Funding

This work was done as part of the IDEFICS (http://www.idefics.eu) and I.Family studies (http://www.ifamilystudy.eu/). We gratefully acknowledge the financial support of the European Union within the Sixth RTD Framework Programme Contract No. 016181 (FOOD), and the Seventh RTD Framework Programme Contract No. 266044.

Declaration of competing interest

The authors have no conflict of interest to declare.

Acknowledgements

The authors thank the children and parents participating in the IDEFICS/I.Family cohort for taking the time to participate in this extensive examination programme. The authors are grateful for the support provided by school boards, school staff and communities, and for the effort of all study nurses and our data managers, especially Claudia Brünings-Kuppe, Willempje Hummel-Bartenschlager, and Sandra Israel-Georgii.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2024.103808.

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