

Risk Factors Of Childhood Obesity: Lessons From The European IDEFICS Study

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Introduction

The prevalence of obesity in children is increasing in most regions of the world^{1, 2, 3, 4}. Recent data indicate that this trend has leveled off in some developed countries like the US, Australia, and some European countries^{5, 6, 7, 8, 9}, but the level is still too high. As the causal pathway leading to obesity already starts early in life it is important to understand the causes and mechanisms leading to this disorder and to find a way for effective primary prevention interventions in young children.

The assessment of the worldwide obesity epidemic is hampered by the fact that different reference systems are used to classify overweight and obesity in children leading to different prevalence estimates^{10, 11}. This problem is aggravated by the use of different anthropometric methodologies in the absence of a commonly accepted standard protocol¹².

The IDEFICS study (Identification and prevention of dietary- and lifestyle-induced health effects in children and infants) investigated the aetiology of diet- and lifestyle-related diseases and disorders with a strong focus on overweight and obesity in a large population-based cohort of 16,228 European children aged 2 to 9 years who were recruited from eight European countries. According to a standardized protocol, weight status and related health outcomes such as blood pressure and insulin resistance, direct behavioral determinants such as physical activity and diet and indirect determinants such as social/ psychological factors and consumer behavior were measured. In this way, the study tried to disentangle the causal pathways leading to obesity and other health outcomes by analyzing the complex interplay of potential risk factors. Details of the objectives, original study design, the proposed measurements and a description of the study sample have been published previously^{13, 14, 15}. Furthermore, the IDEFICS study developed, implemented and evaluated a setting-based community-oriented intervention program for primary prevention of obesity in a controlled study design¹⁶. For this purpose, in each country intervention and control regions were selected with a comparable socio-demographic profile. In the intervention regions, a coherent set of intervention modules were implemented, focusing on diet, physical activity and stress-coping capacity captured in six key messages.

In this chapter we will present the design of the aetiological part of this multi-center cohort study. In addition, using the six key messages as a starting point some major results will be discussed, where we will focus on potential risk factors of childhood obesity.

Design, subjects and methods

Study subjects

A cohort of 16,228 children aged 2 to 9 years was examined in a population-based baseline survey in eight European countries ranging from North to South and from East to West (Sweden, Germany, Hungary, Italy, Cyprus, Spain, Belgium, Estonia) from autumn 2007 to spring 2008. This baseline survey (T0) was the starting point of the prospective cohort study with the largest European children's cohort established to date¹⁵. Exactly the same survey modules were deployed at baseline (T0) and at follow-up (T1) two years later.

The study was not designed to provide a representative sample for each country. All children in the defined age group who resided in the defined regions and who attended the selected primary schools (grades 1 and 2), pre-schools or kindergartens were eligible for participation. Children were approached via schools and kindergartens to facilitate equal enrolment of all social groups. In addition to the signed informed consent given by parents, each child was asked to give verbal assent immediately before examination. Participants were free to opt out of specific modules like blood drawing. Thus, the results presented below are based on different subgroups and varying sample sizes, which are described in more detail in the respective original articles.

Questionnaires

Parents completed a self-completion questionnaire to assess gestational, behavioral and socio-demographic factors and a children's eating habits questionnaire (CEHQ) to record food frequency and dietary habits. The latter was complemented by a computer-based 24-hour dietary recall (24-hdr). Parents were offered assistance in filling in the questionnaires. In addition, a face-to-face medical interview was conducted with one parent.

Educational attainment according to the International Standard Classification of Education (ISCED)¹⁷, family income (using country-specific categories based on the average net equivalence income), employment status, dependence on social welfare and migration background of parents were recorded.

Examinations

The examination program included standard anthropometric measures¹⁸, clinical parameters such as blood pressure, collection of urine, saliva and blood for further medical parameters and genetic analyses, and accelerometer to assess physical activity. Additional examinations were only applied in subsamples, either because they were not feasible in small children (e.g. physical fitness tests, sensory taste perception) or because they were expensive (e.g. ultrasonography of the calcaneus to assess bone stiffness, analysis of blood fatty acids). Preferably, all examinations of a child took place on the same day but this was not always feasible. As one innovative component of the examination program sensory taste perception was examined where in total five tastes were included, namely sugar and apple flavor in apple juice (the latter was not tested in Cyprus) as well as monosodium glutamate, salt, and fat in crackers. Paired comparison tests were used to assess the preference for each taste. That means each child had to choose his/her preferred food sample out of a pair, which consisted of a reference sample and a modified version. Each child tasted reference before the modified version and then he/she put the preferred sample on a "smiley" on top of a game board. No-preference was not an option. For example, sweet taste was assessed by clear apple juice served in small cups of 30ml at $18 \pm 2^{\circ}\text{C}$ with the reference containing 0.53% added sucrose whereas the high-sugar sample contained 3.11% added sucrose. Sweet was always tested before fat. For fat tasting, crackers were prepared with the reference cracker consisting of water, flour, fat (8%) and salt. The modified cracker contained 18% fat. High-sweet (high-fat) preference was recorded when the child chose the sweetened juice (added fat cracker) over the basic food sample. All food samples were produced centrally and shipped to the survey centers. For further details on these and other examination modules see^{19, 20, 21}.

Blood collection: We aimed to obtain fasting blood from all children via either venipuncture or capillary sampling. It was anticipated that a sizeable number of children would refuse the venipuncture even with local anaesthesia with EMLA patches provided. To ensure that basic data on metabolic disturbances was available for as many children as possible a point-of-care analyzer was used to assess blood glucose, HDL and LDL cholesterol and triglycerides in one drop of capillary blood from the fingertip on the spot. All blood, serum, urine and saliva samples were transferred to a central bio-repository to coordinate the laboratory analyses and to ensure standardized storage and handling of samples²².

Physical activity: To monitor physical activity children wore a uni-axial accelerometer (ActiGraph® or ActiTrainer®) on a hip belt over three consecutive days including one weekend day. In school children the accelerometer was combined with a Polar® heart rate monitor using a chest belt. Resting heart rate was assessed in conjunction with the physical fitness tests. Accelerometry was complemented by an activity diary that was completed by parents over the measurement period.

Physical fitness: Components of the physical fitness tests were adopted from the European battery of cardiorespiratory and motor tests (Eurofit battery) (flamingo balance test, back saver sit and reach, handgrip strength, standing broad jump, 50 m sprint, shuttle-run test)²² that were restricted to school children.

Bone stiffness: Heel ultrasonometry which had shown good correlations with bone mineral density assessed by dual-energy-x-ray absorptiometry (DEXA) in adults²⁴ and children²⁵, as well as a high prognostic value of bone fractures in adults²⁶ was included as an optional component to assess bone stiffness of the calcaneus of the left and right foot.

Quality management

All measurements followed detailed standard operating procedures (SOPs) that were laid down in the general survey manual and finalized after the pre-test of all survey modules²⁰. Field personnel from each study center participated in central training and organized local training sessions thereafter. The coordinating center conducted site visits to each study location during field surveys to check adherence of field staff to the SOPs. Questionnaires were developed in English, translated to local languages, and then back translated to check for translation errors. All study centers used the same technical equipment that was purchased centrally to maximize comparability of data.

Databases and computer-assisted questionnaires included automated plausibility checks. All numerical variables were entered twice independently. Inconsistencies identified by additional plausibility checks were rectified by the study centers.

To further check for the quality of data, sub-samples of study subjects were examined repeatedly to calculate the inter- and intra-observer reliability of anthropometric measurements²¹. In addition, the reliability of questionnaires was checked by re-administering the CEHQ and selected questions of the parental questionnaire to a convenience sample of study participants^{27,28}. Food consumption assessed by the CEHQ was validated against selected nutrients measured in blood and

urine²⁹. The new method to analyze the fatty acid profile in a dried drop of blood was compared to the standard analysis of serum and erythrocytes from venous blood. A validation study was carried out to compare uni-axial and tri-axial accelerometers in children and to validate them using doubly labeled water as the gold standard, and to also validate body composition measures using 3- and 4-compartment models³⁰. Ultrasonometry was compared to DEXA to assess bone mineral density in a sample of children from Sweden and Belgium³¹.

Risk factors

Key messages

The intervention mapping protocol³² was applied to develop the components of the IDEFICS intervention³³. Based on the major suspected risk factors for the development of obesity, i.e. physical activity, dietary and stress-related behaviors, the IDEFICS intervention focused on three main intervention areas formulated as six key messages³³: (1) increase daily physical activity levels, (2) decrease daily television (TV) viewing time, (3) increase the consumption of fruit and vegetables, (4) increase the consumption of water, (5) strengthen parent-child relationships and (6) establish adequate sleep duration patterns (see Figure 1).

Nutrition 	Physical activity 	Stress 
Daily water → Less soft drinks	Reduce TV-viewing	Spend more time together → Family time
Daily fruit & vegetables	Daily PA → Safe bicycle lanes → Outdoor playing	Adequate sleep duration





Figure 1: The six key messages of the IDEFICS intervention, illustrations were used in the corresponding leaflets for parents and children

We searched the literature for accepted national or international recommendations regarding the health-related behaviors listed above with respect to the prevention of childhood obesity (for details see³⁴) and determined the percentage of children who “spontaneously” complied with these recommendations at baseline. Figure 2 shows the overall percentage of children adhering to these recommendations. A more detailed figure is given in³⁴.

In the following, we will first summarize some main results related to the behaviors addressed in the IDEFICS intervention before highlighting some additional results as e.g. regarding genetic susceptibility.

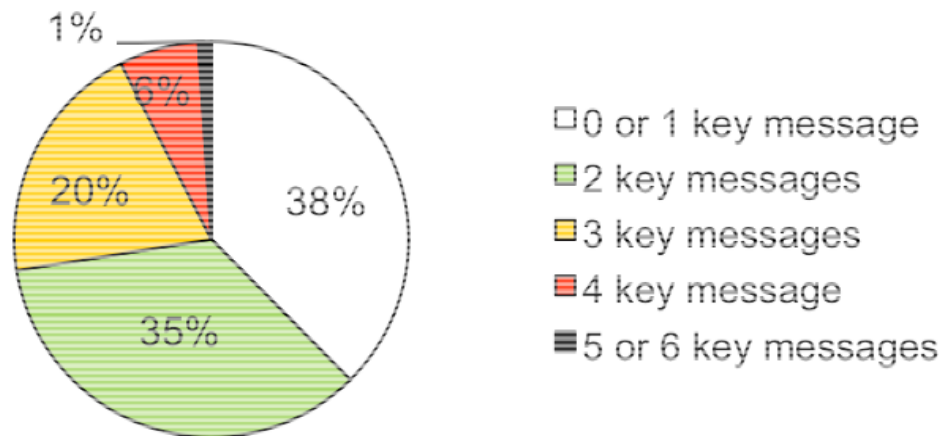


Figure 2: Percentage of children adhering to recommendations based on the six key messages of the IDEFICS intervention

Main results related to key messages

Diet: Numerous sources of measurement error have been encountered when operating with dietary data. In young children, dietary data are commonly assessed through parental proxies, which may result in additional measurement error. Meals or snacks not observed by the proxies may lead to underreporting of certain foods and total energy intake whereas difficulties in estimation of portion sizes/consumption frequencies as well as social desirability may lead to both, over- or underreporting³⁵. In IDEFICS, the prevalence of underreporting and over reporting estimated based on age- and sex-specific Goldberg cut-offs were 8.0% and 3.4% (24-hdr data), respectively³⁶. The prevalence of underreporting increased with BMI z-score, household size and was higher in low income groups. Especially social desirability and the parental perception of their child's weight status seemed to affect the reporting accuracy. When analyzing diet-obesity associations, the associations were strongly affected or even masked by measurement errors where Börnhorst et al.³⁷ found that consideration of the reporting status and inclusion of a propensity score for misreporting were useful tools to counteract attenuation of effect estimates.

Due to these problems to correctly assess children's dietary behavior it is difficult to reveal individual associations between diet and overweight/obesity: Using a principal component analysis, Pala et al.³⁸ identified four major dietary patterns: snacking, sweet/fat, vegetables/whole meal, and protein/water in children's dietary behavior assessed by food frequency questionnaires. In a multilevel mixed regression analysis of the longitudinal data with change in BMI category³⁹ from thin/normal weight at T0 to overweight/obese at T1 as outcome, adjusted for baseline BMI, age, sex, physical activity and family income, they observed a lower risk of becoming overweight/obese for children in the highest tertile of the vegetables/whole meal pattern compared to children in the lowest tertile. Further effects of dietary behavior can be observed taking TV viewing additionally

into account as potential risk factor.

TV viewing: Lissner et al.⁴⁰ investigated the association between daily TV time and the presence of a TV/video/DVD in the child's bedroom and overweight /obesity by estimating odds ratios adjusted for sex, age and parental education. Both, having a TV in the child's bedroom and consumption daily TV time of more than 60 minutes showed a positive association with the weight status of children in all countries⁴⁰. It could also be shown that, independent of taste preferences, children who watched more TV had a higher propensity to consume foods high in fat and/or sugar⁴⁰.

Moreover, associations between screen habits and sweetened beverage consumption were observed which could also be seen longitudinally: children who were exposed to commercial TV at baseline (T0) had a higher risk of consuming sweetened beverages at T₁⁴¹. A further longitudinal analysis revealed a substantial impact of TV viewing and other screen habits on the consumption of sugary drinks and on increase in BMI⁴².

Physical activity: A 'movability index' was developed as a tool for urban planners to reflect opportunities for physical activity in the urban environment of children. Based on geographical data, the index integrated different urban measures such as the availability of destinations, i.e. playgrounds, green spaces and sport facilities, as well as the street connectivity considering intersections, foot paths and cycle lanes that were both assessed using a so-called kernel density approach (Figure 3). Additionally, residential density and land use mix were included in the index. In a pilot study that was conducted in the intervention region in Germany, it was shown that opportunities for physical activity in the urban neighborhood of school children, i.e. short routes and particularly the availability of destinations, were positively associated with physical activity levels⁴³.

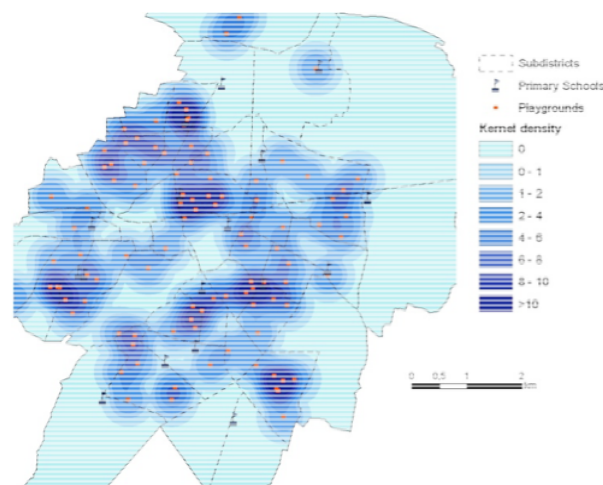


Figure 3: Availability of playgrounds within the German intervention community, Delmenhorst, estimated via kernel density

The analysis of physical activity concentrated on its effect on bone stiffness and weight status. The duration of moderate-to-vigorous physical activity (MVPA) showed huge variations across Europe⁴⁴ and had a protective effect against overweight/obesity, in particular in school-age children.

The prevalence of obesity was elevated in children exercising less than the recommended 60 minutes moderate-to-vigorous physical activity per day (Figure 4⁴⁵).

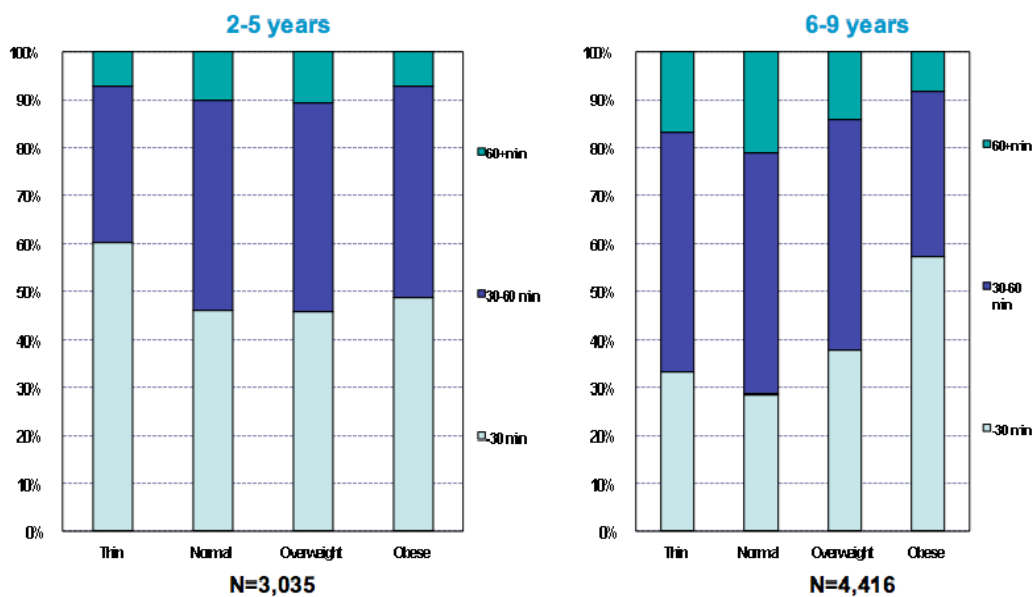


Figure 4: Duration of MVPA (60 sec. interval, Evenson) by age and weight

Family life: Based on the parental questionnaires, a “health-related quality of life score (QoL)” adapted from the Questionnaire for Measuring Health-Related Quality of Life in Children and Adolescents KINDL⁴⁷, a “difficulties score” and a “pro-social behavior score”, where the latter two were adapted from the Strengths and Difficulties Questionnaire⁴⁸ and two family lifestyle measures were constructed. The health-related QoL score showed a substantial variation among all countries. Based on a generalized mixed model with country as random effect, adjusted for sex and age group a negative association between the QoL and overweight/obesity was observed regardless of the socio-economic status of the families. In additional analyses, we especially considered the question whether parents and their children share family meals at least one per day (Do you sit down with your child when he/she eats meals?) as a proxy for family life during meals. Here, we observed a clear gradient of an increasing prevalence of overweight/obese children ranging from a prevalence of 17.1% among those sitting always together to a prevalence of 36.2% among those who reported to never/rarely sit together during meals.

Sleep: Sleeping behavior was investigated with respect to the factors influencing sleep duration, the association of sleep duration and obesity, and the physiological changes involved in this association. Sleep duration showed marked variation across Europe, but exhibited an ecological correlation with the prevalence of overweight/obesity⁴⁹. This correlation was confirmed by individual level analysis, as sleep duration was negatively associated with weight status, particularly in school-age children (see Table 1)⁵⁰.

Adjusted OR*	>10h to < 11h	>9h to < 10h	< 9 h
Pre-school	0.93 (0.63; 1.36)	1.08 (0.73; 1.61)	1.38 (0.87; 2.19)
School	1.46 (0.96; 2.22)	1.88 (1.23; 2.86)	3.53 (2.24; 5.54)
All	1.10 (0.84; 1.45)	1.36 (1.03; 1.80)	2.22 (1.64; 3.02)

*adjusted for age (continuous), ambient temperature (continuous), European region (north versus south)

Table 1: Odds ratios (OR) and 95% confidence intervals (CI) for the association between sleep duration and overweight/obesity (reference > 11 hours)

Multivariate linear regression and quantile regression models confirmed an inverse relationship between sleep duration and measures of overweight/obesity. The estimate for the association of sleep duration and body mass index (BMI) was approximately halved after adjustment for fat mass (FM), but remained statistically significant. The strength of this association was also markedly attenuated when adjusting for insulin mainly for the upper BMI quantiles. This means that the inverse relationship between sleep duration and BMI is mainly explained by the association between sleep duration and FM. Insulin may explain part of this association, in particular at the upper tail of the BMI distribution.

Additional results

Bone stiffness: Sioen et al.⁵¹ investigated the association between various markers of body fat and the bone status that was assessed as calcaneal bone stiffness by ultrasonography. Partial correlation analyses, linear regression analyses, and ANCOVA stratified by sex and age groups showed that pre-school children with higher BMI had a lower calcaneal stiffness index (SI), while primary school children with higher BMI had a higher calcaneal stiffness index. After adjusting for fat-free mass, both pre-school and primary school children showed an inverse association between BMI and calcaneal stiffness. Thus, fat-free mass seems to be a confounder in the association between SI and weight status in primary school children but not in pre-school children. We concluded that muscle mass is an important determinant of bone stiffness.

Genetic susceptibility (for abbreviations please see Table 2): The analysis of the FTO gene (Ref.-SNP 9939609) showed that the odds ratio for overweight/obesity was elevated by 40% among children carrying the AA-allele as compared to the TT-allele. Similar positive associations were found for waist circumference, waist-to-height ratio and the sum of skinfold thicknesses. These associations were confirmed in the longitudinal analysis even after adjustment for age, sex, country, intervention group and BMI at T₀.

It was also investigated⁵³ whether NMU single nucleotide polymorphisms (SNPs) and haplotypes, as well as functional ADRB2 SNPs, are associated with bone stiffness in children. An additional question was whether NMU and ADRB2 interact with each other. The reasoning behind this question is that energy metabolism and bone mass are both regulated by the neuromedin U, encoded by the NMU gene, which is a hypothalamic neuropeptide, while effects of catecholamine

hormones and neurotransmitters in bone are mediated by the beta-2 adrenergic receptor, encoded by the ADRB2 gene. After adjusting for multiple testing, the stiffness index (SI) was significantly associated with all NMU SNPs. A non-significant decrease in SI was observed in ADRB2 rs1042713 GG homozygotes, while children carrying SI-lowering genotypes at both SNPs (frequency=18.4%) showed much lower SI than non-carriers. Thus, it was for the first time shown that the NMU gene impacts on the regulation of bone strength through an interaction with the ADRB2 gene.

Genetic marker	Abbreviation
Adrenoceptor beta 2	ADRB2
Carnitine palmitoyltransferase 1A	CPT1A
Fat mass and obesity-associated gene	FTO gene
Fatty acid synthase	FASN
Insulin receptor	INSR
Leptin receptor	LEPR
Messenger ribonucleic acid	mRNA
Neuromedin U	NMU
Peroxisome proliferator-activated receptor α	PPAR α
Solute carrier family 27 (fatty acid transporter), member 2	SLC27A2

Table 2: List of genetic markers and corresponding abbreviations

Biomarkers: The analysis of transcriptional biomarkers in peripheral blood showed the following: high expression levels of CPT1A, SLC27A2, INSR, FASN, or PPAR α were indicative of a lower risk for the insulin-resistant or dyslipidemia state associated with obesity, whereas low LEPR mRNA levels appeared as a marker of high low-density lipoprotein cholesterol, independently of body mass index⁵⁴.

Sensory taste perception: A unique feature of the IDEFICS study was the assessment of taste thresholds and taste preferences in order to reveal possible associations with overweight/obesity in a population-based approach with a large number of subjects. The cross-sectional analysis⁵⁵ of the baseline survey showed that both fat and sweet taste preference were independently associated with weight status. Children with a taste preference for added fat and those with a taste preference for added sugar had significantly higher odds for being overweight/obese after adjusting for possible confounders. The positive associations with overweight/obesity were seen in all age groups and both sexes, but most pronounced in girls.

Conclusion and future perspectives

The above summary of some of the results obtained from the IDEFICS cohort confirms that childhood obesity results from a complex interplay of a variety of health-related lifestyle factors. The living environment, social conditions, economic pressures and family lifestyles have drastically changed over recent decades. Often both parents are working and the time spent together with their children is limited. Self-prepared meals from local ingredients are replaced by fast and ready-made foods. Concerns about safety on the streets, limited availability of play spaces, exposure to TV and increased time playing computer games have pushed physical activity out of the daily lives of young people. These changes profoundly impact children's health, particularly those in the most vulnerable groups.

Building on the IDEFICS cohort, the I. Family study (www.ifamilystudy.eu) wants to unravel the factors at play and their complex interplay in even more detail as e.g. the determinants of dietary behavior and food choice. Its ultimate aim is to identify targets for effective interventions and to support policy development, enabling more families to make healthier choices. Some of the IDEFICS children are now experiencing changes around puberty, as they are in the transition between childhood and adulthood. Even if children have adopted healthy eating and activity patterns, their lives change considerably as they become teenagers. Healthy routines can easily be lost and replaced by unhealthier habits, perhaps because of the influence of marketing or peer pressure. This transition phase has to be carefully studied to get a deeper insight into the effects of changes in lifestyle that may maintain health or may cause ill health from a life-course perspective.

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