**The LIFE Child study – overview of the study program and acquired data of a deeply phenotyped population-based perinatal and pediatric cohort in Germany**

**Tanja Poulain1\*, Ronny Baber1, 2, Mandy Vogel1, Diana Pietzner1, Toralf Kirsten1,Anne Jurkutat1, Andreas Hiemisch1, 3, Anja Hilbert4, 5, Jürgen Kratzsch2, Joachim Thiery2, Michael Fuchs6, Christian Hirsch7, Franziska G. Rauscher8, Markus Loeffler1, 9, Antje Körner1, 3, 4, Matthias Nüchter1, Wieland Kiess1, 3, 4 and the LIFE Child study team**

**1**LIFE Leipzig Research Center for Civilization Diseases, University of Leipzig, Philipp-Rosenthal-Strasse 27, 04103 Leipzig, Germany

**2**Institute of Laboratory Medicine, Clinical Chemistry, and Molecular Diagnostics (ILM), University of Leipzig, Liebigstrasse 27, 04103 Leipzig, Germany

**3**Department of Women and Child Health, Hospital for Children and Adolescents and Center for Pediatric Research (CPL), University of Leipzig, Liebigstrasse 20a, 04103 Leipzig, Germany

**4**Integrated Research and Treatment Center Adiposity Diseases, University of Leipzig, Philipp-Rosenthal-Strasse 27, 04103 Leipzig, Germany

**5**Department of Medical Psychology and Medical Sociology, University of Leipzig, Philipp-Rosenthal-Strasse 55, 04103 Leipzig, Germany

**6**Section of Phoniatrics and Audiology, Department of Otorhinolaryngology, University of Leipzig, Liebigstrasse 10-12, 04103 Leipzig, Germany

**7**Department of Pediatric and Preventive Dentistry, University of Leipzig, Liebigstrasse 12, 04103 Leipzig, Germany

**8**Department of Ophthalmology, University of Leipzig, Liebigstrasse 10-14, 04103 Leipzig, Germany

**9**Institute for Medical Informatics, Statistics, and Epidemiology, University of Leipzig, Härtelstrasse 16-18, 04107 Leipzig, Germany

\*Corresponding author: e-mail address: [tpoulain@life.uni-leipzig.de](mailto:tpoulain@life.uni-leipzig.de), telephone number: +49 (0)341 97 16737, fax number: +49 (0)341 97 16729

The LIFE Child study is a large population-based longitudinal childhood cohort study conducted in the city of Leipzig, Germany. As a part of LIFE, the Leipzig Research Center for Civilization Diseases, it aims to monitor healthy child development from birth to adulthood and to understand the development of civilization diseases such as obesity and allergy. In order to achieve this objective, more than 5000 children and their families are planned to participate in a comprehensive study program comprising medical, psychological, and sociodemographic assessments as well as the collection of biological samples. In two subcohorts, the birth cohort and the obesity cohort, additional specific assessments are performed. Optimal data acquisition, process management, and data analysis are guaranteed by a professional team of physicians, certified study assistants, quality managers, scientists and statisticians. Due to the high popularity of the study, more than 3000 children have already participated until the end of 2015, and two thirds of them participate continuously. The large quantity of acquired data allows LIFE Child to gain profound knowledge on the development of children growing up in the 21st century. This article reports the number of available and analyzable data and demonstrates the high relevance and potential of the study.

Keywords: longitudinal study, cohort study, children, obesity, pregnancy, epidemiology

**Introduction**

The LIFE Child study (clinical trial number NCT02550236) is a population-based longitudinal cohort study conducted in Leipzig, a city in central Germany with more than 500.000 inhabitants. It is part of the LIFE study, a large research project of the University of Leipzig aiming at monitoring the development of lifestyle diseases over the life span. While the LIFE Adult study focused on the development of civilization diseases in adults, especially in the elderly population [1], the LIFE Child study evaluates the period from pregnancy to adulthood [2].

With recruitment age ranging between the 24th week of gestation and 16 years of child age and annual follow-ups, the study combines a cross-sectional and a longitudinal design and covers a broad age range. Recruitment started in 2011 and will continue until 2021. Until 2015, more than 3000 children and their parents had participated, and some of them had already completed their fourth annual follow-up. As recruitment continues, new assessments are integrated to address upcoming research questions. In addition to the cooperation with institutions from the University of Leipzig, the Max Planck Institute for Human Cognitive and Brain Sciences, or the Integrated Research and Treatment Center Adiposity Diseases in Leipzig, the LIFE Child team is interested in sharing their expertise and engaging in collaborations with new research partners.

In the last years, several (birth) cohort studies have been established [3]. Examples in Europe are the Generation R study [4], the Avon Longitudinal Study of Parents and Children (ALSPAC) [5], or the Danish National Birth Cohort [6]. Also in Germany, further large cohort studies exist [7–9]. However, as research is in development, it is important to establish new cohort studies that are able to answer upcoming research questions by using new methods. In LIFE Child, the very detailed study program (containing the collection of DNA, blood, hair and urine, the examination of different cardiovascular, metabolic and other body functions, as well as the assessment of personal traits, habits, environmental and sociodemographic factors) guarantees a particularly profound phenotyping of children growing up in the 21st century. The main objectives of the LIFE Child study are described in the following paragraphs.

**Research questions and hypotheses**

The basic concept behind the LIFE Child project is the concept of salutogenesis, i.e., the main focus of the study is on the health of children. The hypothesis is that health and normal child development depend on many internal and external factors that operate even before birth. Internal factors of interest are physiological, e.g., genetic and biological, parameters as well as psychological aspects such as personality and life style. External factors investigated in LIFE Child are the social environment and social class, medical care and medication, but also environmental parameters such as residential area, school system, or air pollution. The interplay of these factors is expected to influence the long-term development and overall wellbeing of children. Therefore, the main question that LIFE Child aims to answer is how these factors interact and which aspects of child development they affect.

In addition to the objective of monitoring normal child development, LIFE Child aims to describe the development of civilizations diseases, i.e., diseases that are linked to lifestyle and can be observed frequently in Western societies. The civilization disease that is most widely examined in LIFE Child is overweight/obesity. The main interest in this field is to detect internal and external risk and protective factors that influence the development, i.e., the onset, aggravation or improvement, of overweight. Another research question is how suffering from overweight or obesity impacts children’s quality of life and accelerates the development of comorbid diseases.

LIFE Child is a project in the field of applied research, i.e., the knowledge gained in LIFE Child is aimed to be put into practice in order to improve medical and psychological care and therefore children’s wellbeing. By taking measurements and biological samples from a large number of children it is, for example, possible to create new reference values that can be used in hospitals and clinics. At the same time, new methods or medical equipment can be validated and this might in the future improve or facilitate clinical practice and research.

**Study cohorts**

All children and parents participating in the LIFE Child study are invited to the study center – the Research Center for Civilization Diseases – in Leipzig. They mainly stem from the city or the close proximity of Leipzig. The secondary school attended by most of the children (69%) is the ‘Gymnasium’ (leading to the highest German secondary school degree). 22% attend the ‘Oberschule’ (leading to the medium school degree), and 9% attend other school forms. As in other cohort studies [4, 8, 10], household income and educational level of mothers and fathers suggest a selection towards a higher socioeconomic status. Following the Winkler Index (an Index of the socio-economic status based on household income, education, and occupational prestige [11]), 14% of participating children belong to the lower, 41% to the middle, and 45% to the higher social milieu.

All participating children complete the **basic study program**. Children that pass this program only, constitute the **LIFE Child health** cohort. Depending on the age of children, participation in this program takes between two and six hours. It covers interviews, examinations, psychological and motoric tests, questionnaires, and the collection of biological samples. Some assessments are completed by children and parents, others by children only. Additionally, whole school classes are invited to the study center and pass the basic study program. At the end of 2015, the LIFE Child health cohort consisted of 2900 children (51% male) between one and 20 years of age. In the five years since study initiation, more than 600 children have already passed their fourth follow-up.

There are currently two subcohorts that are examined in more detail within LIFE Child, the **LIFE Child birth** cohort and the **LIFE Child obesity** cohort. In addition to the basic study program, participants of these subcohorts pass a more detailed program. The aim of the LIFE Child birth cohort is to detect behavioral, biological and environmental factors during pregnancy, birth or in the early postnatal period that might influence future health and the development of diseases. Previous studies underlined, for example, the role of nutrition and diabetes during pregnancy in early child development [12, 13]. In the LIFE Child birth cohort, assessments start during pregnancy (24th and 36th week of gestation). At birth, samples of cord blood and placental tissue are collected. Before being integrated in the LIFE Child health cohort (at the age of one year), infants are examined at two time points in their first year of life, at three months and at six months. Until the end of 2015, more than 500 pregnant women had already participated in the study. 400 infants (51% male) had participated at the age of three months, and 79% of them had completed the study program at six months.

The LIFE Child obesity cohort comprises a group of overweight or obese children between the ages of six and 20 years and a normal weight control group. By establishing this cohort, the LIFE Child study aims to identify facets of children’s behavior, environment and biological predispositions that are associated with normal weight or overweight, respectively, and to study the development of comorbid diseases (e.g., metabolic disorders). Research in this field is essential, because the prevalence of overweight in childhood has increased dramatically and obesity is known to cause severe damages such as increased blood pressure, insulin resistance, or diabetes [14–17]. In the LIFE Child obesity cohort, 300 overweight or obese children (49% male) have been recruited by the end of 2015, and 30 of them have already passed their fourth follow up.

Figure 1 demonstrates the development of recruitment of children of each cohort and of pregnant women since study initiation. Figure 2 shows the number of recruited study participants in each age group (from the 24th week of gestation until the age of 20 years), including information on the number of follow-ups.

**Fig. 1** Development of recruitment of children (health, birth, and obesity cohorts) and pregnant women (birth cohort) from 2011 (initiation of LIFE Child) to 2015

**Fig. 2** Age distribution and number of follow-ups of recruited children (health, birth, and obesity cohort) and pregnant women (birth cohort) from 2011 (initiation of LIFE Child) to 2015

W = Week of gestation, M = Age of children in months, Y = Age of children in years

**Assessments**

The assessments in LIFE Child comprise interviews, examinations, tests, questionnaires, and biological samples. A short clinical examination is passed by all children at the beginning of each study day. It comprises an auscultation of the lungs, an inspection of the skin, and a temperature measurement. Biological samples are collected from nearly all children and parents. Blood samples are analyzed directly after collection or sent to the biobank. Medical and psychological measurements are assessed in specific age groups or cohorts. Most of the psychological measures are standard questionnaires, others are created for the use in the LIFE Child study and are, after having proven their validity and reliability, intended to be published and disseminated.

*Medical assessments in children*

One focus of the LIFE Child study is on assessing the physiological and medical health status of participants (see Table 1). In addition to a conventional anthropometry (covering skin fold thickness, weight, height, the circumference of arm, leg, waist, neck, hip, thorax, and abdomen, as well as the biparietal diameter), a 3D Body Scanner (VITUS XXL 3D) is used. It scans the whole body with non-hazardous laser beams and therefore represents a very detailed, objective, and rapid method to measure the human body [18].

Allergies, dental problems, reduced visual performance, and physical inactivity can have severe negative consequences for children’s wellbeing and health [19–22]. Furthermore, the knowledge on the typical development in these fields of child health is limited and therefore needs to be extended. In addition to the detailed anthropometric assessment, study participants therefore undergo examinations of their cardiovascular and metabolic system, teeth, eyes, respiratory function, physical activity, risk to allergy, or speaking and singing voice. The dental exam includes a detailed inspection of teeth, gingiva, and jaw function (e.g., caries, misalignment, periodontitis, overbite/overjet, craniomandibular dysfunction) as well as a questionnaire on children’s oral health-related quality of life [23, 24]. The eye examination consists of an objective measurement of refractive error, the assessment of visual acuity, ocular biometric measurements of the eye (e.g., axial length and corneal radii) and detailed 3D volume scans of the retina and optic nerve by optical coherence tomography. A corresponding interview records factors associated with the prevalence of refractive error, e.g., time of outdoor activity. The voice analysis explores genetic, hormonal, and environmental factors affecting the voice and provides information on typical volume and pitch range of the voice. A standardized voice range profile was used to examine the speaking and singing voice.

In the LIFE Child obesity cohort, specific examinations of children’s metabolic system (oral glucose tolerance test (oGTT), basal metabolic rate), their cardiovascular system (electrocardiography (ECG)), or their liver function (fibroscan) are performed. In the oral glucose tolerance test, insulin and glucose are measured every 15 to 30 minutes during a time period of 120 minutes (according to the WHO criteria), thereby offering an excellent investigation of metabolic processes and the establishment of reference values that will be of use in clinical practice.

**Table 1** Medical assessments in children participating in the LIFE Child study. Information refers to the time period between study initiation in 2011 and the end of 2015. Numbers are rounded.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Assessment | Type | Age range in years | Cohort | Acquisition period | Number of measurements | Number of persons | Number of max. visit |
| **Anthropometry**  Conventional  Body Scan | E  E | 0-19  5-18 | H, B, O  H, O | 2011-15  2011-15 | 8000  4400 | 3400  2100 | 6  4 |
| **Metabolic**  Basal metabolic rate  Electrical bioimpedance  analysis  oGTT | E  E  E | 8-19  5-18  6-19 | O  H, O  O | 2014-15  2013-15  2011-15 | 100  2700  1000 | 100  1600  600 | 1  3  5 |
| **Cardiovascular**  Blood pressure  ECG | E  E | 0-19  6-19 | H, B, O  O | 2011-15  2011-15 | 8000  700 | 3400  500 | 6  4 |
| **Dental**  Examination of teeth and gingiva  Examination of jaw function | E  E | 1-18  10-18 | H, O  H, O | 2011-15  2011-15 | 5100  2200 | 2700  1200 | 4  4 |
| **Eye/Vision**  Optical coherence  tomography  Examination of refractive error, ocular biometry, and visual acuity | E  E | 4-18  3-18 | H, O  H, O | 2015  2014-15 | 200  2000 | 200  1500 | 1  2 |
| **Physical activity**  Motor skills  Accelerometry | T  E | 6-18  6-19 | H, O  H, O | 2011-15  2012-15 | 5100  600 | 2300  400 | 5  4 |
| **Lung function**  Spirometry | E | 6-18 | H, O | 2011-15 | 3400 | 1800 | 4 |
| **Allergy**  Allergy questionnaire [25, 26] | Qa | 0-1 | B | 2012-15 | 1100 | 600 | 3 |
| **Miscellaneous** Fibroscan  Medication Puberty status Speaking and singing voice  Neurological exam  Hand scan | E  A  E  E  E  E | 8-19  0-19  0-18  6-17  0-18  2-19 | O  H, B, O  H, B, O  H, O  H, B, O  H, O | 2013-15  2011-15  2011-15  2011-15  2011-15  2011-15 | 200  5800  7300  2400  5300  5800 | 200  2900  3100  1300  2700  3000 | 1  5  5  4  5  5 |

A = Anamnesis, E = Examination, Q = Questionnaire, T = Test, H = Health cohort, B = Birth cohort,   
O = Obesity cohort, oGTT = Oral glucose tolerance test, ECG = Electrocardiography  
a External assessment (by parents)

*Psychological assessments in children*

Another focus in LIFE Child are psychological, social and environmental factors influencing the health of children. Table 2 summarizes these assessments. In order to gain insight into the (changing) life styles of children, their media consumption, leisure time activities, and consumption of drugs (e.g., cigarettes, alcohol) are assessed. Psychosocial aspects that are assessed in LIFE Child are quality of life, body perception, personality, risk behavior (sensation seeking), and susceptibility to hyperkinetic disorders. The cognitive development of children between the age of three months and 3,5 years is assessed by using the Bayley Scales of Infant and Toddler Development, third edition [27], a standard instrument measuring the cognitive, motoric and language development of infants. In collaboration with the developers of the test, Pearson Clinical Assessments, LIFE Child contributed to the German normalization of the third test version. Another focus of questionnaires is on children’s nutrition and sleep.

**Table 2** Psychological assessments in children participating in LIFE Child. Information refers to the time period between study initiation in 2011 and the end of 2015. Numbers are rounded.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Assessment | Type | Age range in years | Cohort | Acquisition period | Number of measurements | Number of persons | Number of max. visits |
| **Life style**  Media consumption Leisure time activities  Consumption of nicotine, alcohol, and drugs | Qa  Qa  Q | 4-18  1-14  10-19 | H, O  H, O  H, O | 2011-15  2011-15  2011-15 | 4600  5300  3000 | 2100  2500  1400 | 5  5  5 |
| **Psychosocial aspects**  Life events  Quality of life:  KIDSCREEN-27 [28]  SDQ [29]  Body Esteem Scale  Sensation Seeking: AISS [30]  Hyperkinetic diseases:  DISYPS-KJ [31] | Q  Q  Qa  Q  Q  Q | 10-19  8-18  3-17  8-18  14-19  7-19 | H, O  H, O  H, O  H, O  H, O  O | 2011-15  2011-15  2011-15  2011-15  2011-15  2011-15 | 3100  4000  5800  4000  700  900 | 1400  1800  2700  1800  400  500 | 5  5  5  5  5  5 |
| **Cognitive development**  Bayley Scales [27] | T | 0-3 | H, B, O | 2011-15 | 1200 | 700 | 5 |
| **Nutrition**  Food Frequency Questionnaire [32]  Child Feeding Questionnaire [33]  Eating Disorder Examination-Questionnaire [34] | Q  Qa  Q | 6-19  2-15  8-18 | O  H, O  H, O | 2011-15  2011-15  2011-15 | 700  4900  2500 | 500  2400  1300 | 4  5  5 |
| **Sleep**  Sleep Self Report [35]  Children’s Sleep Habits Question-naire (CSHQ) [36] | Q  Qa | 8-18  0-14 | H, O  H, B, O | 2012-15  2011-15 | 2300  4400 | 1400  2200 | 3  5 |
| **Miscellaneous**  School record | Q | 7-18 | H, O | 2011-15 | 4100 | 1900 | 5 |

Q = Questionnaire, T = Test, H = Health cohort, B = Birth cohort, O = Obesity cohort  
a External assessment (by parents)

*Medical and psychological assessments in parents*

Parents of children also perform examinations (e.g., anthropometry, voice analysis) and questionnaires (see Table 3). In the LIFE Child birth cohort, (future) mothers are examined in even more detail. In the 24th week of gestation, they perform an oGTT. This examination allows the detection of gestational diabetes, a discussed risk factor for pregnant women as well as for unborn children [37, 38]. Additional assessments in either the 24th or 36th week of gestation include questionnaires on nutrition, allergy, and sleep habits during pregnancy.

**Table 3** Medical and psychological assessments in parents accompanying their children in LIFE Child. Information refers to the time period between study initiation in 2011 and the end of 2015. Numbers are rounded.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Assessment | Type | Age range in years | Cohort | Acquisition  period | Number of measurements | Number of persons | Number of max. visits |
| **Anthropometry**  Body scan | E | 21-53 | H, B, O | 2011-15 | 5800 | 2700 | 6 |
| **Metabolic**  oGTT | E | 21-41 | B | 2011-15 | 400 | 400 | 1 |
| **Allergy**  Allergy Questionnaire [25, 26] | Q | 21-41 | B | 2011-15 | 900 | 600 | 4 |
| **Eye/Vision**  Examination of refractive error | E | 27-55 | H, O | 2013-15 | 1300 | 1000 | 2 |
| **Life style**  Leisure time activities | Q | 22-53 | H, B, O | 2011-15 | 5600 | 2500 | 4 |
| **Psychosocial aspects**  Perceived health: PHQ [39]  Attachment to partner: Bochum Adult Attachment Questionnaire  [40, 41]  Personality:  BFI-10 [42] | Q  Q  Q | 20-53  21-45  23-53 | H, B, O  H, B, O  H, B, O | 2011-15  2011-15  2011-13 | 8000  1300  1200 | 3100  700  1200 | 7  5  1 |
| **Nutrition**  Food Frequency Questionnaire [32] | Q | 21-41 | B | 2011-15 | 500 | 500 | 1 |
| **Sleep**  Berlin question-naire for preg- nant women [43] | Q | 21-41 | B | 2011-15 | 600 | 400 | 3 |
| **Miscellaneous**  Speaking and singing voice Fertility | E  Q | 25-69  22-42 | H, O  H, B, O | 2011-15  2012-15 | 500  1000 | 500  600 | 1  5 |

E = Examination, Q = Questionnaire, H = Health cohort, B = Birth cohort, O = Obesity cohort, oGTT = Oral glucose tolerance test

*Laboratory measurements*

Serum, whole blood and urine are sent to the Institute of Laboratory Medicine, Clinical Chemistry and Molecular Diagnostics for highly standardized same day analysis of up to 77 biomarkers (see Table 4). The analyzed biomarker panel is specific for the different cohorts (children of different ages, pregnant women, nursing women, children in the obesity cohort). Depending on the volume of blood drawn the measurements can vary between participants even from the same age and cohort. Nucleic acids are processed and analyzed as described elsewhere [1]. The number of genome wide analyzed DNA and RNA is shown in Table 5. For the whole blood analysis of 26 amino acids, free carnitine and 34 acylcarnitines native EDTA whole blood is spotted on filter paper and the dried blood spot cards are stored at - 80 °C after 3 h of drying until batch analysis. Sample pretreatment, measurement and analysis of data are described in detail elsewhere [1, 44, 45].

**Table 4** Laboratory analysis in study participants of the LIFE Child cohorts

|  |  |
| --- | --- |
| Group | Biomarkers |
| Electrolytes | sodium, potassium, chloride, magnesium |
| Liver function | alanine transaminase, aspartate transaminase, gamma-glutamyltransferase, bilirubin (total and direct), total protein, albumin |
| Kidney | creatinine, cystatin C, urea, uric acid |
| Cardiac markers | creatine kinase, troponine T high sensitive, N-terminal prohormone of brain natriuretic peptide |
| Lipid metabolism | cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, apolipoprotein B, apolipoprotein A1, trigycerides, lipoprotein (a) |
| Glucose metabolism | glucose, insulin, C-peptide, glycated hemoglobin (HbA1c) |
| Iron metabolism | transferrin, ferritin |
| Vitamins | folic acid, vitamin B12 |
| Bone metabolism | alkaline phosphatase, phosphate, calcium, osteocalcine, beta-crossLaps, calcitonin, propeptide of type I collagen, parathormone, 25-hydroxy vitamin D3 |
| Growth | insulin-like growth factor 1, insulin-like-growth-factor – binding-protein-3 |
| Endocrine function/hormones | cortisol, luteinizing hormone, follicle stimulating hormone, estradiol, testosterone, sex hormone-binding globulin, dehydroepiandrosterone sulfate |
| Thyroid function and antibodies | thyrotropin (TSH), free triiodothyronine, free thyroxine, TSH receptor antibodies, thyroglobulin antibodies, thyreoperoxidase antibodies |
| Inflammatory mediators | interleukin 6, C-reactive protein high sensitive |
| Allergy diagnostics | specific immunoglobulin E sx1 (timothy grass,rye, birch, mugwort, C. herbarum, D. pteronyssinus, cat, dog), fx5 (hen’s egg, cow’s milk, fish, wheat, peanut, soy), total immunoglobulin E |
| Hematology | complete blood cell count with differential, reticulocytes |
| Urine | albumin, creatinine, immunoglobulin G, alpha-1-microglobulin, total protein, urine dip stick |

**Table 5** Biomarker analysis of participants of the LIFE Child study by age, cohort, maximal number of measurements and number of participants. Information refers to the time period between study initiation in 2011 and the end of 2015. Numbers are rounded.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Biomarker group | Age range in years\* | Cohort | Number of measurements\* | Number of participants\* |
| Electrolytes | 0 – 51 | H, B, P, N, O | 6800 | 3600 |
| Liver function | 0 – 51 | H, B, P, N, O | 6800 | 3600 |
| Kidney | 1 – 45 | H, P, O, | 6500 | 3300 |
| Cardiac markers | 0 – 51 | H, B, P, N, O | 7400 | 3600 |
| Lipid metabolism | 0 – 51 | H, B, P, N, O | 7400 | 3600 |
| Glucose metabolism | 6 – 51 | H, P, N, O | 7000 | 1900 |
| Iron metabolism | 1 – 51 | H, P, N, O | 5500 | 2100 |
| Vitamins | 0 – 51 | H, B, P, N, O | 6000 | 3600 |
| Bone metabolism | 0 – 51 | H, B, P, N, O | 8000 | 3600 |
| Growth | 0 – 18 | H, B, O | 3200 | 1400 |
| Endocrine function/hormones | 3 – 51 | H, P, N, O | 5000 | 2000 |
| Thyroid | 0 – 51 | H, B, P, N, O | 8000 | 3600 |
| Inflammatory mediators | 0 – 51 | H, B, P, N, O | 7000 | 3600 |
| Allergy diagnostics | 0 – 45 | H, B, P, O | 5000 | 2300 |
| Hematology | 0 – 51 | H, B, P, N, O | 8000 | 3600 |
| Urine | 0 – 51 | H, B, P, N, O | 7500 | 3600 |
| metabolomic profile | 0 – 51 | H, B, P, N, O | 7500 | 3600 |
| gene expression | 0 – 18 | H, B, O | 1000 | 1000 |
| genome wide genotyping | 0 – 18 | H, B, O | 2500 | 2500 |

H = Children from the health cohort, B = Children from the birth cohort, P = Pregnant women, N = Nursing women, O = Obesity cohort  
\*For lack of space, children and parents are not separated

*Biobanking*

In the LIFE Child study stabilized (Tempus, Thermo Fisher Scientific) and unstabilized whole blood, serum, EDTA-plasma, urine, breast milk, peripheral blood mononuclear cells (PBMC, CPT-Vacutainer, Becton Dickinson), and dry blood cards are collected (see Table 6). Besides those liquid samples, stool (Stratec Molecular, Germany), hair, and biopsies of umbilical cord and placenta are stored. DNA isolation is realized within 48 hours after blood withdrawal on the Autopure LS platform (Qiagen) with chemistry by Qiagen and Stratec Molecular. RNA isolation is done in batches using the Norgen I RNA purification kit (Norgen Biotek). The ethics committee of the University of Leipzig (Reg. No. 264-10-19042010) allowed to draw a blood volume of the thousandth part of body weight in ml. Between 4 and 26 aliquots of serum and plasma are produced depending on the age range of the study participants (see Table 6). Together with the other biomaterials up to 49 aliquots per study participant can be collected in 2D-barcoded cryotubes (FluidX) and automatized in straws (CryoBiosystems IMV), using standardized operating procedures. The samples should be stored within 2 hours post blood withdrawal at – 80 °C or at temperatures lower than – 150 °C in the gas phase of liquid nitrogen [1].

**Table 6** Aliquots per participant sorted by biomaterial, age range and cohort of the LIFE Child study. Samples are aliquoted in straws (0.3 ml) and cryo-vials (up to 2.0 ml) and stored in the gas phase of liquid nitrogen   
(< - 150 °C) and in ultra-low temperature freezers (- 80 °C), respectively. From each Tempus tube a RNA sample can be isolated. Information refers to the time period between study initiation in 2011 and the end of 2015. Numbers are rounded.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Biomaterial | Age range in years\* | Cohort | < - 150 °C\* | - 80 °C\* | Number of participants\* |
| Serum | 0 – 51 | H, B, P, N, O | 105000 | 18000 | 6000 |
| EDTA-plasma | 0 – 51 | H, B, C, P, N, O | 90500 | 4000 | 6000 |
| Urine | 0 – 51 | H, B, P, N, O | - | 65000 | 6000 |
| PBMCs | 3 – 51 | H, P, N, O | 4000 | - | 6000 |
| Breast milk | 20 – 51 | N | - | 4600 | 200 |
| Dry blood spot cards | 0 – 51 | H, B, P, N, O | - | 11400 | 6000 |
| Stabilized whole blooda | 1 – 51 | H, P, N, O | - | 6600 | 6000 |
| DANN | 0 – 51 | H, B, P, N, O | - | 10000 | 6000 |
| RNA | 1 – 18 | H, O | - | 1000 | 1000 |
| Stool | 0 – 3 | H, B | - | 300 | 200 |
| Hairb | 0 – 51 | H, B, P, N, O | - | 10000 | 6000 |
| Umbilical cord biopsy | 0 | B | - | 1600 | 500 |
| Placenta biopsy | 0 | B | - | 1400 | 500 |

H = Children from the health cohort, B = Children from the birth cohort, P = Pregnant women, N = Nursing women, O = Obesity cohort  
< - 150 °C = Aliquots stored in the gas phase of liquid nitrogen at temperatures below – 150 °C, - 80 °C = Aliquots stored in ultra-low temperature freezers at – 80 °C, PBMCs = Peripheral blood mononuclear cells  
a = Stabilized whole blood in Tempus tubes, b = Hair stored at room temperature  
\*For lack of space, children and parents are not separated

**Quality management**

The LIFE Child team strives for optimal data quality and therefore exhibits an elaborated quality management system. Clinical assessments and interviews are conducted by physicians (pediatricians, gynecologists, dentists, eye specialists) or nurses. The other assessments are conducted by professional study assistants consisting of psychologists, sports and nutritional scientists. At study initiation, the whole study program was tested in a pilot study. Before a new assessment is integrated in the study program, the study team is trained and certified by internal or external experts and the procedures of each assessment are documented in detail. After the initial training, one study assistant continues to regularly supervise the quality of the assessment, to certify new assistants and to recertify assistants that have been absent for a longer period of time. Additionally, the team meets weekly in order to exchange on problems encountered. The quality of acquired data (e.g., the amount of missing or erroneous values) as well as the inter-rater reliability is assessed regularly by a central data management team and reported to the whole study team. In the rare case of unsatisfactory results, the training is intensified.

**Data management**

*Data acquisition*

Acquisition, storage and processing of assessed data is organized and supported by the central data management team. For medical and psychological assessments, three ways of data acquisition have been implemented: online, offline, and appliance-based. In the online way of data acquisition, data are captured and directly (i.e., during the assessment) entered into an electronic input form. Most of the data are collected in this way. In the offline way of data acquisition, data are initially documented manually (paper-pencil-version) and entered into the input form after the assessment. This is the case if direct data entry would be too distracting for the children, e.g., during the assessment of their cognitive and language skills. In the appliance-based way of data acquisition, data are initially recorded by medical devices, e.g., the Body Scanner, and extracted later on.

Collection, preparation, and transfer of biological samples are organized and recorded by an in-house developed laboratory information and management system (LIMS) called CryoLab. After preprocessing, one portion of the samples is transferred to and directly analyzed by the central laboratory unit of the University Hospital. Another portion is stored in the biobank.

Every night, all collected data are transferred and integrated into the central LIFE Research Database hosted by the LIFE Research Center for Civilization Diseases. Twice a day, a copy of all data is sent to a central server located at the University of Leipzig. From there, additional backups are sent to three tape libraries positioned at different university institutions.

*Data availability*

LIFE Child is happy to share acquired data with interested researchers of all fields. In order to obtain the relevant data, scientists are required to write a research proposal including main hypotheses, work plan, a list of items intended to be analyzed, and a data use agreement of all collaborators. Research proposals are evaluated by a specific LIFE committee. After approval of the proposed research project, cooperations can be initiated and data are made available.

**Ethics, data privacy**

The study was designed in accordance with the declaration of Helsinki [46] and under the supervision of the Ethics Committee of the University of Leipzig (Reg. No. 264-10-19042010). Each participant is informed about the study program, the long-term use of data, potential risks of participation, and the right to withdraw from the study. Informed consent is obtained from all individual participants included in the study. In the rare cases of relevant incidental findings (e.g., a new clinical diagnosis), these are reported to the families as well as their primary care physicians [47].

In order to ensure data privacy, each participant receives several pseudonyms. The first, primary, pseudonym is linked to personal and contact information. The further, secondary, pseudonyms are created as soon as researchers work with the respective data. For each research project, an independent pseudonym is created. The different members of the LIFE Child team have access to only one of either the primary pseudonym or a secondary pseudonym. It is therefore impossible to link personal information to analyzed data.

**Recruitment, retention, and evaluation**

Study participants are recruited via advertisement at different institutions such as university hospitals, local clinics, public health centers, kindergartens, schools, and partner study centers. Detailed information, including a video, on the study program and the possibility to participate are also published on the homepage of LIFE (life.uni-leipzig.de).

In order to keep recruited participants interested in the study, different retention strategies are applied and regularly adapted. At each visit, participants receive a small monetary incentive as well as a little present. Pregnant women receive an ultrasound video of their baby. In order to stay in contact between two visits, the LIFE Child team is sending Christmas and birthday cards as well as newsletters.

To check satisfaction of participants with the study program, parents as well as children complete an evaluation form at the end of each study day. Figure 3 displays word clouds containing the most frequent responses given by children and parents on the question of what they liked most during the study day. 99% of parents and 96% of children participating in LIFE Child reported that they could imagine participating in the study in the next year. 67% of all children performed at least one follow-up. In order to improve this already high participant engagement, the LIFE Child team is exploring factors that might explain attrition, drop-outs, or the cancelation of appointments [48].

**Fig. 3** Word clouds showing the most frequent responses given by children and parents on the question of what they liked most during the study day

**Summary and discussion**

This article describes the aims, development, and structure of the LIFE Child study and reports the current amount of data available for further analysis. LIFE Child is a population-based cohort study examining children from birth to adulthood. Through the cross-sectional and longitudinal design, the study is able to provide portraits of children’s health and behavior in different age groups and, at the same time, descriptions of their individual development over a long time period. Whereas the basic study program is performed by all participating children, two subcohorts pass an even more comprehensive program, thereby providing detailed information on the prenatal and early postnatal development (LIFE Child birth cohort) and on the development of overweight and obesity (LIFE Child obesity cohort).

Strengths of the study are the broad age range, the detail of phenotyping, and the comprehensive methodology. Participants are aged between three months and 19 years and pass a study program covering the collection of biological samples, the examination of important body functions, and the assessment of skills, traits, and habits. Other strengths of the study are the adaptive study program and the availability of data for interested researchers of different scientific fields. This provides the opportunity to answer upcoming research questions and to initiate cooperations. Taken together, the study has the potential to provide profound knowledge on the development of children growing up in the 21st century.

**Compliance with Ethical Standards**

**Funding:** This publication is supported by LIFE – Leipzig Research Center for Civilization Diseases, University of Leipzig. LIFE is funded by means of the European Union, by means of the European Social Fund (ESF), by the European Regional Development Fund (ERDF), and by means of the Free State of Saxony within the framework of the excellence initiative. The Integrated Research and Treatment Center Adiposity Diseases is funded by the German Federal Ministry of Education and Research (grant 01EO1501).

**Conflict of interest:** The authors declare that they have no conflict of interest.

**Ethical approval:** All procedures performed in studies involving human participants are in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent:** Informed consent is obtained from all individual participants included in the study.

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