BMJ Open

Infants' immunisations, their timing and the risk of allergic diseases (INITIAL): an observational prospective cohort study protocol

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To cite: Wrenger J, Martin DD, Jenetzky E. Infants' immunisations, their timing and the risk of allergic diseases (INITIAL): an observational prospective cohort study protocol. *BMJ Open* 2023;**13**:e072722. doi:10.1136/bmjopen-2023-072722

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2023-072722).

Received 14 February 2023
Accepted 11 June 2023

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ABSTRACT

Introduction Vaccinations are considered to have a large impact on disease control, hence a multitude of vaccines in infancy is recommended. Retrospective studies suggest a possible relation between timing, kind or number of vaccines given in the first year of life and the subsequent incidence of allergic diseases. It must be clarified whether a causal relationship exists to ensure safety and reduce vaccine hesitancy.

Methods and analysis Due to the high recommendation rate of vaccines, a long-term randomised controlled trial is not considered as ethically acceptable. Therefore, this study aims to observe prospectively the allergic incidence at the age of 5 years after various vaccine interventions in the early months of life.

Parents of infants up to the age of 4–6 weeks will be recruited before the first recommended vaccination. Relevant prognostic factors for allergies, status of immunisation and general health will be evaluated up to the age of 5.

Allergic symptoms will be assessed by the International Study of Asthma and Allergies in Childhood-questionnaire and a medical confirmation of the allergy is mandatory. The main objective is to compare the incidence of asthma, atopic dermatitis, rhinoconjunctivitis, food allergy or any of these atopies at the age of 5 between infants who were not vaccinated or were vaccinated according to recommendations in the first year of life.

The sample size calculation with about 4000 participants can prove a 5% difference to the basic prevalence with about 80% power and global 5% alpha error for the five primary endpoints adjusting according to Bonferroni-Holm and assuming a rate of 10% not early vaccinated infants.

Ethics and dissemination The study was registered (DRKS00029677) and has received approval by the ethics committee of Universität Witten/Herdecke (no. 113/2022). The results will be published.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The prospective longitudinal cohort study design will assess incidence in various allergic diseases like atopic dermatitis, rhinoconjunctivitis, asthma and food allergy in relation to time, kind and number of vaccinations in children up to 5 years of age.
⇒ This study allows various analyses regarding possible long-term effects of vaccinations that have been largely unclear so far.
⇒ The study design, based on the observations of parents and paediatric documentation, allows double-checked study data collection.
⇒ A major limitation is lack of randomisation, possible loss-to-follow-up, missing data or lack of technical access that could lower the validity of the study sample.
⇒ The number of delayed-vaccinated infants may be too small, the influencing factors too numerous, the recruitment too challenging and the observation period of 5 years too short to show relevant differences.

INTRODUCTION

Vaccinations with defined antigen doses are considered to be one of the largest public health achievements worldwide.[1] It is presumed that many diseases and deaths have been prevented by them.[2] Accordingly, vaccination schedules include an increasing number of vaccinations over time, particularly for infants. But as highly effective drugs, vaccines have the potential to produce negative side effects, although those are presumed to be rare.[3]

At the same time the number of children younger than 5 years of age with atopic diseases has increased especially in high-income countries.[4 5] As possible factors influencing this development socioeconomic status, genetic aspects, parental smoking or inner-city residence and many others are discussed.[6] However, the impact of the increasing number of vaccinations during the first year of life on this development is not considered. Besides the number of vaccines administered, their timing, which differs widely comparing different national recommendations, could be of importance for this topic. There are hints that delaying the time of the first vaccination could reduce the incidence of food allergy and atopic dermatitis.[7] On the other hand in many countries

worldwide a start of immunisation as early as possible in life is considered essential for the infants' protection against severe disease.[8] In Germany it is recommended to start immunisation against rotavirus within 6 weeks of age followed by vaccination against tetanus, diphtheria, pertussis haemophilus influenzae type B, poliomyelitis and hepatitis B including two boosters. With 10 months of age immunisation against measles, mumps, rubella and varicella is recommended. At 24 months of age at least 79.1% of children have received immunisation against tetanus, diphtheria, pertussis haemophilus influenzae type B, poliomyelitis and hepatitis B. At 15 months of age 89.1% have received the first measles, mumps and rubella immunisation and 83% have the first varicella immunisation.[9]

Especially for the immunisation of infants it is unknown if a high burden of diseases could be a result of early vaccinations.[10] But the scientific evidence through studies is uncertain and long-term consequences are largely unknown. For example, both an increased prevalence of asthma and other atopic diseases in vaccinated children[11 12] and protective effects of specific vaccinations in early childhood have been described.[13] More recent studies tend to conclude that negative long-term effects may occur, but there are only a few. Yet, those studies show qualitative deficiencies like missing definitions of study outcomes or not fully blinded research teams.[14] In addition, studies looking at the prevalence of allergic reactions after vaccination tend to look at a short period after vaccination, not at long-term effects[15] and often do retrospective studies.[16] Thus, prior symptoms that may indicate a link to an adverse reaction to vaccination but are not severe enough for parents to consult their physician are not recorded.

Another difficulty with recent studies in the context of vaccination is the focus on different aspects. Due to the complexity of vaccination, most studies focus on one aspect and, for example, compare the effect on atopic diseases of vaccines with the vaccine-preventable disease,[17] focus on different types of vaccines like inactivated or live-attenuated vaccines,[18–20] adjuvants[21] or on vaccines in special populations like the anthroposophical community.[22] They do not focus on a whole vaccine programme in a whole population, and compare it to absolutely unvaccinated children[23] so it is difficult to compare the different studies and relate them to an entire population.

Therefore, one reason to do a prospective cohort study is to be able to map the impact of an entire vaccination programme on the population compared with absolutely no vaccination in the first year of life. Another aspect is the possibility to record atopic diseases that are too rare to be measured in a randomised control trial.

Further ethical concerns may make it difficult to conduct other types of studies. To assess side effects of pharmaceuticals, randomised control trials are necessary and present the methodical standard. Because it is seen as ethically inappropriate to withhold vaccinations from infants for a period of 5 years, it is impossible to create a randomised control group. Therefore, it is necessary to conduct a study of the highest possible level of evidence which is a prospective planned observational study with a clear a priori design, sample size calculation, defined confounders and study endpoints. Due to the lack of high quality in recent studies the objective of this study is to identify differences in the development of atopic diseases like asthma, atopic dermatitis, rhinoconjunctivitis and food allergy in children who receive vaccinations based on the national schedule of vaccination in the first year of life and those who receive no vaccination during the first year of life.

The objective of this cohort study is to contribute to the understanding of the possible effects of vaccination on allergy development in children. As a preventive measure, vaccinations are given to healthy children, therefore they have to meet high safety standards. Because they are given to a large number of children worldwide, the impact of possible unknown effects is of high relevance. Furthermore, additional knowledge about possible positive as well as negative effects supports an informed, free decision of parents. It is therefore helpful to prevent possible vaccination hesitancy, which is defined by the WHO[24] as one of the greatest threats to people's health worldwide, on the one hand and exclude allergic increase on the other hand. In addition, because immunisation status is not systematically recorded in Germany, this study can provide information on the immunisation status of 1-year-old children.

METHODS AND ANALYSIS

Study design

Vaccines aim to ensure immunity against specific infections and hence may modulate the immunity in general. Existing vaccine efficacy studies often use surrogates, but safety aspects as well focus on a short period after vaccination. Long-term randomised studies against placebo do not exist and even long-term unvaccinated control groups are scarce. Long-term randomised intervention studies with a group without vaccination are considered as unethical, due to the expected increased risk of infections. Therefore only the free choice of time,[7] kind[25] and number[21] of vaccination could be evaluated in a study design.

Existing studies assuming the relationship of immunity intervention due to vaccinations and allergic diseases seem to be mainly retrospective, at least in the definition of research question. Further they consider often very specific either time or specific kind or number of vaccination. This limits external validity noticeable. Hence this protocol describes a long-term, prospective cohort study. The protocol was registered in an international register in August 2022: https://drks.de/search/de/trial/DRKS00029677.

During the first year of life the immune system is developing; concomitant most vaccinations are given as inactivated immune intervention in the first year of life.

This question was already retrospective raised,[26] but not prospective investigated. Therefore, the primary outcome of this study aims at the comparison between the group which were vaccinated according to recommendations in Germany and those not vaccinated during the first year of life. Other comparisons than time, for example, regarding kind and number are possible in a large prospective cohort, but are not the primary research question.

In the context of vaccination the parental view is often neglected, hence this study is parent based. Due to this fact, the workload for treating physicians is reduced and the interaction bias between parents and physicians has to be recorded. Parents are asked to record allergic symptoms validated as disease by a physician.

As a possible follow-up study it is considered to invite children with allergic diagnoses after the end of the study period to undergo more detailed atopy diagnostic like skin allergy tests, measurement of total IgE and/or specific IgE in serum, blood count of eosinophiles and measurement of the pulmonary lung function if it has not been done before. For this further examination a separate funding and additional informed consent will be obtained.

Sample selection

Study participants, that is, expectant or new parents, are recruited by various professionals: midwives, obstetrical clinics and gynaecologists or other professionals who work with young families, like social workers. After the birth families are approached by the paediatrician of family physician at appointment for the U3 (a routine preventive medical check-up in Germany at the age of 4–5 weeks) about the possibility to participate in this observational study with distributed flyers.

Physicians and other interested professionals/stakeholders have to register on the study website (www.initial-studie.de) in order to receive flyers for distribution to parents. For external validation, the number and source of recruited participants can thus be recorded. Expectant or new parents are invited either via above mentioned flyers or further multipliers-related advertisements such as posters, websites and newsletters. If recruitment rates of multipliers and parents are not achievable in this way, undirected solicitation such as social media may be used additionally.

Inclusion and exclusion criteria

Expectant or new parents (a) are informed via the study website www.initial-studie.de and have to consent electronically (b) via registration in a separate Research Electronic Data Capture (REDCap)-database.[27 28] Therefore, access to digital devices and an email address (c) is mandatory for study registration and participation. Affiliation with the German healthcare system and sufficient knowledge of German language (d) are needed.

If the infant at registration is older than 12 weeks (e) or another child of the same parents already participates in the study (f) the parents will be excluded from analysis with this child.

Data collection

Parents should register and hence give consent to participate in the study until 6 weeks of age of their child. In exceptions, participation is possible latest at 12 weeks of age, but without considering the vaccination advice aspect.

The parents are invited via email to fill out electronic surveys, stored in REDCap system.[27 28] During the 5 years, parents are interviewed 10 times, with most interviews occurring in the first and second years of life. After that, they receive survey questionnaires on each birthday.

Parents receive an additional email reminder 1 and 2 weeks after scheduled survey dates to record vaccination and treatment, symptoms and any disease.

In case of parental uncertainty, preventive medical check-ups, vaccination reports or clinical report can be uploaded as scan, screenshot or photo. They have to be then documented by study personnel.

Parents will be invited to answer the electronic questionnaires when their children reach certain age limits, which are based on preventive medical check-up dates and vaccination (cf. table 1).

Quality control

Contact information and endpoint variables are mandatory, other information, such as confounder variables are voluntary. Certain relevant fields are randomly checked

Table 1 Survey schedule of INITIAL study

Age of child (months)/separate surveys	<1½	1½	3	5 and 7	12	16	24, 36 and 48	60
Informed consent	X	X						
Family background (confounder)		X						
Decision-making		X	X					
Vaccination and health status (group definition, confounder, endpoints)			X	X	X	X	X	X
Allergy questionnaire (endpoints)					X		X	X
Closing—family background (confounder)								X
Optional: further laboratory investigations								(X)

regarding completeness and conclusiveness by the study personnel. These queries are documented in a separate, hidden case report form.

To receive a double-checked primary endpoint, parents have to validate reported allergic diseases by uploading documentation prepared by their doctor.

Definition of vaccination group (with complete recommendation or without any or other subgroups in the first year of life) will be performed independent from definition of validated allergic disease at 5 years of age. An independent expert team may be then formed for both specific definitions after study closure for final analysis. Approved analysis data sets will then be combined for blinded statistical analysis.

Patient and public involvement

Possible multipliers were already involved in the study design and contributed their scientific questions. They are asked to actively participate in the recruitment and provide feedback on the way the study is promoted. In order to achieve acceptable study compliance, in addition to transparency, the public must be involved via scientific publications, posters, websites, newsletters or conferences.

During the study process parents are also involved and get the option to communicate wishes and suggestions for improvement of data collection. During online conferences and group discussions parents get help on their questions regarding the report forms and can bring in their ideas regarding scientific questions and analyses.

Measurements

Allergy questionnaire

To assess the typical symptoms of allergic diseases, parents are asked to answer on every child's birthday a specific allergy questionnaire from the 'International Study of Asthma and Allergies in Childhood' (ISAAC-questionnaire).[22]

Allergy

The ISSAC questionnaire covers the atopies asthma, atopic dermatitis and rhinoconjunctivitis during the past year.

They focus on aspects that are predominantly also mentioned in the corresponding guidelines, like the German Guidelines Asthma—Diagnosis and Therapy,[29] the 'Guidelines of care for the management of atopic dermatitis' of the American Academy of Dermatology[30] and the guidelines of the European Academy of Allergy and Clinical Immunology.[31]

With regard to asthma development, the ISAAC-questionnaire does not consider if the patient stayed in hospital because of respiratory obstruction or if skin testing or measurement of specific IgE in serum was positive. Those aspects are evaluated in the health status.

In addition, the definition of food allergy is not covered by the ISAAC-questionnaire. It follows the guidelines of Sk2 guideline on the management of IgE-mediated food allergies (Worm *et al*, 2021). Assessed symptoms are:

- Vomiting, nauseas, diarrhoea, abdominal pain, haematochezia.
- Dyspnoea or cyanosis.
- (Dry) cough.
- Eczema, itching, swelling of lips/tongue/palate.
- Weight loss, failure to thrive, food refusal.
- Dizziness, syncope, anaphylaxis, shock.

Of course, parents report on the health status, whether any of the endpoints have been diagnosed by a physician in the meantime.

Vaccination and health status

Vaccination is documented according to the schedule of the 'Ständige Impfkommission'.[32] Parents are asked if their child got vaccinated on every survey answering a medical questionnaire. To assess the vaccination strategy, possible vaccination-related reactions and diseases typical for atopic genesis, parents are asked to continuously note vaccination dates, type and name of vaccine, time and kind of reaction (eg, fever or rash), symptoms or diseases that the parents interpret as being vaccination-related. When parents are not sure about the given vaccine, they can upload a scan of their child's vaccine passport.

Children count as completely vaccinated when they received two rotavirus vaccines, three shots of the sixfold vaccine against tetanus, diphtheria, pertussis haemophilus influenzae type B, poliomyelitis and hepatitis B and one shot against measles, mumps, rubella and varicella whereas the varicella vaccination can also be given as a single vaccination. Only children immunised with in Germany approved vaccines are included as fully vaccinated. Children are counted as unvaccinated when they received no vaccination in the first year of life at all.

Additional symptoms and medical interventions are as well reported in the health status, such as medical diagnoses and measures, including allergies or atopy relevant symptoms (cf. see above), medication, physician contacts and possible confounders for the allergy endpoints.

The selection of confounders is based on questionnaires of previous studies with similar objectives,[13 33] analyses of influencing factors[6 34] and a scoping literature search prognostic factor in allergy reviews (online supplemental appendix 1). To assess possible confounders for atopy the following aspects will be asked initially:

- Demographic data of the parent supplemented by the question about name and city of the visited office and animals with fur living in the household.
- Health data of the child at birth.
- Probiotics for babies.
- Data about the pregnancy (age, medication, health status, smoking).
- Smoking status of parents and household.
- Siblings and other children living in the household.
- Allergic and chronic diseases in the family of origin.
- Attitude towards vaccination assessed via 7C-Scale (Betsch *et al*, 2018).

Other possible confounders will be assessed during the study period or in the end by an additional parental questionnaire:

- Dealing with breast feeding and infant formula.
- Commencement of supplementary food.
- Characteristics of nutrition (omnivorous, vegetarian, vegan, unprocessed cow's milk).
- Pollutants in the household.

Primary study endpoint

Five primary outcomes are assessed: The occurrence of atopic dermatitis, rhinoconjunctivitis, asthma, food allergy or any of these allergic diseases at 5 years of age.

Secondary study endpoints

Secondary endpoints are the description of the vaccination distribution in children younger than 5 years focusing on the kind, number and time of vaccination also compared with the recommended strategy, other allergies and other measuring points (eg, at 1 and 3 years of age). Another endpoint is the description of the kind and time of vaccine advice and the parents' decision-making process. This endpoint will be described in a separate study protocol (DRKS00030716).

Sample size calculation

The calculation of the size of participants is based on the prevalence of asthma (3.6%), atopic dermatitis (12.4%) and rhinoconjunctivitis (4.5%) in German children between 3 and 6 years of age reported by Robert Koch Institute.[5] The prevalence (4.6%) of positive IgE and symptoms for the outcome 'food allergy' is based on table 1 in the review of Nwaru *et al*.[35]

For each of the five endpoints we calculate with 1% probability of type 1 error and 20% type two error two-sided in a four-field test (χ^2 test). A clinical difference of 5% in development of any of the above-mentioned allergies between vaccinated and unvaccinated children in the first 5 years of life is assumed as highly relevant.[5 13 14 25 36]

These retrospective studies differ considerably in the ratio of unvaccinated to vaccinated, but as well in the endpoints, group definition and observation period. We assume and calculate with a ratio between 1:9 unvaccinated versus complete vaccinated infants in the first year of life. Therefore, the needed sample size is not only determined by the base prevalence and assumed relevant difference, but as well by the ratio between comparison groups (cf. table 2). With up to 25% loss to follow-up about 4500 (rhinoconjunctivitis) to 9000 (atopic dermatitis) participants would be needed.

Study duration

The recruiting period of participating key persons and hence participating families is set for about 3 years until the end of 2025, the study is planned to close 5 years later in 2030. If on average each week about 75 families participate, after 120 weeks the ideal sample size of 9000 participants will be achieved. It is planned to include at least 150 key persons. With 800 000 births in Germany in 2021, about 15 000 births are born each week. Considering this, about 0.16% of all German births have to be covered per year with this parent-based cohort.

Analysis plan

After the decision is made to close the study for the primary endpoints, a final group definition between 'regular', 'early vaccinated' and 'not vaccinated' during the first year of life will be made, blinded to the endpoints. The final group definition has to consider the achieved sample size. Further, the occurring endpoints will be medically verified, also blinded to the comparison groups. Thereafter, both data sets will be merged for independent statistical analysis.

Allergy and confounder prevalences with CIs for each predefined group will be reported as descriptive statistics. The inference analyses will be performed with univariate logistic regressions to calculate possible ORs in addition to prevalence differences between groups. In the statistical analysis plan, exact additional multivariate logistic regression analyses will be defined, adjusting or stratifying for the above mentioned collected confounders. Further secondary endpoint analyses and sensitivity analyses may be added after knowledge about descriptive statistics. In further subordinate comparisons, various vaccination times and the times of onset of the allergic symptoms will be considered.

Table 2 Exemplary sample size calculation

Type of atopy:	Asthma	Rhinoconjunctivitis	Atopic dermatitis	Food allergy
Current base prevalence in Germany at the age of 3–6 years	3.6%	4.5%	12.4%	4.6%
Needed sample size for 5% increase to base prevalence to either group and 1:3 ratio (25% without)	1636	1848	3368	1872
Needed sample size for 5% increase to base prevalence to either group and 1:9 ratio (10% without)	**3580**	**3990**	**7140**	**4030**

Bold values indicate the choosen expected ratio.

We will compare children who were vaccinated in the first year of life with unvaccinated children at this time with regard to the occurrence of the previously defined atopic symptoms. This kind of test was already used in previous studies with similar outcomes.[13] We will stratify for relevant and hitherto described confounding factors. The complete statistical analysis plan with items according to the DEBATE statement[37] will be published on the study website before first analyses, but after first experience with recruitment and discussion with participating doctors and families.

Dealing with bias and limitations

Without the possibility of randomisation, a prospective observational cohort study relying on physician validated parental sources is already an improved approach to current evidence. Nevertheless, it has to deal with different kinds of bias. To reduce the effect of selection bias,[38] we plan to adjust or stratify the results for as much as possible relevant confounders. Therefore we compare our list of confounders to those of previous studies[13 16 33] and extend it with additional reviews and literature.[34 35] Due to the voluntary participation of parents, we cannot exclude the possibility that certain groups of persons (eg, vaccine hesitant or non-vaccine hesitant) will participate more. Therefore, the vaccination attitude of the parents is recorded additionally at the beginning of the study and the assumed group size is calculated according to recent data.[9]

As described in quality control, we reduce possible detection-bias through verified, blinded and guideline-based definition of outcomes.

We have chosen parental documentation to ensure reports of safety aspects that may not come into awareness of treating physicians and to reduce workload for professionals. But recruitment of participating families is still a challenge of this study, due to efforts in reporting and endurance. As an investigator initiated a trial, financial resources may be too limited.

Recruitment may further originate from different medical offices or sources with different specialisation, hence it may be possible that this study has to deal with performance-bias. To examine those effects and to enhance external validity, physicians are requested to register their office. Further, the number of ordered flyers is recorded. Additionally, parents can document their treating office in the survey. Further questions regarding the type of advice and care will be asked. This specific evaluation is described in a separate study protocol (DRKS00030716).

The planned study design includes a long study period and the confirmation of parental reports by doctors. It is possible that families will drop out, move or change doctors during the trial period and their reports could be missing. To reduce the dropout rate the efforts for participants is kept as low as possible and additional information and interaction offers addressing parental interests will be added as motivators, such as a study newsletter for participant engagement. Therefore we have already established a study website www.initial-studie.de.

A problem of concern is the comparison group definition, which even may have to be changed in the course of the study, if one group becomes too small, cf. sample size calculation. If not enough delayed vaccinated infants are gathered, other subgroups have to be defined with additional scientific advice. The study team is open for participants and professional advice regarding additional aspects or modifications to be considered. Already with the study protocol, we try to transparently document these considerations.

Finally, despite the long study period, the 5-year observation period might be too short to show relevant differences in allergy development or changes in vaccination schedule could complicate interpretation. This family-based birth cohort opens the gateway for further investigations and aims to shed light on the field of immunity development.

ETHICS AND DISSEMINATION

The ethical correctness of this study was examined and approved by the ethics committee of University Witten/Herdecke (no. 113/2022). The authors try to ensure a high rate of transparency and to ensure personal data protection at the same time. Anonymised data will be made public via peer-reviewed publications and reasonable research requests. Especially participating parents and inviting physicians' offices are invited to submit and discuss research questions. Information on the course of the study will be provided in German on the website www.initial-studie.de on a regular basis.

Contributors JW, EJ and DDM planned the study after discussion with several unmentioned scientists and physicians interested in the topic. JW and EJ wrote the study protocol and planned the cohort study. As supervisor, DDM approved the manuscript and made language editing.

Funding JW is a research associate at the registered association 'physicians for individual vaccination decision' (Ärztinnen und Ärzte für individuelle Impfentscheidung e.V.). Currently, the study is supported by the Gerhard Kienle Chair's own funds from the non-profit Software AG foundation grant for 2023-2027, as well as volunteer efforts as part of a thesis. For study extensions and validation of biological parameters, further funding requests will be necessary.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Consent obtained from parent(s)/guardian(s).

Provenance and peer review Not commissioned; externally peer reviewed.

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Appendix 1: Influencing factors for Atopic Dermatitis, Asthma, Rhinoconjunctivitis and Food Allergy

The search was done in December 2021 in PubMed. Only Meta-Analyses were included. The terms were (atopic rhinitis) AND (children) AND ((determinants) OR (influencing factors)), (136 articles), (asthma) AND (children) AND ((determinants) OR (influencing factors)) (860 articles), (atopic dermatitis) AND (children) AND ((determinants) OR (influencing factors)) (120 articles) and (food allergy) AND (children) AND ((determinants) OR (influencing factors)) (129 articles). When necessary, more recent studies were supplemented. (**D:** Dermatitis, **A:** Asthma, R: Rhinoconjunctivitis, **F:** Food Allergy)

Factor	D	A	R	F	Reference
Psychological Aspects					
Prenatal mental disorders		x			(1)
Stress or depression of the mother		x			(2)
Mental disorders of parents		x			(3)
Attention deficit hyperactivity disorder		x	x		(4)
Air pollution					
Passive smoking	x	x			(2)
Air pollution in the household (e.g. from stoves)		x			(5)
Cooking with gas stove		x			(6)
Nanoparticles		x			(7)
Fine dust			x		(8)
Air pollution in general		x			(9)
Microbial aerosols			x		(10)
Household Allergens					
Household Allergens		x			(2)
Cats and dogs	x	x	x		(11)
Indoor fungi (Penicillium, Aspergillus, Cladosporium)		x			(12)
Dampness and mold in the house			x		(13)
Staphylococcus aureus		x	x		(14)
Household microbes		x			(2)
Medical conditions					
Hypertension during pregnancy		x			(15)
Atopic disease of parents		x			(16)
Asthma			x	x	(17)(18)
Food Allergy		x			(18)
Simultaneous occurrence of other atopic diseases	x	x	x		(19)
Diabetes mellitus of the mother	x	x			(20)
Type 1 diabetes of the child		x			(21)
Sleep-related breathing disorder/sleep apnea			x		(22)
Rhinovirus infection in the first 3 years of life		x			(23)
Vitiligo	x				(24)
Otitis media			x		(25)

Medication					
Contraceptive pill		x	x		(26)
Paracetamol during pregnancy		x			(27)
Acid suppressants in pregnancy		x			(28)
Acid suppressants in early life				x	(29)
Antibiotics during pregnancy	x	x		x	(30)
Antibiotics in the first 3 years of life		x		x	(31,32)
Measles and pertussis infection		x			(33)
Diet/Weight					
Overweight of the child		x			(34)
Overweight of the mother during pregnancy/ severe weight gain of the mother during pregnancy	x	x			(35,36)
Rapid weight gain as infant		x			(37)
Low birth weight		x			(37)
Underweight of the mother during pregnancy	x				(38)
Vitamin D		x			(39)
Vitamin D during pregnancy		x		x	(40,41)
Vitamin A, D, E, zinc, selenium deficiency		x			(42,43)
Folate intake during pregnancy		x			(44)
Soft drinks		x			(45)
Breastfeeding	x	x	x		(46)
Raw cow's milk		x			(47)
Probiotics	x			x	(48–50)
Fruit and vegetables intake		x			(51)
Mediterranean diet		x			(52)
Fish	x	x	x	x	(53)
Omega-3 supplementation during pregnancy		x			(54)
Early introduction of egg and peanut				x	(55)
Pesticides		x			(56)
Other					
Second generation immigrants compared with first		x			(57)
Ethnic affiliation		x			(58)
Rural residential area		x			(59)
Autumn/winter birth	x				(60)
Cesarean section and female sex		x			(61)
Cesarean section		x			(62)
Birth in the 34^{th} -36^{th} week of pregnancy		x			(63)
Preterm birth		x			(37)
Male gender		x	x		(64)
Social disadvantage		x			(65)
Physical activity		x			(66)
Daycare attendance	x	x	x		(67)

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