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Integrated summary report on recommendations on potential interventions focused on modification of early-life stressors

LifeCycle report D9.6

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List of Abbreviations

ATHLETE: Advancing Tools for Human Early Lifecourse Exposome Research and Translation BF: breastfeeding CENTRAL: Cochrane Central Register of Controlled Trials CINAHL: Cumulative Index to Nursing and Allied Health Literature EBRBs: energy balance-related behaviours ISRCTN: International Standard Randomised Controlled Trial Number LBW: low birth weight OB: obesity OW: overweight RCT: randomized controlled trial WP: work package

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Executive summary

The objective of Task 9.3 was to develop overall and subgroup-specific recommendations for age-window specific, feasible and effective intervention strategies for modifying exposure to early-life stressors to improve life-course health trajectories. In Task 9.3. we took the work of Task 9.2 (Subtasks 9.2.1-9.2.4) forward. The aim was to integrate the results of the four reviews done in Task 9.2 as much as possible into recommendations for intervention strategies before and during pregnancy, in infancy or in early childhood. Specific subgroups of interest included socio-economic and ethnic groups, or subgroups identified at increased risk based on other parental or infant characteristics. Specific European geographical areas or subpopulations were also of interest.

As part of Task 9.3 we organized a workshop (Milestone 24) with the topic: "Complex interventions to tackle early life stressors - Evidence form LifeCycle WP9". The half-day workshop was held online during the 10th General Assembly Meeting in October 2021 with around 60 attendees including LifeCycle partners and representatives from external cohorts. After the presentations of findings of the four systematic reviews from WP9, a plenary discussion on the complex picture of intervention strategies was started. Conclusions from the workshop were used to continue the work in Task 9.3.

Overall, we developed key aspects for a general review strategy in WP9 to identify potential interventions focused on the modification of early-life stressors including socio-economic, migration, urban environment and lifestyle related exposures in the first 1000 days of life. The evidence gathered in the four reviews was used to identify ingredients for successful interventions to improve future interventions. This deliverable report D9.6 outlines limitations and knowledge gaps identified in each of the reviews and discusses general recommendations to improve future intervention studies.

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1. Introduction

Early life is an important and unique window of opportunity for improving health and health trajectories of children. Early life is defined as the time spanning from conception through pregnancy until infancy to the child's second birthday, which corresponds to the first 1000 days of life. During this critical time period, exposures to stressors can lead to developmental adaptations, which can have long-term consequences on health and wellbeing (1, 2). It is therefore of great public health interest to optimize early-life conditions as they have a tremendous potential to improve life-course health trajectories of individuals and their future children through transgenerational effects (3). Timely interventions in early life are recognized as a key to enhancing children's life chances. They are likely to be more effective in reducing inequalities and disease risks, and in improving health outcomes across the lifecourse than interventions beginning in later life (2, 4).

Despite increasing research on the associations between exposures in the prenatal and postnatal period with physical and psychological outcomes in later life, it seems still a challenge to translate these findings into impactful interventions (5). One of the aims of the LifeCycle project was to review and integrate evidence based on findings from LifeCycle studies and from other observational studies and translate these findings into recommendations for intervention strategies.

In this deliverable report D9.6 we will present the main key messages derived from the four reviews carried out within WP9 (Subtasks 9.2.1-9.2.4). The reviews were focused on four different early-life stressor groups: socio-economic differences; ethnicity, migration and integration; urban environment; and lifestyle of parents and young children. We identified limitations and knowledge gaps in each of the reviews and will discuss recommendations to improve future intervention studies. Furthermore, we will draw general conclusions from the findings of the four reviews and synthesize them into overall recommendations for intervention strategies focused on the modification of early-life stressors.

2. Review from Subtak 9.2.1: Socio-economic differences

The systematic review on the impact of income-support interventions on life course risk factors and health outcomes during childhood: a systematic review in high income countries (PROSPERO Registration ID number CRD42020178543) was led by UNITO.

2.1 Summary

This review aimed to assess whether socioeconomic interventions provided in the first 1,000 days of life can affect socioeconomic stressors and ultimately change the health trajectory of children and adults. For the purpose of the review, we focused on income support strategies, defined as all the measures taken by government to provide an adequate income to their citizens via different benefit schemes, which can be implemented within different policies with different aims and objectives. Under this definition, interventions of interest included social protection, taxation and fiscal policies, welfare to work and minimum wage interventions. The health outcomes of interest were only those relevant for LifeCycle and grouped under mental health, cardiovascular, metabolic and respiratory conditions. Only studies from high income countries were included. In terms of study design we only

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considered interventions delivered within the first 1,000 days of life and those whose impact was assessed either via a randomised controlled trial or a quasi-experimental design. Overall 18 studies met the inclusion criteria. Studies were largely coming from North America, including United States and Canada (15/18). 13 out of 18 studies looked at birth weight. The remaining 5 studies looked at mental health outcomes. A large part of studies included in the review looked at the impact of earned income tax credit on birth weight in the United States (7/18).

Overall, most of the interventions looking at the impact on birth weight found a positive effect (11/13), although the magnitude of this effect was typically small. Impact evidence for mental outcomes were less conclusive as impact findings were more mixed with only 2 studies out 5 documenting a clear positive impact. Findings seem to be robust to type of intervention and impact evaluation utilized with the exception of studies adopting a randomized controlled trial design that consistently failed to detect an impact.

2.2 Limitations and research gaps

This review suggests a positive and robust effect of income support strategies on some of the outcomes of interest, but:

- A consistent positive effect could be only detected for birth weight, but not for mental health outcomes.
- The observed effect size is typically small: several explanations can justify this (including the size of the benefit provided and the socioeconomic status of recipients of the intervention at baseline); however, given the large population typically covered by these interventions we can speculate that at population level the public health impact of these interventions can be large.
- Because of the stringency of the inclusion criteria, we could only include in this review a limited number of studies. This raises concerns about the generalizability of the impact findings to other study settings (other than North America) and health outcomes different from those of interest in this review.
- No study attempted to formally explore the causal pathways underlying the observed impact. As such, the mechanism underlying the observed impact remains uncertain and no obvious conclusion can be drawn on why some interventions did not produce the expected impact nor how these interventions can be optimised to maximise their impact.

In terms of research gaps, there is clearly a scope to invest more in the evaluation of the child health impact of macro-level socioeconomic interventions either by financing more and more rigorous impact evaluations or by diversifying the health outcomes under evaluation. There is a mandate to investigate the role of alternative methodologies (to RCTs and quasi-experimental designs) including observational studies as well as mathematical modelling (i.e. microsimulations) to fill the numerous knowledge gaps in this field. There is also a need to improve our information systems and allowing a better and more consistent collection of social determinants data, possibly on a routinary basis, so to allow a better understanding on how health inequalities are generated and perpetrated and how

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interventions should be best tailored to tackle them. The question of 'what works?' should be more correctly replaced by 'what works for whom and why?'. There is an urgent need to unpack the effect of these interventions to understand better how the effect of these interventions is mediated and what factors along the causal pathways can be targeted to maximise the impact of these interventions.

2.3 Recommendations for future interventions

The literature on the role of social determinants of health is overwhelming and the impact evidence gathered in this and similar systematic reviews are sufficient to advocate for income support strategies to become part of a standard package of prevention and care for vulnerable households/parents if child inequalities are to be reduced.

Future interventions will have to be designed to: 1. Better quantify the magnitude of the health impact of these policies; 2. Diversify the impact under investigation both in terms of health outcome and population subgroups of interest.

Impact evaluations will have to be conducted along rigorous process evaluation to better understand determinants of failure or success.

The massive investment on social protection during the covid-19 pandemic offers an unprecedent opportunity to quantify and understand the impact of welfare policies on global health.

3. Review from Subtask 9.2.2: Ethnicity, migration and integration

The systematic review on the effectiveness of interventions during the first 1000 days to improve energy balance-related behaviours or prevent overweight/obesity in children from socio-economically disadvantaged families: a systematic review (PROSPERO Registration ID number CRD42020166483) was led by INSERM.

3.1 Summary

This systematic review addressed the effectiveness of interventions during the first 1000 days of life to improve energy balance-related behaviours (EBRBs, i.e.: breastfeeding (BF), other feeding practices, diet, physical activity, sedentary behaviours or sleep), or prevent overweight/obesity (OW/OB), in children from socioeconomically disadvantaged families. Intervention studies (RCTs or quasi-experimental designs) had to include a control group, i.e. a group of parents/infants who were not exposed to the intervention or who received 'usual care'. The search, performed in January 2020 (PubMed/MEDLINE, EMBASE, CINAHL, PsycINFO, and Scopus), included articles from peer-reviewed English language journals published between 1990 and 26th January 2020, inclusive.

The 31 selected studies corresponded to 22 distinct interventions. Studies assessed the effectiveness of interventions on a variety of domains, outcomes within domains, at diverse time points, making it impossible to synthesize the findings quantitatively. We found three types of interventions, i.e. those specifically aimed at preventing OW/OB in children; those mostly focused on promoting healthy feeding practices and diet; and broad parenting programs aimed at enhancing the general health and bonding of the mother-child dyad. Overall, despite a large variability regarding the internal validity of the 22 interventions

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analysed, their focus on the most disadvantaged families suggests some beneficial impact on the risk of OW/OB, as well as its associated behavioural factors. Anthropometric outcomes were favourably impacted in 4 out of 13 studies; BF in 9/17; other feeding practices (mostly age at complementary feeding) in 9/15; dietary intakes in 6/7; physical activity in 3/5; sedentary behaviour in 1/3; and sleep in 1/2.

3.2 Limitations and research gaps

Despite the known influence of smoking during pregnancy on the risk of childhood OB, none of the interventions aimed at preventing OB had a focus on smoking prevention. Rates of smoking are usually higher in disadvantaged pregnant women, with the opposite observed for BF: supporting pregnant women to diminish (or stop) smoking, along with the promotion of BF and healthy EBRBs, would probably enhance the efficacy of OB prevention actions implemented in the first 1000 days; but this needs to be further evaluated. Conversely, smoking was a target of few of the broad parenting programs starting antenatally; but none of them were assessed for their impact on anthropometric outcomes beyond birth. Therefore, we cannot exclude that they had some unmeasured impact on OB risk later in childhood.

Across the 22 interventions reviewed, the entry point was essentially the mother, and the focus was on the mother-child dyad. Social support to the mother was provided by a variety of delivery agents, or peers, but programs that engaged fathers or any other trust person, who are a potential support of the mothers too, are scarce.

Beyond social support, none of these interventions incorporated structural components (such as vouchers to access foods and services at lower prices), which are essential to enabling individual agency in adverse conditions of living. Only such holistic, multilevel and proportionated interventions are susceptible to address the issue of social inequalities, thus future research has to fill this gap. Such complex interventions are more likely transferable when they are developed based on participatory approaches. Besides, methods mixing quantitative and qualitative assessments are required for more in depth process evaluations, prior to their implementation at larger scales. Pilot, qualitative, and follow-up studies are also important for improving both internal and external validities.

3.3 Recommendations for future interventions

Programs seem more effective to prevent OW/OB when they target first-time mothers, are multi-behavioural, start during pregnancy and continue at least two-year post-partum. Home-visiting is adapted to reach disadvantaged families, but health-care centre based interventions, though less frequent in the current review, seem effective too, as long as a multidisciplinary team is involved. Social support is also enhanced when group sessions with peers complement one-on-one support. When ethnic/racial minority groups are targeted, lay support, bilingual delivery agents, and culturally sensitive tools, improve engagement of families and impact on outcomes (especially feeding practices). Co-designing these tools with recipients, whether booklets or videos, is also suggested to improve their up-take. All in all, the most effective interventions targeting socio-economically disadvantaged families are likely those that assemble the three types of interventions identified in the present review, i.e. broad parenting programs, including a smoking component,

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implemented over the first 1000 days, with an additional focus on feeding practices and the various EBRBs. Such comprehensive interventions will presumably optimize the physical and psycho-social health of the mother, mother-child bonding, along with the general lifestyle, health (including the risk of OB) and development of the child, and therefore both generations. Given the relevance of involving recipients and stakeholders in the development of actions when these are aimed to be scaled-up and generalized, bottom-up initiatives and participatory approaches seem important whatever the socio-cultural characteristics of the population targeted. Grounding programs within a theoretical framework also seems important. However, beyond the frequent focus on individual agency towards behaviour change, it is important to help socio-economic disadvantaged mothers identify and use the various resources available at the local scale (for parenting, housing, employment, childcare, etc.), which will foster their empowerment and help navigate through parenthood with increased self-efficacy. Additionally, even if this still has to be evaluated in future research, supporting disadvantaged families with structural facilitators enabling healthy behaviours is likely a major ingredient for sustainability of changes, and health equity.

4. Review from Subtask 9.2.3: Urban environment

The systematic review on primary school-based interventions to promote a healthy urban environment for children aged 5 to 12 years: a systematic review of recent literature (PROSPERO Registration ID Number CRD42020187668) was led by ISGlobal.

4.1 Summary

This systematic review addressed a broad question on the effectiveness of primary schoolbased interventions on the built environment to promote health and mitigate urban hazards in childhood. Targeted participants were school-aged children of 5 to 12 years old enrolled in primary schools from urban areas of Europe and high-level income countries in the rest of the world. School-based interventions were defined as either delivered within, around, or along the path to school, for a whole class, or the entire school. They should be focused on changes to the school-built environment to reduce exposures levels to road-traffic noise, air pollution, or promote active travel to school, and improve the visibility, availability, accessibility, or time children spent in green spaces during school hours. We did not exclude studies based on the comparison. At a minimum to be eligible, studies needed to include outcomes in children on either cardiometabolic, respiratory, cognition and behaviour effects, physical activity and active travel to school, or changes in the exposure levels to air pollution, road traffic noise, and green spaces. We found 39 studies: 16 on green spaces, 10 on air pollution, 13 on active travel to school, and any intervention on traffic-related noise. In totality, air pollution interventions focused on improvements of air quality indoor by using built-in ventilation devices or ventilation strategies. Most interventions on green spaces focused on increasing the number of time children spent in nature during school hours. Active travel interventions were always multicomponent with built environmental changes related to improvements of sidewalks and others pedestrian facilities. Overall specific-exposure studies reported: (i) mixed effects of higher ventilation rates indoor on

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cognition performance; (ii) better short-term cognition, behaviour, and physical activity, especially in girls, from lessons in nature and recess in nature; and (iii) a relatively small positive effect of multi-component active travel intervention on biking and walking to commute (from 5 to 20% after at least one year). In general, the capacity of studies to infer causality was weak, with mainly before and after designs, small sample sizes, and short period evaluation post interventions. Considering all these limitations, including the limitations related to the review itself, we found some evidence of potential health benefits from interventions on green spaces relating to lessons in nature and an increase of active travel from safe route programs including infrastructure improvements.

4.2 Limitations and research gaps

Overall, the studies presented poor internal validity due to data collection, intervention timing, selection of sites, weak reporting concerning the intervention features, intervention timing, population (children and schools), expected intervention, study design, and statistical analyses. Also, the time between implementation and evaluation seemed insufficient to evaluate the intervention effect and rule out novelty and learning-effect. Future studies should target interventions to mitigate road-traffic noise around schools since it is recognized as a health threat. Also, authors should report information on intervention adherence and fidelity. Controlled studies design are lacking. Studies should consider and report the level of deprivation at schools areas and enrollments and how the intervention addresses (or not) these issues.

More specifically, air pollution intervention studies should include health-related endpoints, and personal assessment of the exposure. For green spaces, studies should assess the quality and type of green and account for residual confounding and exposure out of the school. Finally, active travel studies evaluation should measure the details on the previous infrastructure and programs implemented before the main intervention, the level of implementation to avoid type 3 error (a potential null impact of the interventions were not caused by implementation failure), and to evaluate the impact of each component of the intervention (what works for whom, how and under what circumstances).

4.3 Recommendations for future interventions

Based on the abovementioned limitations, we can not define the best components for future interventions. However, interventions on urban hazards are essential, especially during vulnerable life stages such as childhood. For instance, there is sufficient scientific evidence that noise and air pollution exposure are health threats. Nevertheless, building upon the findings of our research, we can provide some guidance: (i) school-based interventions should consider the burden on teachers and students, and also their preferences; (ii) urban exposures are not static and affect each other. Therefore, future interventions should account for the harmful and benefits of co-exposures. For instance, to what extent active travel to school reduces or increases air pollution exposure; (iii) A holistic approach with multiple interventions and strategies seems most effective.

Specifically, promoting structural changes in the school building seems difficult and limited. Future interventions to mitigate air pollution should be considered the implementation of

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clean area zones and green barriers around schools. Furthermore, a non-retrofit strategy such as reprograming the ventilation system to avoid traffic rush hours may be a first step to improve air quality indoor in heat seasons under specific conditions (later school starting at 9 am). For active travel, it seems clear that multicomponent interventions are more efficient, and built environment changes are necessary to support behaviour changes. Also, for these interventions, school-level characteristics are key in designing the intervention, considering students' grades, local culture, and needs. Another relevant hint is considered that infrastructure and support for bike and walk may require specifically built environment improve time spent in green spaces using outdoor classes as a potential approach. The studies included in this review reported a minimal time of 30 minutes per week. It is already well-known that children from deprived neighborhoods are more exposed to urban hazards. Interventions should not increase this social gap.

5. Review from Subtask 9.2.4: Lifestyle

The systematic review on nutrition interventions in the first 1000 days of life and long-term health outcomes in high-income countries: a systematic review of randomized controlled trials (Registration ID Number CRD 42020167893) was led by LMU.

5.1 Summary

This systematic review was focused on the evidence around the impact of nutrition intervention programs implemented during the first 1000 days of life on long-term child and adolescent health outcomes (cardio-metabolic, respiratory and mental health). Nutrition programs were defined as programs focused on diet, lifestyle/nutritional intake and on improving nutritional knowledge and healthy dietary behaviours. Targeted participants were healthy adults in the preconception and prenatal period as well as parents of children up to 2 years of age and children up to 2 years of age. Samples should have been reflective of their communities. Outcomes of interest were clinical measurements related to cardiometabolic, respiratory and mental health, as well as behavioural outcomes like diet practices, nutritional intake and health knowledge. Minimum follow-up time was 12 months. We included randomized controlled trials and cluster randomized trials. We searched four databases (PubMed, CINAHL, CENTRAL, EMBASE) and two trial registries (clinicaltrials.gov, ISRCTN). 53 articles were included, representing 14 different interventions conducted in eight countries. Results were synthesized narratively. Six studies had a followup \leq 2 years, seven studies had a follow-up from > 2 to 5 years and one study had a 20-year follow-up. Target period for the interventions was infancy and early toddlerhood (14 studies), while four studies started already during pregnancy. Recipients of the interventions in all studies were parents or mothers. Looking at the intervention type, four studies used nutrition education only, four studies combined multiple nutrition interventions (e.g. nutrition education and meal planning or complementary food or supplements) and six studies used a lifestyle intervention combining nutrition education with for example physical activity or parenting education. Evidence on cardio-metabolic

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health was insufficient as only two studies were available. Outcomes were focused on cardiovascular measures (e.g. blood pressure, metabolic syndrome) and lipid and biochemical profile. Four studies reported outcomes on mental health showing no effect. They were focused on self-reported status of psychological wellbeing and quality of life as well as on cognitive development and school performance. We did not identify a study on respiratory health. All studies showed mixed results for dietary behaviour, with some intervention effect on reducing unfavourable and increasing favourable diet behaviour. They were mainly focused on food and nutrition intake, on eating behaviour and food preferences and dietary scores/patterns.

The review explored an understanding of current evidence surrounding early life nutrition interventions and their long-term health impact investigated in RCTs. Overall, there is no strong evidence to support the impact of nutrition interventions on clinical long-term health outcomes apart from obesity as the latter was not covered by the review. However, we can summarize that the modification of nutritional behaviours seems feasible and there is preliminary evidence on improvements in cardiovascular risk factors (based on only 2 studies).

5.2 Limitations and research gaps

There was moderate concern of bias in all studies. The blinding of participants and personnel was the domain with most concern, but expected for the nature of these interventions as it is impossible to blind participants and study personnel. An additional source of bias was incomplete outcome data (high attrition) in the studies and the adherence to intervention was not well reported.

We could not conduct a meta-analysis due to methodological and statistical heterogeneity of data and incomplete numerical reporting of outcomes. Especially for mental health and dietary behaviour there was high heterogeneity in the reporting of measured outcomes. Overall, there was a lack of studies with long-term health outcomes. Most of the studies had five years or less follow-up time, which is short to investigate long-term effects. We found just one study with a follow-up until adolescents/adulthood (20 years). On the other hand, we did not assess the effect on short-term behaviour changes or outcomes as we were specifically interested in long-term outcomes. We took only the latest follow-up point of outcomes assessed if multiple reports were available.

We found that most of the included studies were not focused on relevant clinical endpoints. In our review we identified more studies focused on secondary outcomes like clinical surrogate measurements and less on primary outcomes. Surrogate measurements are usually easier to measure and more likely to be collected from all participants, although they do not always provide a relevant clinical picture.

We found insufficient evidence on different target periods. There was no study on interventions that started during preconception and only four studies starting their intervention during pregnancy. Due to these findings there is no clear answer which periods of life are most promising for interventions.

In addition, it should be noted that we excluded all studies focused solely on obesity and overweight as an outcome as we wanted to specifically identify the impact of the respective

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interventions on LifeCycle relevant outcomes beyond obesity and overweight. The latter were covered by previous reviews of other researchers.

5.3 Recommendations for future interventions

Based on the limitations described above, we can formulate some suggestions for future interventions. First of all, longer follow-up of intervention studies should be considered when possible. Additionally, the sample size should be planned sufficiently to be able to assess relevant outcomes and later effects. Relevant outcomes should be chosen using standardized and comparable measures. If possible, clinical endpoints should be targeted. It would be desirable to promote more homogeneity in the outcome measurement (e.g. core outcome sets for mental health or dietary behaviour). Future interventions should gain further insight into different target periods, especially on interventions starting during preconception and pregnancy. In addition, it is an important point to evaluate programs and to report the adherence to interventions in order to see whether interventions affect the targeted behaviours and whether study participants follow recommendations. Genderspecific effects should be characterized as it may require different implementation strategies for interventions in boys and girls.

6. Conclusion

The concepts of the four reviews were somewhat different and deliver a rather complex picture. The review from Subtask 9.2.1 showed that income support strategies should be part of a standard package of prevention and care for vulnerable households/parents. The review from Subtask 9.2.2 found that theory-based, participatory research and multi-behavioural programs with close contact to participants seem more fruitful. From the review from Subtask 9.2.3 we can concluded that school-based programs to increase active travel and integrating/improving green spaces seem to have positive (health) effects. The review from Subtask 9.2.4 showed that the early modification of nutritional behaviours seems feasible with sustainable effects into later childhood.

The evidence gathered is not sufficient to allow the formulation of clear policy recommendations, but some ingredients for successful interventions and improvement of intervention strategies were shown and discussed:

- Start in pregnancy (or before) and continue into infancy;
- Use of bottom up/participatory design (families, teachers, health care professionals, stakeholders, communities);
- Take account of the individual in their environment (social, cultural and institutional context), focusing on strong barriers for vulnerable groups;
- Involve fathers (partners);
- Apply interdisciplinary work to enable multilevel interventions;
- Include longer follow-up to look for sustained effects;
- Embed qualitative research before and during interventions to evaluate the needs of the target population and to better understand the efficacy of interventions;
- Look for graded effects on outcome rather than categorical effects (LBW, obesity);

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• Use standardized outcomes that can be compared and joined with other interventions and observational studies.

Do we need intervention studies?

Intervention studies are essential to justify public health decisions. RCTs are only one part of evaluating public health interventions and cannot easily be performed for all health behaviours and outcomes. However, evaluation of interventions is important to justify implementation of policy changes and to leverage public investment. Impact evaluation provides evidence of what works and what does not, which is essential not only to not replicate interventions that are not efficient, but also to better invest available resources. Thus, public funding of intervention studies is necessary. However, follow-up time should be adequate to evaluate persisting effects. Furthermore, policy changes with the aim to improve health or with potential health effects should be accompanied by impact research to better understand determinants of failure or success, and to get better insights into mediators of successful policy interventions.

Public health actors and researchers should also consider alternative research strategies such as within-cohort approaches. To achieve such goals political and public health actors and researchers of a region/communities have to come together to plan a long-term health strategy that incorporates the collection of individual health data over time to build a cohort that can be used to assess the impact of interventions. Examples of this strategy can be found in the Born in Bradford's Better Start program (6) and in the SARPHATI cohort (Amsterdam) (7).

7. Contribution of partners

The deliverable report D9.6 for Task 9.3 was jointly prepared and reviewed by all partners of WP9. Subtask 9.2.1 was prepared by UNITO, subtask 9.2.2 by INSERM, subtask 9.2.3 by ISGlobal in collaboration with BTHFT and subtask 9.2.4 by LMU. During the workshop for Milestone 24 all WP leaders of LifeCycle took part. The results of the reviews and the recommendations were discussed in several video conferences together with WP10 and WP11 leaders.

8. Deviations from original plan

This Deliverable has been fulfilled fully in line with the original plan as stated in the Grant Agreement.

9. Dissemination activities

Review results were disseminated by internal presentations within the LifeCycle Consortium, but also in meetings with external partners of the ATHLETE consortium and the EndObesity consortium. All reviews are currently being prepared for manuscript publication in relevant journals or are already under review.

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10. References

1. Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. N Engl J Med. 2008;359(1):61-73.

2. Hanson MA, Gluckman PD. Early developmental conditioning of later health and disease: physiology or pathophysiology? Physiol Rev. 2014;94(4):1027-76.

3. Balbus JM, Barouki R, Birnbaum LS, Etzel RA, Gluckman PD, Sr., Grandjean P, et al. Early-life prevention of non-communicable diseases. Lancet. 2013;381(9860):3-4.

4. Hanson M, Gluckman P. Developmental origins of noncommunicable disease: population and public health implications. Am J Clin Nutr. 2011;94(6 Suppl):1754S-8S.

5. Gaillard R, Wright J, Jaddoe VWV. Lifestyle intervention strategies in early life to improve pregnancy outcomes and long-term health of offspring: a narrative review. J Dev Orig Health Dis. 2018:1-8.

6. Dickerson J, Bird PK, McEachan RR, Pickett KE, Waiblinger D, Uphoff E, et al. Born in Bradford's Better Start: an experimental birth cohort study to evaluate the impact of early life interventions. BMC Public Health. 2016;15:711.

7. Ujcic-Voortman JK, Hall JT, Johannes M, Seidell JC, Verhoeff AP. Sarphati Amsterdam: a dynamic research infrastructure. Eur J Public Health. 2020;30(Supplement 5).

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