LifeCycle

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Report on approaches for causal inference in the context of life course trajectory analyses

Work package 7 - Task 7.1 - Deliverable 7.1

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1. Introduction

The WP7 of LifeCycle focuses on specific methodological aspects of importance for the EU Child Cohort Network and life course research in general. It aims at developing an integrated analysis strategy to apply causal inference methods, model longitudinal data and health trajectories; assessing approaches to analyse multiple exposure data in the context of longitudinal modelling; and, at the same time, enhancing, inside and outside LifeCycle, the knowledge and use of causal inference approaches and methods to model longitudinal data.

The Task 7.1 focuses on causal inference methods and integrates theoretical and applied aspects. Three main areas of interest were initially identified in LifeCycle: (1) Methods to strengthen evidence of causal effects; (2) Mediation analysis; and (3) Transportability and population-specific marginal effects. This deliverable covers these three aspects. Its results contribute also to future WP7 deliverables, specifically to the demonstration of the analytical strategies with tutorials (Deliverable 7.4) and the development of courses on causal inference methods and longitudinal modelling in the context of life course analyses (Deliverable 7.5).

2. Work performed

2.1. Searchable database of method materials of importance for causal inference in life-course epidemiology

One of the objectives of WP7 is to enhance the knowledge and use of causal inference approaches, as well as methods to model longitudinal data, within LifeCycle. We intend to provide access to all members of LifeCycle to a variety of methodology materials on the topic of causal inference and longitudinal modelling. For this purpose, we created a searchable database filled in by internal experts as they come along with materials of interest for the broad audience of LifeCycle members. The materials are selected based on their relevance to the specific research projects conducted within LifeCycle and their readability by non-specialists. By accessing the database, any member who wants to get familiar with the field can have a rapid overview of the methods and challenges. This database can also be the basis for deeper study of the field.

The web application, hosted at Telecom Italia SPC Cloud infrastructure and available at https://lifecycle.cpo.it, was built with Ruby on Rails and MySQL. The interface is user-friendly and intuitive with filters and export functionalities (Figure 1). It has been filled by ten contributors

since 23 April 2018 and contains 70 items as of 15 November 2020. Each item is described through 17 features: unique id, title of the work, source online, type of work (educational, tutorial, review, or research paper), year of publication, topic (causal inference, longitudinal data, or both), authors, reference, key words, short summary, comments, open access (yes or no), contains codes for reuse in statistical packages (yes or no), date of entry in the database, date of update, contributing member, and full text link (if open access). A total of 87% of the records are open access publications, and 29% of the publications contain programming codes.

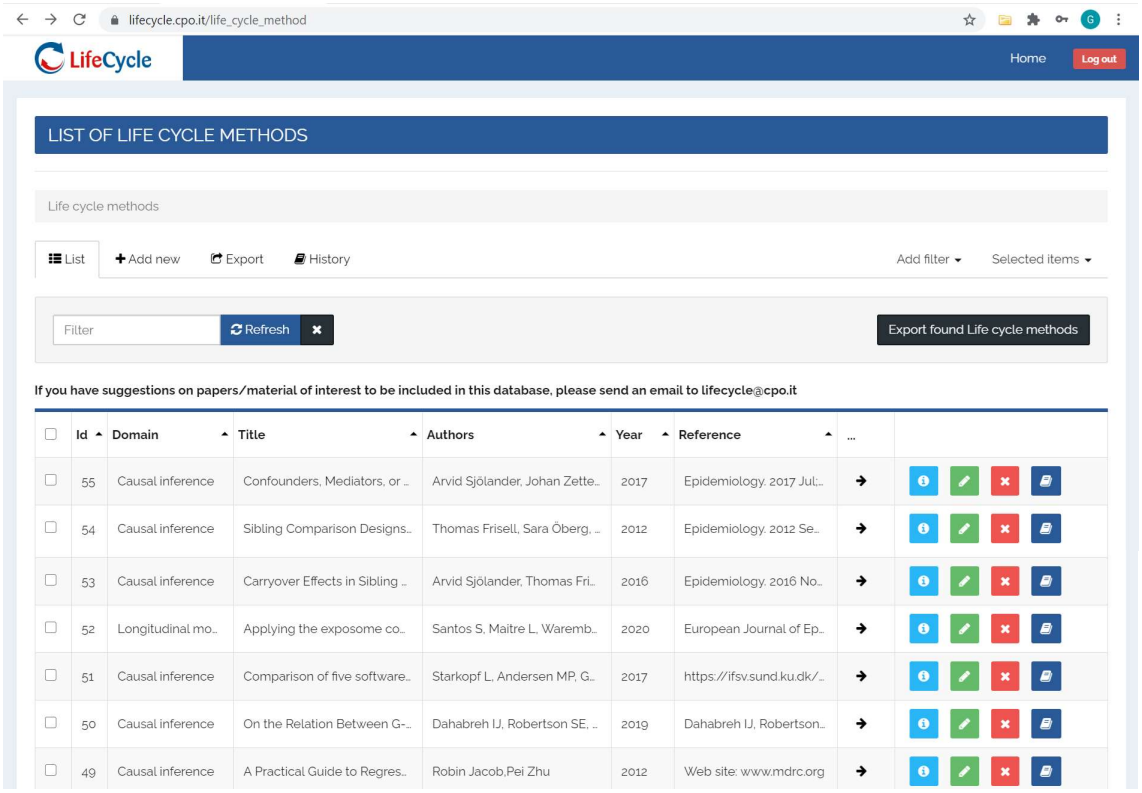

Figure 1: Print screen of the searchable database.

Among the 70 items, 49 have a focus on causal inference, nine on longitudinal modelling, six pertain to both topics, and the remain six to the recently added field of exposome and omics. The majority (35 items) are educational papers or books, while 16 are tutorials, reviews, or textbooks, 11 are applied methods papers, and eight are original methods papers. Table 1 provides a full

description of the contents of the database, including the methodological approaches covered. Note that we report here on the full database, while some contents pertain to Task 7.2 (methodological approaches for longitudinal modelling/health trajectories) and to Task 7.3 (methodological approaches for the analysis of multiple stressor data).

We started monitoring its usage since 1 September 2020 and between that date and 15 November 2020 it had been accessed 53 times by 24 individual users. Work is ongoing to display the database on the LifeCycle cohort data catalogue portal developed by WP1, which will increase visibility, as the catalogue portal is used by any investigator planning a project (internal or external to LifeCycle).

Table 1. Contents description of the methods database, as of November 13th, 2020.

Characteristics of entered reference	N	(%)
Total	70	
Type		
Educational paper or book	35	(50.0)
Tutorial	11	(15.7)
Applied methods	11	(15.7)
Original methods paper	8	(11.4)
Review or textbook	5	(7.1)
Covered methodological approaches*		
Mediation analysis	20	(28.6)
Instrumental variables, incl. Mendelian randomization	10	(14.3)
Modelling trajectories of exposures	10	(14.3)
Data dimensionality reduction	9	(12.9)
Sibship comparison	6	(8.6)
Generalizability and transportability	5	(7.1)
Negative control design	4	(5.7)
Regression discontinuity	3	(4.3)
Others	8	(11.4)
Year of publication		
2000-2009	3	(4.3)
2010-2014	21	(30.0)
2015-2020	46	(65.7)
Open access publication		
Yes	61	(87.1)
No	9	(12.9)
Contains programming codes		
Yes	20	(28.6)
No	50	(71.4)

*Categories are not mutually exclusive.

2.2. Reviews of causal inference methods of relevance for LifeCycle

2.2.1 Published methods papers

The four methods journal articles summarized in this section have been led by WP7.

Santos S, Zugna D, Pizzi C, Richiardi L. Sources of confounding in life course epidemiology. J Dev Orig Health Dis 2019;10(3):299–305. doi: 10.1017/S2040174418000582

Summary

In epidemiologic analytical studies, the primary goal is to obtain a valid and precise estimate of the effect of the exposure of interest on a given outcome in the population under study. A crucial source of violation of the internal validity of a study involves bias arising from confounding, which is always a challenge in observational research, including life course epidemiology. The increasingly popular approach of meta-analyzing individual participant data from several observational studies also brings up to discussion the problem of confounding when combining data from different populations. In this study, we review and discuss the most common sources of confounding in life course epidemiology: (i) confounding by indication, (ii) impact of baseline selection on confounding, (iii) time-varying confounding (Figure 2) and (iv) mediator–outcome confounding. We also discuss the issue of addressing confounding in the context of an individual participant data meta-analysis.

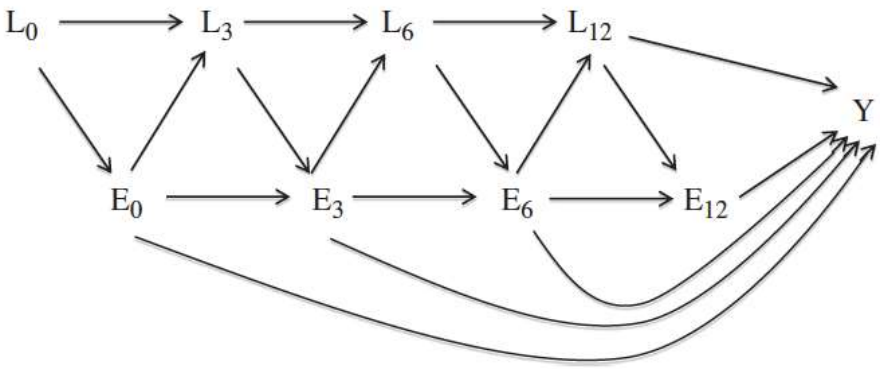

Figure 2. Directed acyclic graph representing time-varying confounding. Y is the outcome, E_t the time-dependent exposure and L_t the time-dependent confounder of the E_t–Y association.

We discuss the example in which E_t represents breastfeeding measured at different time points, and L_t is the infant's weight measured at the same time points. Infant weight can affect current

breastfeeding status and may also be affected by breastfeeding at the previous time point. Infant weight is thus both a confounder and a mediator and traditional approaches to control for confounding may produce biased results.

This paper has been the key resource in preparing the e-learning module on confounding within WP11.

Richiardi L, Pearce N, Pagano E, Di Cuonzo D, Zugna D, Pizzi C. Baseline selection on a collider: a ubiquitous mechanism occurring in both representative and selected cohort studies. J Epidemiol Community Health 2019;73:475–80. doi:10.1136/jech-2018-211829

Summary
There is debate as to whether cohort studies are valid when they are based on a source population that is non-representative of a given general population. This baseline selection may introduce collider bias if the exposure of interest and some other outcome risk factors affect the probability of being in the source population, thus altering the associations between the exposure and those risk factors (Figure 3). We argue that this mechanism is not specific to 'selected cohorts' and also occurs in 'representative cohorts' due to the selection processes that occur in any population. These selection processes are for example linked to the life status, immigration and emigration, which, in turn, may be affected by environmental and social determinants, lifestyles and genetics. We provide real-world examples of this phenomenon using data on the population of the Piedmont region, Italy. In addition to well-recognised mechanisms, such as shared common causes, the associations between the exposure of interest and the risk factors for the outcome of interest in any source population are potentially shaped by collider bias due to the underlying selection processes. We conclude that, when conducting a cohort study, different source populations, whether 'selected' or 'representative', may lead to different exposure–outcome risk factor associations, and thus different degrees of lack of exchangeability, but that one approach is not inherently more or less biased than the other. The key issue is whether the relevant risk factors can be identified and controlled.

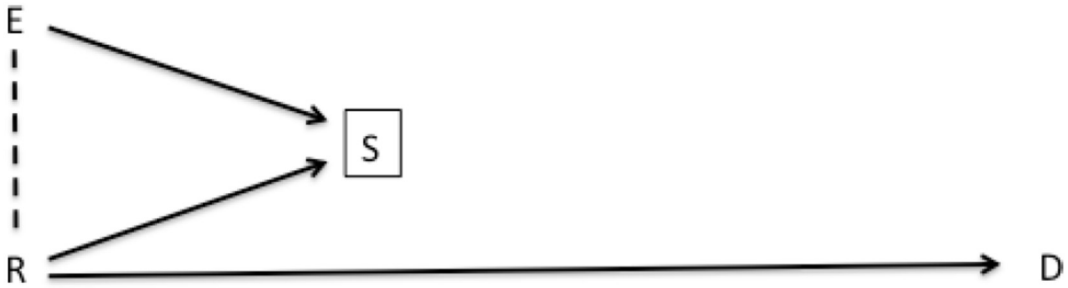

Figure 3. Directed acyclic graph of collider bias induced by selection in the source population S. The square around a variable means conditioning on that variable. The dashed line implies induced association. E is the exposure of interest and R is a risk factor for the disease D of interest.

We argue that this mechanism occurs both in selected cohorts and in cohorts that are representative of the general population, due to the selection processes that occur in any population.

Zugna D, Richiardi L. Effects decomposition in mediation analysis: a numerical example [in Italian]. Epidemiol Prev 2018;42:127–33. doi: 10.19191/EP18.2.P127.041

Summary
Mediation analysis aims to decompose the total effect of the exposure on the outcome into a direct effect (unmediated) and an indirect effect (mediated by a mediator). When the interest also lies on understanding whether the exposure effect differs in different sub-groups of study population or under different scenarios, the mediation analysis needs to be integrated with interaction analysis. In this setting it is necessary to decompose the total effect not only into two components, the direct and indirect effects, but other two components linked to interaction. The interaction between the exposure and the mediator in their effect on the outcome could indeed act through the effect of the exposure on the mediator or through the mediator when the mediator is not totally explained by the exposure. We describe options for decomposition, proposed in literature, of the total effect and we illustrate them through a hypothetical example of the effect of age at diagnosis of cancer on survival, mediated and unmediated by the therapeutical approach, and a numerical example (Table 2).

Table 2. Numerical example and decompositions. A: exposure, M: mediator, Y: outcome; CDE: control direct effect; PDE: pure direct effect, TDE: total direct effect; PIE: pure indirect effect; TIE: total indirect effect.

A	M	Risk	Y=1	Y=0	Total
0	0	1%	100	9900	10000
0	1	3%	150	4850	5000
1	0	2%	10	490	500
1	1	20%	200	800	1000

$$CDE(m = 0) = 0{,}030 - 0{,}010 = 0{,}020$$
$$CDE(m = 1) = 0{,}200 - 0{,}020 = 0{,}180$$
$$PDE = 0{,}180 * 500/10.500 + 0{,}020 * 10.000/10.500 = 0{,}028$$
$$TDE = 0{,}180 * 1.000/6.000 + 0{,}020 * 5.000/6.000 = 0{,}047$$
$$PIE = (0{,}020 - 0{,}010) * (1.000/6.000 - 500/10.500) = 0{,}001$$
$$TIE = (0{,}200 - 0{,}030) * (1.000/6.000 - 500/10.500) = 0{,}020$$

This example has been used and discussed extensively in the workshop on mediation analysis carried out in Task 7.5

Popovic M, Fasanelli F, Fiano V, Biggeri A, Richiardi L. Increased correlation between methylation sites in epigenome-wide replication studies: impact on analysis and results. Epigenomics 2017;9(12):1489–502. doi: 10.2217/epi-2017-0073

Summary
Aim – To show that an increased correlation between CpGs after selection through an epigenome-wide association studies (EWAS) might translate into biased replication results. Methods – Pairwise correlation coefficients between CpGs selected in two published EWAS, the top hits replication, Bonferroni p-values, Benjamini–Hochberg (BH) false discovery rate (FDR) and directional FDR r-values were calculated in the NINFEA cohort data. Exposures' random permutations were performed to show the empirical p-value distributions. Results – The average pairwise correlation coefficients between CpGs were enhanced after selection for the replication (e.g., from 0.12 at genome-wide level to 0.26 among the selected CpGs), affecting the empirical p-value distributions (Figure 4) and the usual multiple testing control. Conclusion – Bonferroni and Benjamini–Hochberg FDR are inappropriate for the EWAS replication phase, and methods that account for the underlying correlation need to be used.

Figure 4. Skewness of p-value distributions from the analyses of the association between smoking-related (n = 4794) and sex-related (n = 2544) CpG sites and permutations of maternal smoking during pregnancy and child's sex from 10,000 replications. 'Random' indicates random permutations of both CpG sites and exposure under study.

In the presence of a higher correlation between CpG sites, due to pre-selection of the CpG for replication, the skewness of the p-value distributions has a larger variation and is shifted toward positive values (right-skewed distributions) compared with the distributions of genome-wide randomly selected CpG sites.

These results have implication specifically for WP8 that focuses on DNA methylation.

2.2.2 Reviews for the preparation of the tutorials

As detailed in Milestone 12, WP7 has been working to produce four tutorials in the field of causal inference (Deliverable 7.4). The areas were chosen for their relevance to the field of life-course epidemiology and for gaps in the literature on how to implement the various methodological strategies. The tutorials will aim at comparing different methods and the interpretation of their

resulting estimates, by providing numerical case studies relevant to life-course epidemiology. We report below a summary of the preparatory work conducted so far for the development of the tutorials, which will be delivered as part of Deliverable 7.4 (M60).

a. Mediation analysis with multiple mediators

Mediation analysis aims at estimating to what extent the effect of an exposure on an outcome is explained by a given set of mediators on the causal pathway between the exposure and the outcome. In other words, it aims at decomposing the total effect of the exposure on the outcome into the indirect effect (ie, explained by the mediators) and the direct effect (ie, not explained by the defined set of mediators). Traditional statistical approaches do not take into account the potential interaction between the exposure and the mediators and are restricted to linear and log-linear models, or logistic models in the case of rare outcomes. Counterfactual approaches are more flexible and provide a definition of assumptions required to identify the direct and indirect effects and interpret their causal relevance.

In the field of life-course epidemiology, researchers often deal with research questions involving multiple mediators, hence several causal pathways. The difficulty involved in the identification and estimation of direct and indirect effects increases as the number of mediators increases.

We reviewed recent statistical methods to analyse multiple sequential mediators in a causal inference framework. These methods can be applied using available statistical packages, but they may require some extra effort with respect to data preparation and programming. We considered the following four methods: the inverse odds ratio weighting approach (Tchetgen Tchetgen, 2013; Nguyen et al, 2015); the inverse probability weighting approach (VanderWeele and Vansteelandt, 2014); the imputation approach (Vansteelandt et al, 2012) and the extended imputation approach (Steen et al, 2017). These methods vary in the types of estimates that can be obtained (marginal or conditional estimates), the level of decomposition of the total effect that can be performed (two- or three-way decompositions), and the required regression models (Table 3).

In the tutorial, the four approaches are applied to the example depicted in Figure 5, on the role of potential mediators in the relationship between maternal mental health during pregnancy and the risk of wheezing in offspring between 6 and 18 months old. Specifically, maternal mental health will be measured as occurrence of depression and/or anxiety, and the investigated mediators will be low birth weight, preterm birth, and delivery with caesarean section jointly, as well as respiratory infections in the first six months of life.

This tutorial is already very well advanced and is expected to be published in the coming months.

Table 3. Regression models required by each of the four approaches. IORW: inverse odds-ratio weighting.

	Statistical approach			
Models for	IORW	Weighting	Imputation	Extended imputation
Outcome	√	√	√	√
Mediators				√
Exposure	√	√		
Nested counterfactual			√	√

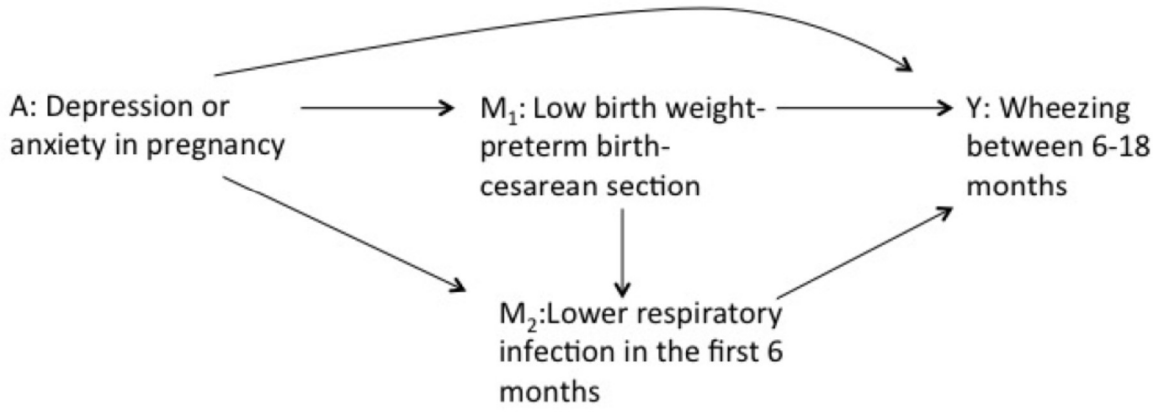

Figure 5. Directed Acyclic Graph (DAG) representing the hypothesized causal structure of the case study used for the multiple mediator analysis tutorial. Confounders are not included for simplicity.

b. Non-genetic instrumental variables and other methods for natural experiments

Instrumental variable (IV) analysis has been commonly used for many years in sociology, education, pharmacology, and economy, but in comparison rather underutilized in life-course epidemiology until recently. Developments in array technologies to measure common genetic

variants (Single Nucleotide Polymorphisms (SNPs)) led to a parallel increase in the use of Mendelian randomisation (MR), a method that uses genetic variants (most commonly, but not exclusively SNPs) as an IVs (Lawlor et al, 2008). MR exploits Mendel's laws of segregation and independent assortment creating a scenario where genetic variants are randomly allocated from parents to offspring, with evidence that at a population level they are less likely to be associated with the many socioeconomic, environmental, behavioural confounding factors that can distort estimates obtained from conventional observational analyses. Non-genetic IVs comprise exogenous factors that randomly impact a population under study. Their most common application is in the context of natural or pseudo-experiments, tough they are also increasingly used in randomized clinical trials (RCTs) to quantify the effect of intervention targets (rather than intervention effects) and have been used for some time to obtain per-protocol effects of randomized interventions. Epidemics and famines have been historically used as IVs to study the causes of diseases, while more recent use of non-genetic IVs in epidemiology has been largely limited to pharmacoepidemiology and social epidemiology. For example, geographical or temporal variations in medical prescriptions and population-level policies, such as legislative, regulatory, and fiscal policies, have been used as instruments to study the aetiology of social and health outcomes. However, the relative rarity of "shock events" or strong exogenous instruments for exposures, more complicated research design, and often small and more gradual effects, still hamper the widespread use of non-genetic IV in epidemiology.

We focus here on non-genetic IVs in life-course epidemiology, specifically on policy-related IVs (Greenland, 2000; Baiocchi et al, 2014), and fuzzy regression discontinuity design (Lee and Lemieux, 2010; Cattaneo et al, 2020; Cattaneo et al, in press) in the context of birth cohort research. Considering the setting where we aim at estimating the causal effect of an exposure on an outcome, with X denoting the exposure, Y the outcome, and C a set of confounding factors, then Z can be used as an IV if it satisfies the following three properties: (i) Z is associated with X (*relevance* criterion), (ii) Z affects Y only through its effect on X (*exclusion restriction* criterion), and (iii) Z is independent of all variables that influence Y not through X (*exchangeability* criterion) (Figure 6). For example, if we were to investigate the causal relationship between caesarean delivery (X) and wheezing in infancy (Y) independently of many potential confounders, such as maternal age, educational level, gestational hypertension, etc. (C), then we could use a an IV approach using the prevalence of caesarean deliveries (Z) by geographical areas in a certain setting or its temporal changes, knowing that the decision to perform caesarean section depends not only on the relative and absolute indications but also on the maternal and obstetrician preferences.

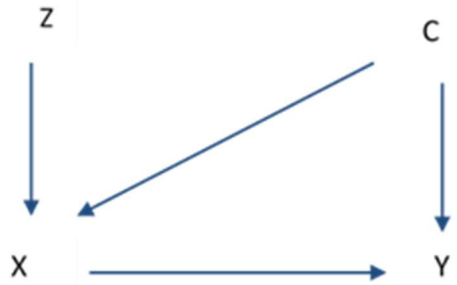

Figure 6. Directed Acyclic Graph (DAG) representing simple causal structure with a valid instrumental variable. A: exposure, Y: outcome, C: set of measured and unmeasured confounding factors, Z: instrumental variable.

The second approach that we focus on is the fuzzy regression discontinuity design (RDD). It is a quasi-experimental approach that can be thought of as an extension of an IV analysis, and applied in circumstances where an exogenous source of variation arises from a continuously measured variable (assignment or rating variable) with a clearly defined cutoff point above or below which the population is at least partially assigned to a treatment/exposure. Assignment variable creates a discontinuity in the probability of the treatment/exposure at threshold, where the direction and magnitude of the jump is a direct measure of the causal effect of the treatment/exposure on the outcome for subjects near the cut-point. In the counterfactual framework, RDD can be seen as a "local randomization". Continuous measures that determine treatment/exposure eligibility are subject to random variability due to measurement error, sampling variability, and chance factors. This implies that individuals close to the threshold are expected to be exchangeable, i.e. individuals just below the threshold are on average similar on all observed and unobserved baseline characteristics to those just above the threshold except for the exposure/treatment. This scenario creates a design similar to an RCT and if the exchangeability assumption holds any difference in outcome on the two sides of the threshold will be caused by the treatment/exposure. The main assumptions/conditions of RDD are therefore: i) continuous assignment variable, ii) the threshold is set prior to the observed data and is not changed after observation (no sign of manipulation of the eligibility criteria to be below/above the threshold), and iii) individuals close to the threshold should be very similar, on average, in observed and unobserved characteristics (exchangeability). The latter is considered plausible for relatively narrow windows around the threshold.

When the assignment rule perfectly determines exposure (from 0 to 1 at threshold) regression discontinuity takes a sharp design (e.g. imposed policy measures). In contrast, if the assignment rule affects the probability of exposure creating a discontinuous change at the threshold, but without an extreme 0-to-1 jump regression discontinuity takes a fuzzy design (e.g. optional participation in programs, imperfect compliance, or spillover effects). The fuzzy RDD is therefore analogous to non-compliance in an RCT and estimates the intention-to-treat (ITT) impact of the treatment/exposure, i.e. the effect of the eligibility rather than the treatment/exposure itself on the outcomes of interest. Within a fuzzy RDD, estimate of the treatment/exposure effect around the cutoff point, where treatment and comparison units are most similar, is obtained with the local average treatment effect (LATE) estimator, which does not necessarily apply to individuals with assignment variable further away from the threshold. The threshold indicator can be seen as a special case of a binary instrumental variable for the treatment/exposure and the LATE as causal effect of the treatment/exposure at the threshold in a population of compliers. An example to this would be to investigate the effect of caesarean delivery on the risk of wheezing in infancy, using the indicative threshold of 4000 grams predicted weight at birth for recommending prophylactic caesarean deliveries.

This tutorial is currently under development, with analysis being conducted to choose the most relevant educational examples in life-course epidemiology.

c. Transportability

In the medical domain, substantial effort has been put in generating internally valid estimates in experimental studies. Yet it remains difficult to apply results from experimental studies to populations outside the study sample suffering from the same disease. In other words, many methods are available and employed for testing internal validity, but limited effort is made in testing generalizability, or external validity. Testing the external validity of scientific findings is nevertheless crucial for the application of knowledge across populations.

The transportability theory introduced by Pearl and Bareinboim in 2011 provides a robust method for describing the causal relationships of experimental variables and the circumstances that allow findings to be transported to additional populations. It uses relations expressed through a graphical causal model to describe which variables' probability distributions can be "transported" between populations. While this theory has been developed in the context of causal models typically obtained from RCTs (i.e. for the purpose of transporting RCT results to an observational setting), it is realistic to apply similar methods with probabilistic models applied to observational

data. This is particularly relevant to LifeCycle endeavour as in life course epidemiology exposure-outcome relationships and resultant estimates are derived from observational studies through probabilistic modelling. Transporting estimates obtained from observational studies however adds a layer of complexity and requires to combine methods for causal inference and transporting effect estimates in order to minimize biases inherent to observational studies and to account for differences between study and target populations that could influence the causal effect estimate on the population of interest (Josey et al, 2020).

Only three transportability methods have been fully described to date for observational studies, all using the framework of the potential outcome. The targeted maximum likelihood estimation (TLME) was first introduced in the transportability setting by Rudolf and van der Laan (2017). This approach uses a set of "clever covariates" to update the conditional means of the potential outcome and involves the G-computation setup. The second method is an augmented estimator that combines an exposure, sampling, and outcome model, introduced by Dong et al. in 2020, and further extended by Josey et al. (2020). This approach assumes that each unit in the target population is prescribed a vector of known sampling weights and proceeds with estimating the inverse odds of sampling. The third method developed by Josey et al. (2020) was called the full calibration approach. It combines the calibration estimator approach of Chan et al. (2015), which corrects for exposure groups heterogeneity through balancing weights, with a vector of estimated sampling weights, which attempts to remove bias induced by the differences of the covariate distribution between the study sample and the target population. Each method comes with various constraints and advantages, which must be mitigated depending on the setting and how confident one can be in the different imposed assumptions.

Josey et al. (2020) provided a comprehensive tutorial with simulated data and one illustrative example: comparing the effect of two monotherapies for diabetic adult patients. In our tutorial we intend to describe and compares the methods in the field of life-course epidemiology, where the exposure is not a therapeutic as mostly investigated in transportability method paper but rather an exposure or stressor occurring early in life.

d. Triangulation

Triangulation in aetiological epidemiology refers to integrating evidence from different data-sources and/or different methods where the different data-sources and methods have different and unrelated key sources of bias (Lawlor et al, 2017). The idea behind this is that where these different data-sources/methods have given consistent results (whether that is a null, protective or

detrimental effect of an exposure) we have more confidence that is the correct effect, as it would be very unlikely to get the same result from different sources of bias. Triangulation required a prior risk of bias assessment with explicit details of the likely direction of biases. Thus, where results from different data sources/methods are inconsistent, this prior work can help determine what further analyses are needed to move closer to the causal effect.

Whilst we (Lawlor et al, 2017; Pearce et al, 2019) and others (Munafo and Davey Smith, 2018) have described the theory behind triangulation, provided examples of its use, and used it in some applied papers in LifeCycle (e.g. Brand et al, 2019) it is still a relatively new concept in epidemiology and practical guidance on how to use this approach is lacking. Furthermore, to date the focus has been on integrating different data/methods to provide a qualitative overall result (i.e. whether the integrative evidence supports no causal effect or a beneficial or detrimental effect) rather than attempting to quantify a causal effect or range of plausible effects. In current on-going work we are exploring methods for such quantification. For example, one approach could be to compare the least biased causal estimate from each method/dataset and where these are qualitatively consistent, provide bounds within which the causal effect lies. Where such bounds suggest a narrow range, all with similar clinical/public health implications, a strong quantitative conclusion could be drawn. A further approach we are developing is the use of Bayesian methods to combine the estimated causal effects with our defined sources of bias included as prior distributions.

In the triangulation tutorial we will focus on the practical approach to undertaking triangulation, highlighting the need to identify data-sources and methods, define likely sources of bias and undertake informed specific risk of bias assessments to clearly specify sources of bias (and where possible) the likely direction of these, and use this work to inform main and sensitivity analyses (ideally with all of this published as an analysis plan). Then subsequently completing main and sensitivity analyses for each data-source/method and interpreting and comparing results in the context of the described risk of bias assessment and likely direction of any bias with different methods. We will also acknowledge that this is an iterative process, with the likelihood that changes are made to the analyses plan as results from different methods emerge and emphasising the importance of published analysis plans that have explicit rationales and dates where any changes are made. We will use case studies of relevance to LifeCycle in the tutorial and we will also include some examples of providing bounds of causal effect estimates and quantified effects incorporating distributions of expected bias as priors in Bayesian analyses.

2.3. Applied examples in LifeCycle

Some original research articles published by the LifeCycle project have a specific methodological component addressed by WP7. We provide below two published examples, one on baseline collider bias and one on mediation analysis. Several more papers are expected in the coming years.

Pizzi C, Popovic M, Isaevska E, Rusconi F, Moirano G, Merletti F, Richiardi L. Socioeconomic inequalities in reproductive outcomes in the Italian NINFEA birth cohort and the Piedmont Birth Registry. Epidemiol Prev 2020;44(5-6) Suppl 1:136-41. doi: 10.19191/EP20.5-6.S1.P136.083

Summary
Background – Socioeconomic inequalities in reproductive outcomes have been consistently reported in several countries. In a European collaborative study conducted in 2012 whose aim was to investigate the association between socioeconomic position (SEP), measured through maternal education, and preterm delivery inconsistent results were found for the NINFEA birth cohort. However, NINFEA contributed to that study with the first 2,500 pregnancies only, and estimates were not adjusted for any potential confounders assuming that SEP is a distal exposure, that could not be affected by other preterm risk factors. Objectives – To investigate the relationship between SEP and the reproductive outcomes using the entire NINFEA cohort and compare the results with the population-based Piedmont Birth Registry (PBR), accounting for potential baseline collider bias both in the cohort and in the registry. Design – Observational study. Setting and participants – 5,323 NINFEA singletons, whose mothers registered into the study before the 36th week of gestation, were analysed. Analyses on maternal education were replicated in the 2011 PBR of 35,318 singletons live births. Factors affecting the likelihood of being a member of the NINFEA study or becoming pregnant in the general population were treated as potential confounders to adjust for baseline collider bias. Main outcome measures – The association of maternal education and a recently developed household income indicator with both preterm delivery (<37th weeks of gestation) and low birth weight (<2,500 gr) were analysed. Results – In the NINFEA cohort, low SEP was positively associated with both preterm delivery and low birth weight, with slightly stronger associations for household income, especially on low birth weight (Table 4). Results were consistent with those obtained in the PBR data, where an inverse relationship between maternal education and the two reproductive outcomes was found. In both populations, there was confounding due to maternal age and parity, showing that independently of the nature of the source population, baseline factors that affect the probability of being a member of such source population have to be accounted for to allow causal inference. Conclusions – Low SEP is associated with adverse reproductive outcomes in a contemporary Italian population.

Table 4. Associations of maternal education and household income with reproductive outcomes in the NINFEA study.

CHARACTERISTICS	PRETERM BIRTH (NO. 4,906)		LOW BIRTH WEIGHT (NO. 4,768)	
	OR_{CRUDE} (95%CI)	OR_{ADJ} (95%CI) [a]	ORC_{CRUDE} (95%CI)	OR_{ADJ} (95%CI) [a]
MATERNAL EDUCATION				
High	–	–	–	–
Medium	0.87 (0.65-1.18)	0.93 (0.69-1.27)	0.71 (0.52-0.98)	0.78 (0.57-1.07)
Low	1.26 (0.70-2.27)	1.47 (0.81-2.66)	1.21 (0.67-2.17)	1.49 (0.82-2.71)
HOUSEHOLD INCOME				
High	–	–	–	–
Medium	0.95 (0.71-1.26)	1.07 (0.80-1.44)	0.93 (0.70-1.24)	1.10 (0.82-1.48)
Low	1.17 (0.58-2.37)	1.63 (0.77-3.46)	1.30 (0.66-2.56)	2.02 (0.98-4.18)

a. Adjusted for maternal age, nulliparity, country of birth, and child region of birth.

Ballon M, Botton J, Forhan A, de Lauzon-Guillain B, Melchior M, El Khoury F, Nakamura A, Charles MA, Lioret S, Heude B. Which modifiable prenatal factors mediate the relation between socio-economic position and a child's weight and length at birth? Matern Child Nutr 2019;15(4):e12878. doi: 10.1111/mcn.12878

Summary

Although several studies have shown a positive association between socio-economic position and size at birth, not enough is known about the modifiable factors that may be involved. We aimed to investigate whether maternal prepregnancy body mass index (BMI), smoking, diet, and depression during pregnancy mediate the positive association between maternal education and birth size. Weight and length z-scores specific for gestational age and sex were calculated for 1,500 children from the EDEN mother–child cohort. A mediation analysis of the associations between maternal education and birth size was conducted with a counterfactual method, adjusted for recruitment centre, parity, maternal height, and age. In the comparison of children of mothers with low versus intermediate education levels, maternal smoking during pregnancy explained 52% of the total effect of education on birth weight. Similar findings were observed with birth length z-score (37%). The comparison of children of mothers with high versus intermediate education levels yielded a non-significant total effect, which masked opposite mediating effects by maternal BMI and smoking during pregnancy on both birth weight and length (Figure 7). Prepregnancy BMI and maternal smoking during pregnancy mediate the positive association between maternal education and birth weight and length z-scores. These mediators, however, act in opposite directions, thereby masking the extent to which healthy prenatal growth is socially differentiated.

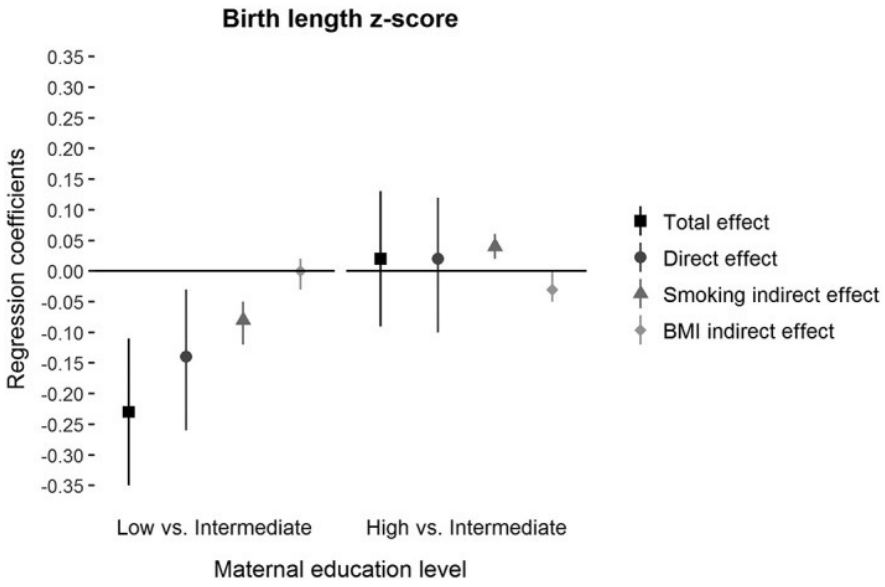

Figure 7. Total, direct, and mediated effects (β and 95% CI) for association between maternal education level and birth length z-scores, mediated by smoking during pregnancy and prepregnancy BMI, adjusted for centre, mother's height, parity, and mother's age at delivery.

3. Conclusions

We have provided in this report a detailed overview of causal inference methods using a range of methodological approaches applicable to various settings, research questions, and data availability. Selected methods specifically applicable to life course epidemiology were made available to the members of LifeCycle through a web-based database, which will soon be disseminated within the EU Child Cohort Network and the broader scientific community. We also published reviews and methods papers with an educational goal, in line with WP7 objectives.

We have also described the preparatory work for the tutorials that will form Deliverable 7.4. These will provide the research community with detailed methods and motivating examples to encourage and facilitate the application of appropriate methods for causal inference in life course epidemiology. Original research papers published by LifeCycle researchers using collider bias and mediation analysis already demonstrate the application of the described methods in the field.

Finally, WP7 is very active in disseminating its work through the organization of workshops and training courses in collaboration with UNIVBIRIS and ERASMUS. These will be fully described as part of Deliverable 7.5 (due M60).

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