Chapter 13

Causal Crypticity

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Causal crypticity is an epistemic norm in the field of maternal–fetal effects science. That is, fetal origins researchers assert causal hypotheses about links between small permutations in the gestational environment and later life outcomes. The causes and effects of these permutations are typically not directly observed but are inferred from variations in developmental outcomes or health risks that occur later in life, often along a decades-long chain of other exposures and experiences. To advance these hypotheses requires field-wide epistemic norms that accept, in most cases, an ineliminable crypticity – meaning both subtlety and elusiveness – in the causes and effects under study.

This feature of Developmental Origins of Health and Disease (DOHaD) science is not the perception of hard-nosed sceptics. Many DOHaD researchers are frank about its causal dilemmas [1–3]. DOHaD scientists have faced fierce criticisms of their theories and findings by scientists who doubt the plausibility of their causal claims [4–7], and scientists in the varied research streams that comprise fetal origins/maternal effects science have been openly debating the question of causality for decades. The search for causal mechanisms propelled the entry of epigenetic methodologies into the field and contributed to the pioneering of new inference causal testing models such as Mendelian randomisation to attempt to examine the plausibility and strength of hypothesised causal relations [8–12].

The crypticity of causality in DOHaD is no standard-issue causality conundrum. As I argued in *The Maternal Imprint: The Contested Science of Maternal-Foetal Effects* (2021), from the field's inception, causal crypticity has been deeply carved into the historical development of the field and will likely continue to be a persistent feature of any research in maternal–fetal effects science, regardless of the amount of data acquired or the sophistication of computational methods employed [13]. Nods to the context-specificity and complexity of causal attributions in DOHaD science do not sufficiently acknowledge the persistent, intransigent crypticity of causality in maternal–fetal effects science, nor do they capture the social dimension of its function as an epistemic style in DOHaD discourse.

High tolerance for causal crypticity can be defined as a field-defining epistemic norm that accepts a persistent state of indeterminacy about the empirical reality, strength, and magnitude of hypothesised causal phenomena that are the object of study. Causal crypticity distinguishes approaches to causal reasoning within DOHaD from certain ideals of scientific inference prising replicable experiments, intervenability demonstrating causal invariability across conditions, and identification of a physiological mechanism [14]. But this does not imply that causal crypticity is particularly epistemically suspect compared to other causality-seeking knowledge projects. Causal crypticity is

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not a term intended to pinion the scientific merit or rigour of DOHaD science but to characterise its epistemic norms to better understand the field's theories, its evidential base, and the judgements that undergird its inferences. My claim is descriptive, not evaluative: causal crypticity operates as an epistemic norm in DOHaD science.

In this chapter, I explicate and develop the concept of causal crypticity, first introduced in Richardson (2021). Causal crypticity can be understood in three ways: as an epistemic norm; as a boundary-delimiting signature of field culture or epistemic style; and as a promissory mode. Contending with causal crypticity as a norm-shaping feature of the knowledge landscape of maternal–fetal effects science, I conclude, demands reflection on strategies for ethical and accountable practices of claimsmaking in DOHaD science, in a world where its findings are received as carrying social implications in arenas ranging from reproductive autonomy to efforts to redress the health implications of racism and intergenerational trauma.

13.1 Crypticity

The term 'cryptic' has multiple connotations, which I embrace. Something that is cryptic may be real but difficult to decode or retrieve. Equally, something that is cryptic can be unclear, and whether it is real or not can be impossible to discern. Phenomena that are cryptic are elusive, shape-shifting, and impermanent in form. DOHaD science connects cryptic effects with cryptic causes. *Cryptic effects* are findings of health outcomes in exposed compared to unexposed populations that are small in effect size and that present inconsistently across different study cohorts; moreover, such crypticity in reported outcomes is persistent and unresolved despite expanding volumes of data. Cryptic effects are typified by DOHaD studies reporting small absolute changes in risk factors for common diseases among populations of healthy, average births exposed to a hypothesised intrauterine variable.

The field's tolerance for causal crypticity is in clear evidence, for instance, in the Dutch famine studies, a touchstone in DOHaD research. The Dutch famine studies are often presented as definitively demonstrating a causal link between nutrition in the womb and obesity and related metabolic conditions, including high blood pressure, diabetes and insulin resistance, and cardiovascular disease. These metabolic outcomes are based on measures taken from a small sample of 422 survivors, in their fifties, who were gestationally exposed to the famine (and matched siblings) during the four months of the acute famine of 1944–1945 in the Netherlands [15]. As researchers will readily agree when queried, the findings from these studies are much less generalisable, and much more contingent and uncertain, than portrayed in the standard textbook narrative. Famine survivors have been found to have, on average, modestly elevated blood pressure compared to non-survivors [16]. Women gestated during the Dutch famine have, on average, an extra few centimetres around the waist, at age 59, than their non-exposed sisters [17]. However, the effect sizes in such findings are small. They are also unstable, appearing and disappearing across different age cohorts and genders/sexes within the study populations. Critical reviews demonstrate that the Dutch famine studies have shown a few, if any, stable metabolic outcomes of significant effect size specifically correlated with in utero exposure to famine [18].

Other statements frequently reiterated in the literature, such as that early exposure to famine doubles the risk of obesity, are, upon examination, not supported by current

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evidence but are statistical relics of dated metrics of what constitutes abnormally overweight body composition from the 1970s [19]. Furthermore, researchers have struggled to identify biological mechanisms that could account for the purported specific causal effects of famine exposure during gestation. A much-celebrated early finding of epigenetic changes in the insulin-like growth factor 2 (IGF2) gene among famine survivors has never been replicated [20, 21]. Subsequent studies attempting to find epigenetic mediators of triglyceride levels among survivors have not withstood causality inference testing [3]. Yet even as effects are causally cryptic – effect sizes remain small, findings are contested and conflicting, and mechanisms are elusive – the Dutch famine studies are presented in the literature as a foundation and model for future work [22], and scientific publications, textbooks, and popular media frequently feature studies of health outcomes among ageing members of the cohort of infants gestated during the Dutch famine as a gold-standard example of the promise of developmental origins science [23].

Causal crypticity characterises the explanations for *cryptic effects* because such cryptic effects are unstable and variable, such that they make non-ideal observations for substantiating a link to a specific cause. In the case of maternal intrauterine effects, in which the direct effects of perturbations during gestation are already challenging to observe, measure, or quantify, causal crypticity is particularly amplified. This is because, due to the many environmental and genetic confounders of early human development, in nearly every case the cryptic maternal effect is an endpoint of complex, multiply confounded causal chains, frequently occurring at a significant temporal distance from the hypothesised initial exposure, which itself is sometimes a confounded, variably defined, difficult-to-measure 'cryptic cause' such as 'stress' or 'metabolic dysregulation'.

Such crypticity is apparent even within maternal–fetal programming science that is often presented as most foundational, most settled, and as presenting the most extreme exposures, the largest effects, and the most incontrovertible findings, as in the Dutch Hunger Winter studies. The field's high tolerance for causally cryptic findings as constituting knowledge helps us understand how such findings, which at best offer support for what may be model-theoretically *plausible* or physiologically *possible,* become concretised as a textbook, settled science, and as known or proven facts within the field of DOHaD.

13.2 Causal Crypticity as an Epistemic Style and Promissory Mode

Tolerance for causal crypticity, as a feature of the DOHaD field's culture, norms, standards, or epistemic style, is apparent in the forms of evidence accepted within the DOHaD field as contributions to scientific knowledge and reflected in its shared assumptions about the questions and objects of interest. For example, the quality of crypticity is arguably constitutive of what makes something a developmental or maternal *effect* rather than, for instance, a birth defect or anomaly. Causal crypticity is, furthermore, integral to the central questions and problems that the DOHaD field addresses and to how it goes about addressing them. As Gemma Sharp, Debbie Lawler, and I have argued, the question of whether maternal–fetal programming effects are *real* is in many senses not a question for researchers in the DOHaD field. For DOHaD researchers, it is indisputable that programmable maternal–fetal effects are real [24]; the question is only

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whether we can see and prove them, given that the biology involved must be very complex and that the pragmatics of studying maternal–fetal effects in human populations is challenging.

Scientific fields are social formations. Sociologists and historians of science posit that scientific fields function most efficiently to advance empirical understanding of phenomena when there is a shared culture of sorts and when the field agrees on its core questions. As a part of this boundary-defining work, fields typically close down or defer certain questions as well as certain epistemological considerations [25–28]. Causal crypticity can be tolerated, one might hypothesise, when it serves other important functions for the field as a social formation. Following scholars of scientific hype [29, 30], one speculation is that causal crypticity may function to keep fetal origins science at the centre of controversy, with findings persistently described as emergent, yet to be validated, still being tested, and even essentially contested. In part because of this, causal crypticity could work cathectically to draw intrigue and to construct a continually self-replicating arc of future speculation and possibility. In this way, causal crypticity may function as an electric current that both makes the field of maternal–fetal effects a flashpoint and draws curious researchers to it.

In this sense, causal crypticity can be understood as a promissory discourse that conveys causal-ish claims that generate excitement and interest [29]. Thus, although the field is now more than three decades old, its claims are frequently presented as offering a new, emergent, and provocative resource for science. It is commonplace to read in publications, to hear at an academic conference on DOHaD, or to find in a media presentation of DOHaD research a statement such as: 'In recent years, research from the field of the Developmental Origins of Health and Disease (DOHaD) has suggested that events before birth can have life-long consequences' [31]. Such broad statements suggesting a powerful causal relation between intrauterine environment and later life health are, technically speaking, perfectly consistent with a collection of unreplicated findings that intrauterine exposure X is associated with small effects on offspring outcome Y in study population Z, yet it also implies stronger and more widely validated causal effects actionable for public health and in the clinic than present evidence can support.

Specifically, causal crypticity may function socially and discursively to generate excitement and interest in the scientific field by pointing towards a future in which knowledge of such cryptic patterns could be harnessed to optimise health outcomes [32]. Notably, cryptic patterns of perturbations linked to outcomes do not promise control or prediction for any particular individual, but at best speak to patterns and trends and to risk categories and potential problems at the level of population groups [33]. These patterns and risk categories generate uncertainty and require *concern* and ongoing *monitoring*.

In a world rife with crises, risk, and uncertainty, the potential for cryptic sources of fetal developmental perturbation requiring ongoing tracking is everywhere. We thus see speculation about the relevance of developmental origins theories to nearly every area of social anxiety and uncertainty, including natural disasters and political or economic crises, from the 9/11 attacks [34–36] to climate change [37–39], to most recently, the COVID-19 pandemic [40–42]. Writing in 2021, Tessa Roseboom and colleagues warned in the *Journal of the Developmental Origins of Health and Disease* that 'the legacy of this pandemic looms large for unborn babies … These individuals, being unseen and unheard, are likely to go unprotected'. The implications of experiencing the pandemic

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while in the womb, these authors assert, will affect an entire generation and 'all of our future societies': 'Today's (unborn) children will drive growth and development in our future societies. [. . .] We must now act to prevent further scarring of the life chances of a generation' [41]. The potential for harm to the 'unborn' is pervasive, as in Figure 13.1, which conceptualises the mother's work, daily hassle, and even the condition of pregnancy itself, as health-imperilling stressors transmuted to the fetus through the mother [42].

DOHaD science on maternal–fetal effects promises to inform public policy to improve future outcomes, but causal crypticity entails that DOHaD research is not, by and large, likely to produce interventions driven by the reversal of biochemical mechanisms at the moment or site of programming [33]. In a field of inquiry characterised by the epistemic style and promissory mode of causal crypticity, interventions, while hoped-for, are ultimately less the order of the day than *demonstrating the possibility or plausibility of harm*. In the case of DOHaD, this harm is conceptualised as a limitation on future potential. That is, DOHaD findings of cryptic effects deliver evidence of limitations or lesions in the potential for life flourishing, from early mortality to educational achievement. Powerful ableist, Western norms and pressures to optimise birth outcomes, complemented by globalist, development economics frameworks for measuring human capital in the metrics of health and at the level of the body, help sustain this promissory mode in maternal–fetal effects science [43–46]. The range of possible future adverse outcomes is so wide that the full implications of the developmental harm can never be fully grasped, only proxied by limited quantitative physiological measures such as adiposity or blood pressure. Moreover, it is argued that these harms are set so early in development that compensating for or redressing the harms will be challenging. DOHaD researchers frequently suggest that early developmental harms might only be redressed in future generations by removing or waiting out the scourge of trauma, poverty, or metabolic deprivation.

13.3 Causal Crypticity in the Context of Big Data and Postgenomic Science

While DOHaD science has long operated with a high tolerance for causal crypticity, the epistemic norm of causal crypticity, as I have characterised it here, increasingly might be said to characterise the knowledge claims and knowledge practices endemic to data-rich, twenty-first-century postgenomic biomedical life sciences, particularly those endeavours operating in complex biosocial causal spaces. Indeed, as commentators have pointed out [47], in many areas of postgenomic biomedicine, causal claims are *not expected* to result from investigations. It is expected that the strength of findings will vary depending on contextual factors and that findings will not replicate across all datasets. Even as researchers strive to validate causal connections, a tolerance for a certain permissiveness with implying the likely causality of observed correlations is increasingly integrated into the norms and culture of postgenomic biomedicine.

There is a broader social context for these shifts in knowledge paradigms in the postgenomic life sciences. The epistemic style of causal crypticity is primed to flourish in a knowledge culture defined by massive information. The epistemology of massive information is defined by constructs such as 'search', trending ideas, chatter, pattern recognition, the notion of 'data mining', network, and systems-like ideas about the

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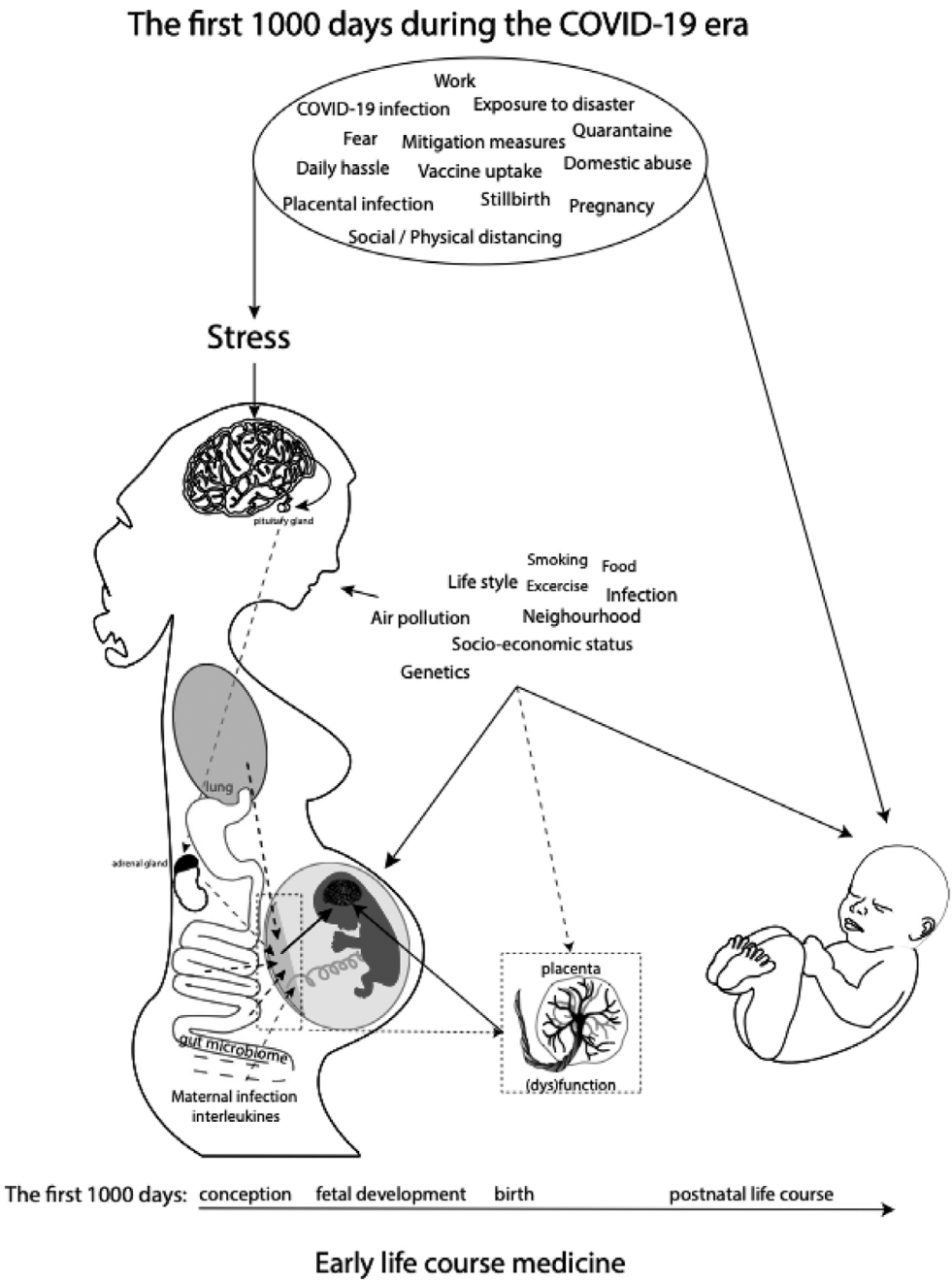

Figure 13.1 'Overview of potential maternal prenatal stressors during the current COVID-19 pandemic as part of the early life course medicine'.
Source: Schoenmakers et al. [42]

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connectivity of all things, total information, emergence, and surveillance [48]. This epistemology contrasts sharply with 'magic bullet' or 'master molecule' approaches to knowledge that are oriented towards control, intervention, and cure [49]. In a knowledge culture embracing causal crypticity, grievance or evidence of harm is not expected to surface as a gaping wound – acute, localisable, and repairable – but as a population-level signal – subtle, elusive, and with harms and benefits of uncertain interpretation.

Similarly in postgenomic science, signals are not expected to be single-gene lesions [50], but polygenic scores or risk calculi that must be carefully contextualised against a backdrop of population genetic structure, developmental context, and social conditions. These sciences, underpinned by genome-wide association studies, multidimensional forms of social data, and AI-informed analytics, are made up of statistically sophisticated evidence of correlations between biological and social outcomes. While these correlations themselves do not support causal inference, causal crypticity enables a presumption of the likelihood of causality. Findings are narrated within a larger frame that implies a strong assumption that such correlations, summed in their entirety, are evidence supporting an intuition of causality. This shift in epistemic norms is collapsing the twentieth-century oppositional distinction between the complexity-affirming 'dissident' anti-genetic determinist sciences and the reductionist and determinist gene-centric biological sciences [51].

In sum, causal crypticity is an epistemic norm that aligns with the speculative and promissory mode of today's transnational, big data-crunching science, which proposes to mine previously undetected patterns across populations, unlocking a key to who we are and where we are going in our uncertain era of demographic transformation in lifespans and family size, technological change, and environmental crisis. Like these fields, DOHaD pleads for a deferral of judgement and for more space for free investigation, by implicitly suggesting that cryptic patterns long postulated or hypothesised, and for which current evidence is trace-like at best, will soon be detectable as meaningful sources of human variation in health – once we have the data and the proper data mining tools to retrieve those patterns. In this way, within the postgenomic life sciences, DOHaD science offers an index case of the leading edge of a broadening trend of embracing the bold pursuit of cryptic causes.

13.4 Ethical and Accountable Claimsmaking in DOHaD Science under Conditions of Causal Crypticity

In *The Maternal Imprint*, I traced the history of attempts to empirically confirm speculations about the long-term or permanent effects of experiences or exposures in the womb [13]. The book followed three intertwining threads within this history: First, discourses about maternal agency and responsibility for reproductive outcomes. Second, progressive, anti-genetic determinist constructs of the biosocial body position the maternal–fetal relation as a particularly heightened space for the inscription of social and environmental context on the body. Third persistent and unresolved questions about the limits of empirical science in confirming the causal effects of intrauterine perturbations on disease distribution in human populations.

This third, seemingly epistemic dimension, I argued, cannot be fully pulled apart from the other two. This is because bold causal claims in the absence of consistent and convincing evidence of predictive, intervenable effects can only persist if there is a

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powerful social and scientific imaginary carrying them forward. The churning, resilient, charged space of maternal responsibility for optimising reproductive outcomes and the subversive, hopeful, riveting, intuitive, and narratively compelling picture of bodies embedded in environments and social systems are two such imaginaries.

The subtle effect sizes and complex confounding typical of causal claims in DOHaD science are not simply an everyday causal challenge but rather function as both a defining epistemic norm of the field and a future-oriented social discourse. The concept of 'causal crypticity' directs attention to the links between causal crypticity as an epistemic norm, the production of risk categories, and the promissory hype cycle of science.

Fields such as DOHaD are defining the epistemic terrain of postgenomic inquiry, particularly at the interface of the genetic and social sciences [51]. For some DOHaD scientists, the concept of causal crypticity as I have motivated it here may at first provoke defensiveness. Most scientists understand themselves instead to be seeking – even if not always finding – causal relations grounded only on rigorous empirical inference. However, embracing this feature of DOHaD research could make DOHaD a laboratory for grappling with causal crypticity in a reflective and forthcoming manner. This surely includes strengthening frameworks for making causal inferences in the face of causal crypticity, as some already are [2, 52]. But it also includes practices such as rigorously placing risk claims emerging from such sciences in context, in particular through collaboration with social scientists exploring the socio-structural dimensions of health and lifecourse development [53], accurately characterising the degree of uncertainty in scientific findings in this area [54], and educating the consumers of such science in the features of reasoning in a field defined by causal crypticity.

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