HEALTH IN TRANSITION

Translating developmental origins of health and disease science to improve future health in Africa

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THE IMPLICATIONS OF DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE FOR AFRICA: WHAT CAN BE LEARNT FROM AVAILABLE DATA?

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There is a broad spectrum of knowledge globally that shows that specific exposures in early life – during pregnancy and early childhood – might affect what happens at various later stages of life. The scientific field behind this has become known as the developmental origins of health and disease (DOHaD). The underlying mechanisms may be complex, and understanding and analysing the epidemiology of the causes and effects are complicated. Long-term individual data, often across generations, are the best way into understanding the precise nature of such effects. Therefore, much of the research that has been done in this area has happened where detailed, individual data on health and welfare are a routine part of social structures – for example, in Scandinavian countries.

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Nevertheless, it is reasonable to suppose similar exposures and effects might apply within African populations – the difference being that relevant details are much less likely to be documented. Since there is no quick fix for implementing data collection that spans generations, the only indirect clues as to how DOHaD may be affecting Africans is to consider how available data sources might be used in derivative analyses. In this chapter, an example is presented of taking a relationship established elsewhere between breastfeeding and obesity, applied to public-domain estimates on breastfeeding and childhood obesity in Africa, and analysed to estimate the magnitude of the likely consequences of non-breastfeeding on childhood obesity in Africa. This approach is much less rigorous than the ideal situation where specific individuals' breastfeeding histories could be related to their later individual obesity, but it offers some clues as to the likely magnitude of this particular issue in Africa, and offers a proof-of-principle for this general approach.

Introduction

The central hypothesis underlying the concept of DOHaD is that exposures to various risks in utero and early childhood – often characterised as the first 1 000 days – are key drivers of adult health and disease, and such effects may include epigenetic transgenerational inheritance.² Many examples of this have been demonstrated in populations where long-term individual health data have been collected and curated, either in longitudinal birth cohorts or in register-based national information systems. For example, a review of intergenerational studies in Australia and New Zealand found 21 studies, using intergenerational linked data on 38 600 mothers, 14 206 partners and 38 390 babies.³ In countries with long-established national register systems, such as Sweden, individual data exist in a wide range of official registers that, subject to suitable ethical considerations, can be linked and analysed with public health hypotheses and DOHaD effects.⁴

- 2 Heindel, J.J. 2018. The developmental basis of disease: update on environmental exposures and animal models. *Basic and Clinical Pharmacology and Toxicology*, 125(Supplement 3), August: 5-13. [<https://doi.org/10.1111/bcpt.13118>].
- 3 Townsend, M.L., Riepsamen, A., Georgiou, C., Flood, V.M., Caputi, P., Wright, I.M., Davis, W.S., Jones, A., Larkin, T.A., Williamson, M.J. & Grenyer, B.F.S. 2016. Longitudinal Intergenerational Birth Cohort Designs: A Systematic Review of Australian and New Zealand Studies. *PLoS ONE*, 11(3), March:e0150491. [<https://doi.org/10.1371/journal.pone.0150491>].
- 4 Lindgren, U., Nilsson, K., De Luna, X. & Ivarsson, A. Data resource profile: Swedish microdata research from childhood into lifelong health and welfare (Umeå SIMSAM Lab). *International Journal of Epidemiology*, 45(4), May:dyv358. [<https://doi.org/10.1093/ije/dyv358>].

In Africa, however, the situation is very different in that hardly any longitudinal data covering individual lives for 50 or more years exist. An example of a small-scale exception would be the Medical Research Council in The Gambia's data collection at the beginning of 1950, with individual follow-up in the Keneba area.⁵ The collection of health data in Africa has been mostly survey-based, and even repeated large scale surveys like the United States-sponsored Demographic and Health Surveys programme, did not attempt to revisit the same individuals in subsequent survey rounds. Although demographic and health surveys have now covered more than 40 sub-Saharan countries in over 200 cross-sectional surveys, each of which typically involved thousands of households and tens of thousands of individuals, the lack of any individual longitudinal linkages makes these data not immediately amenable to analyses of DOHaD effects.⁶

Because of the lack of ideal data for analysing DOHaD effects in Africa, attention must be given to if and how available data can be used indirectly, possibly together with other information such as outputs from large-scale modelled estimates like those produced by the Global Burden of Disease programme – to derive estimates of the impact of DOHaD effects on contemporary and future health in Africa.⁷

Conceptually characterising DOHaD and its effects

In principle, DOHaD links early-life exposures to later-life outcomes. This section sets out the concepts that might be assessed further in the African context.

An overall concept of measuring DOHaD effects

Since DOHaD is an over-arching mechanism, rather than a disease entity, there has to be consideration of wide ranges of risk exposures and disease outcomes at different stages of life, partially determined by each other, not necessarily in unique 1:1 mapping. No disease entity in adult life is likely to be uniquely caused by a specific developmental exposure, but a fraction of many disease entities could be attributable to particular earlier exposures. An overall understanding of DOHaD effects would, therefore, need to be based on estimating the attributable population

5 Rayco-Solon, P., Moore, S.E., Fulford, A.J. & Prentice, A.M. 2004. Fifty-year mortality trends in three rural African villages. *Tropical Medicine & International Health*, 9(11), January:1151-1160. [<https://bit.ly/32wZDny>].

6 Croft, T.N., Marshall, A.M.J. & Allen, C.K. 2018. Guide to DHS Statistics. *DHS-7: The Demographic and Health Surveys Program*. Rockville, Maryland, USA: ICF International. [<https://bit.ly/3hcPlyp>].

7 Blakely, T. 2018. Major strides in forecasting future health. *The Lancet*, 392, November:e14-e15. [[https://doi.org/10.1016/S0140-6736\(18\)31861-0](https://doi.org/10.1016/S0140-6736(18)31861-0)].

fractions of specific exposure-disease dyads, and then summing over all such dyads to arrive at mortality or morbidity effects attributable to DOHaD.

Figure 3.1 shows a conceptual framework for DOHaD in which the inner circle represents life stages from one generation to the next, and the marginal notes represent various examples of risk exposures, ameliorating strategies and disease outcomes. These examples are by no means exhaustive but serve as illustrations of some of the exposure-disease dyads that might need to be considered in an overall assessment of DOHaD effects.

Figure 3.1 Conceptual framework for DOHaD effects with indicative examples.⁸

- 8 Norris, S.A., Daar, A., Balasubramanian, D., Byass, P., Kimani-Murage, A., Macnab, A., Pauw, C., Singhal, A., Yajnik, C., Akazili, J., Levitt, N., Maatoug, J., Mkhwanazi, N., Moore, S.A., Nyirenda, M., Pulliam, J.R.C., Rochat, T., Said-Mohamed, R., Seedat, S., Sobngwi, E., Tomlinson, M., Toska, E. & Van Schalkwyk, C. 2017. Understanding and acting on the developmental origins of health and disease in Africa would improve health across generations. *Global Health Action*, 10(1):1334985. [<https://doi.org/10.1080/16549716.2017.1334985>].

Characterising specific DOHaD exposure-disease dyads

Before considering exposure-disease dyads at the population level, each such dyad needs to be characterised in terms of what the specific exposure is; what the specific disease outcome is; and what the relative risk to an individual of the specific disease outcome is. Having established that very little is known in Africa about the specifics of DOHaD effects, there are not, in general, going to be specific data on these individual relative risks in African populations. Thus a first major assumption has to be made to proceed – that at the individual level, relative risks of DOHaD exposures as evidenced from other settings are likely to be similar for individual Africans. Making this assumption – even if it is not universally true – will allow the use of the substantial DOHaD literature from settings where more extensive data are available and have been analysed, as the basis for characterising exposure-disease dyads.

Quantifying specific exposures in African populations

A wide range of exposures may be of interest in the DOHaD context, and will generally be time-bound, both in terms of chronological time and age. Examples could include proportions of maternal alcohol consumption during pregnancy; abnormal birth weight; non-fatal birth asphyxia; and lack of breastfeeding. Some data may be available from population surveys, such as demographic and health surveys material, that cover a large proportion of Africa in a reasonably systematic way over recent decades.⁹ Age and sex-specific population proportions subject to particular exposures over a range of chronological time are needed, preferably on a country-by-country basis.

Quantifying specific disease outcomes in African populations

Disease outcomes of interest will largely fall into two categories:

- ☐ deaths in later life from particular causes, or
- ☐ long-term diseases in adult life that reduce healthy life expectancy.

In some cases, specific diseases may cause both losses of healthy years as well as leading to death. Primary data from Africa on cause-specific mortality and reductions in healthy life due to specific diseases are not generally available, but extensive outputs from modelled estimates are produced, for example by the Global Burden of Disease programme, that are also projected into the future.¹⁰

⁹ Blakely, 2018.

¹⁰ Ibid.

Attributing proportions of specific disease outcomes to specific exposures

The combination of retrospective survey data relating to exposures and future projections of disease outcomes create possibilities of relating exposures at a young age to outcomes at older ages. Re-using outputs from modelled estimates is methodologically somewhat risky in that the underlying assumptions of the models are not always explicit. If important assumptions were linking early life exposures to later life outcomes embedded in the estimates, methodological problems could arise in the re-analysis. However, outcomes of interest in the DOHaD context are not likely to be solely, or even mostly, driven by specific early-life exposures, and so this risk is probably not great.

A proof-of-principle example of attributing a DOHaD effect to African populations

As proof-of-principle for the concepts on assessing the effects of DOHaD exposures set out above a specific exposure-disease dyad example is presented here as an illustration. Starting from well-established relationships characterising the protective effects of breastfeeding on childhood and adolescent obesity, we will estimate the proportion of childhood obesity attributable to a lack of breastfeeding for each country in sub-Saharan Africa, over time. A meta-analysis from Harder, Bergmass, Kallischnigg and Plagemann suggests that six months of breastfeeding is associated with at least a 20 % reduction in the risk of childhood obesity.¹¹ Although that finding was not specifically linked to Africa, for this purpose, it will be assumed to be generally applicable.

Data sources

Estimates of the proportion of newborns being breastfed for at least six months, and of obesity levels during childhood and adolescence, are needed for each country in sub-Saharan Africa. Both the World Bank and the United Nations Children's Fund publish point estimates of six-month breastfeeding proportions, though the regularity of observations is patchy, depending on surveys being undertaken.¹²

- 11 Harder, T., Bergmass, R., Kallischnigg, G. & Plagemann, A. 2005. Duration of breastfeeding and risk of overweight: a meta-analysis. *American Journal of Epidemiology*, 162(5), October:397-403. [<https://doi.org/10.1093/aje/kwi222>].
- 12 The World Bank Group. 2019. Exclusive breastfeeding (% of children under 6 months). *UNICEF, State of the World's Children, Childinfo, and Demographic and Health Surveys*. [<https://data.worldbank.org/indicator/SH.STA.BFED.ZS>]; United Nations Children's Fund (UNICEF). 2018. Infant and Young Child Feeding: Exclusive breastfeeding,

Together they provide 267 country-year points for 48 countries in sub-Saharan Africa between 1985 and 2015. The Global Burden of Disease programme has created modelled estimates of obesity rates by country, year and age for the same period.¹³

Data management

For the six-months breastfeeding data, only available for country-years in which an appropriate survey was carried out, a line was fitted through the points for each country to generate a full set of country-year proportions (P_{BF6}) from 1980 to 2015. A lower limit of 0.05 of births having six-months breastfeeding was imposed as a constraint where extrapolations fell below that level. Proportions of births not having six-months breastfeeding ($P_{!BF6}$) were calculated as $1 - P_{BF6}$. Figure 3.2 shows a scatter plot of $P_{!BF6}$ estimates for 48 sub-Saharan countries from 1980 to 2015. Considerable variation exists between countries in terms of level and rate of change over time in these estimates.

Predominant breastfeeding. *UNICEF Data: Monitoring the situation of children and women*. [<https://data.unicef.org/topic/nutrition/infant-and-young-child-feeding/>].

- 13 Institute for Health Metrics and Evaluation. 2015. Obesity and Overweight Prevalence 1980-2015. *Global Burden of Disease Study 2015*. [<http://ghdx.healthdata.org/record/global-burden-disease-study-2015-gbd-2015-obesity-and-overweight-prevalence-1980-2015>].

Figure 3.2 Scatter plot of the estimated proportion of children not breastfed for the first six months, for 48 sub-Saharan countries from 1980 to 2015.

From the Global Burden of Disease estimates, proportions with obesity P_{OBS} and number with obesity N_{OBS} were available for each country-year by sex and age-group (two-four years, five-nine years, 10-14 years, 15-19 years). These estimates are shown for 48 sub-Saharan countries and four age groups from 1980 to 2015 in Figure 3.3.

Figure 3.3 Scatter plot of the estimated proportion of children with obesity for 48 countries from 1980 to 2015.

Population in each group was calculated as N_{OBS}/P_{OBS} . Since the breastfeeding data were not available by sex, P_{OBS} and population for each country-year from 1980 to 2015 were put into a single file not disaggregated by sex.

Linking breastfeeding and childhood obesity data

The breastfeeding and childhood obesity data were merged into a single file covering 48 countries and 459 unique combinations of obesity-year and breastfeeding-year, ranging from P_{BF6} in 1980 with P_{OBS} estimated in 1982 (thus contributing to the two-four years age group) to P_{BF6} in 2013 with P_{OBS} estimated in 2015.

Attributing the effect of missed breastfeeding on the number of obese children

For each of the 22 032 records linking country, obesity-year and breastfeeding-year, the attributable population proportion can be calculated in the standard way, based on the original assumption that six-month breastfeeding leads to a 20 % reduction in childhood obesity. Thus the relative risk of obesity in the absence of six-month breastfeeding $RR_{OBS} = 1/(1-0.2) = 1.25$, and so the population proportion of obesity

attributable to not breastfeeding could be calculated for each country/obesity-year/breastfeeding-year as

$$AF_{P_!BF6} = (P_{!BF6} \cdot x (RR_{OBS} - 1) / (1 + (P_{!BF6} \cdot x (RR_{OBS} - 1)))$$

and hence the number of children with obesity attributable to non-breast feeding could be calculated as

$$N_{OBS_!BF6} = N_{OBS} \cdot x AF_{P_!BF6}$$

Summarising the data over country, time and age-group

It is relatively straightforward to analyse those numbers for sub-Saharan Africa as a whole and specific countries and periods, having done the basic calculation of the number of child-years with obesity attributable to a lack of breastfeeding. The 22 032 records in 3.4 above were collapsed into 5 376 records representing 112 possible obesity-year by age-group combinations for each of the 48 countries. Figure 3.4 shows the % child-years with obesity for each country, by decade, together with the proportion attributable to a lack of breastfeeding.

Figure 3.4 Percentage of child-years with obesity by decade for each country, with proportion attributable to lack of six-month breastfeeding.

Overall findings

The overall analysis covered 10.3 billion child-years over 48 countries during 1980-2015 (3.1 % characterised as obese; 16.1 % of obesity attributed to a lack of breastfeeding). There were considerable differences between countries, with Burundi showing the lowest proportion of obesity (0.97 %) and Equatorial Guinea the highest (10.6 %). Rwanda had the lowest proportion of obesity attributable to a lack of breastfeeding (3.6 %) and Djibouti the highest (19.1 %).

Conclusion

The proof-of-principle example shown above demonstrates the potential of bringing together such data as may be available to estimate the effects of specific exposure-disease dyads in Africa. In this case, the onset of available data for the exposure – lack of six-month breastfeeding – across Africa and a separate dataset on the disease – childhood obesity – were successfully combined to arrive at estimates of the proportion of overall child obesity that could be attributed to the lack of breastfeeding. All estimates, including the source material for breastfeeding and obesity, have to be understood in the context of the assumptions made and methods used.

In principle, a similar process could be followed for other DOHaD exposure-disease dyads, assuming that relevant data sources could be located, and thus arrive at some estimates of the total later-life burden of early life exposures. This process would be a much more complicated task than the relatively simple example for one dyad presented here.