

DOHaD in low- and middle-income countries: a systematic review exploring gaps in DOHaD population studies

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Review

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Abstract

Low- and middle-income countries (LMICs) are disproportionately affected by non-communicable diseases (NCDs), accounting for more than 80% of NCD-related deaths globally. Research into early-life influences on these diseases via the developmental origins of health and disease (DOHaD) paradigm has informed health promotion interventions and policies focused on optimising early-life health. However, little is known about where this research occurs and whether it reaches and reflects the countries most affected by NCDs. This review searched for DOHaD studies that investigated relationships between factors during pregnancy and at birth, with later-life NCD incidence, risk and related mortality. The aim of this review was to identify where DOHaD research has been conducted and whether this focus is appropriate and relevant, given the differential burden of NCDs. Embase, MEDLINE and Scopus were searched, and eligibility screening processes identified 136 final articles. This review found that 49.7% of DOHaD research was conducted on populations within Western Europe, 15.9% in East Asia, 12.7% in North America, 8.3% in Latin America and the Caribbean, and fewer in Australasia, South Asia, the Middle East, the Africas, and Central Asia. When categorised by income, this review found that 76.4% of studies were based in high-income countries, 19.1% in upper-middle-income and 4.5% in lower-middle-income countries. No studies were based in low-income countries. There is therefore a marked disconnect between where DOHaD research is undertaken and where the greatest NCD disease burden exists. Increasing DOHaD research capacity in LMICs is crucial to informing local strategies that can contribute to reducing the incidence of NCDs.

Introduction

Non-communicable diseases (NCDs) are the leading cause of mortality worldwide and are responsible for approximately 41 million deaths each year.¹ Low- and middle-income countries (LMICs) are disproportionately affected by this burden, accounting for 80% of all NCD deaths and over 85% of premature NCD deaths globally.¹ These patterns are predicted to increase over the next 10 years, with a 17% rise in NCD-related mortality overall and a 27% increase in the African region.² While most premature NCD deaths are preventable, LMICs face many barriers in combatting this rise in disease prevalence, including limited access to resources, inadequate infrastructure and a lack of local health research, interventions and policies.³ The World Health Organization has also acknowledged regional patterns of disease burden, identifying that South-East Asia and the Western Pacific regions will have the greatest absolute number of NCD-related deaths over the next few years.⁴ In addition, Pacific Island countries are impacted by increasing rates of risk factors and comprise the top 10 countries in the world with the highest rates of overweight/obesity among adults.⁵ While NCDs and related risk factors are global issues affecting all populations, there are clear, disproportionate burdens experienced in LMICs.

Research examining factors underlying the global NCD burden has included exploration of the impacts of the early-life environment on later metabolic health.^{6,7} This paradigm, named the developmental origins of health and disease (DOHaD), asserts that adverse environmental exposures in the early-life stages, such as during infancy, pregnancy and even before conception, can influence later-life disease risk.⁸ For example, a lack of balanced maternal nutrition during pregnancy, often resulting in low birth weight in offspring, has been associated with an increased risk of developing obesity and NCDs later in life, including type 2 diabetes and heart disease.^{9,10} There is also growing evidence for an intergenerational influence on NCD risk via the maternal or paternal lineage^{10,11} thus perpetuating a cycle of disease across generations. Knowledge that has arisen out of DOHaD research has led to the development of interventions, such as health promotion strategies during pregnancy and school-based health literacy programmes, which target the early-life and adolescent life stages in order to promote healthier outcomes in the future.^{12–15} Early-life nutrition and DOHaD-based research thus plays an important role in contributing to strategies that reduce risks associated with the development

of NCDs later in life. However, to maximise effective dissemination of the knowledge gained, research must be sufficiently focused on populations with the greatest NCD burden in order to break the cycle and influence positive health outcomes.

Across all disciplines, there is an underrepresentation of research occurring in LMICs. One study retrospectively surveyed publications in five high impact health journals over 1 year, classifying articles into four regions: United Kingdom, United States of America, other Euro-American countries (including Europe, Canada, Australia and New Zealand) and the 'rest of the world'.¹⁶ This study found that despite being comprised of 90% of the world's population, the average research contribution from the 'rest of the world' category was only 6.5%.¹⁶ Research barriers identified included limited resources, lack of training and support, and difficulties getting accepted for publication.¹⁶ Despite these challenges, Patel and Sumathipala (2001, p. 406) recognised the urgent need for research 'to reflect the diverse realities of health systems and cultural factors if research is to inform local health policy and practice'.¹⁷

Given the potential of the DOHaD paradigm to promote early-life health to reduce risks related to NCD development, it is crucial that this research is inclusive of countries with high NCD burdens, such as LMICs. The present systematic review searches for published DOHaD research investigating associations between factors during pregnancy and at birth, such as nutrition and birth size, and later-life NCD incidence, risk factors and related mortality. The aim of this review is to identify where these DOHaD investigations take place and whether, given the burden of NCDs, this breadth of current research is appropriate and relevant.

Methods

This systematic review followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement and used the participants, intervention/exposure, comparison, outcome, study design (PICOS) structure to identify eligible studies.^{18,19}

Eligibility criteria

Observational studies that explored relationships between early-life factors, either during pregnancy and or at birth, with later NCD risk, incidence or related mortality, were sought for this review. Table 1 outlines the inclusion and exclusion criteria, including information on participants, exposure, outcome of interest and study design. Published journal articles from 1980 to 23 May 2018 (date of search) were eligible to be considered. Articles that were experiments, reviews, commentaries or based on animal subjects were excluded.

Data sources and search strategy

The systematic search covered publications up until 23 May 2018 across three electronic databases: MEDLINE, Embase (both accessed via Ovid) and Scopus. Each search was comprised of three main groups of keywords: the early-life exposure, the later-life outcome and the stage of life. The early-life exposure keywords included DOHaD, developmental origins of health and disease, FOAD, fetal origins of health and disease, birth factor, early life, maternal diet and maternal nutrition. The later-life outcome keywords included noncommunicable disease, NCD, obesity, overweight, cardiovascular disease, CVD, diabetes, health outcome and later life. The stage of life keywords included offspring, neonate, infant, child, adolescent and adult. The Boolean operator

Table 1. Inclusion and exclusion criteria via PICOS for the selection of studies

Criteria	Inclusion criteria	Exclusion criteria
Participants	Pregnant women (at any gestation stage) and newborns	Animal subjects, pre-pregnancy factors in women
Intervention/Exposure	Maternal factors during pregnancy: <ul style="list-style-type: none"> • Diet/nutritional factors • Body size • Weight gain • Hypertension, diabetes Birth factors, for example, birth size, weight	Other environmental exposures during pregnancy, for example, supplementation, smoking, trauma
Comparison	Not applicable	Not applicable
Outcome of interest	Outcomes in offspring aged ≥ 2 years old <ul style="list-style-type: none"> • NCDs, for example, diabetes, cardiovascular disease, cancers • NCD risk factors, for example, obesity • NCD-related mortality 	Respiratory diseases, mental disorders and communicable diseases
Study design	Observational studies with human subjects	Experimental studies, systematic reviews, editorials, commentaries and animal studies

'AND' was used between each of the three groups, 'OR' within groups and 'NOT' to exclude common DOHaD animal models, such as rodents and sheep. Limits applied to each search ensured the inclusion of only journal articles written in the English language and published from 1980 onwards.

Study selection

Database results were exported to Endnote X8 reference management software, and both internal and external duplicates were removed. Titles and abstracts were independently screened based on the eligibility criteria by S.T, M.H.V and J.L.B. Any studies that could not have eligibility fully confirmed during this stage were held for full-text review. The remaining articles were independently assessed for full-text eligibility by S.T, J.L.B and M.H.V, reaching 85% agreement. All conflicts were discussed and a consensus was reached. No further information was requested from authors and articles were excluded if the full text was inaccessible.

Data extraction and risk of bias assessment

Data were extracted from each article regarding the study setting (variable of interest), early-life exposure, later-life outcome, age of participants and main study findings. Although a comprehensive search across databases was conducted, publication bias was a potential limitation, and thus, an effort was made to retrieve full texts from beyond the database, such as through university library networks. The quality of each study was assessed using the Newcastle-Ottawa star scale and adapted versions, which allowed the evaluation of cohort, case-control and cross-sectional studies.^{20,21} The assessment scale awards stars for factors under three main criteria: selection of study groups, comparability of groups and assessment of the outcomes.^{20,21} The maximum number of stars that could be achieved was eight or nine, depending on the study type.

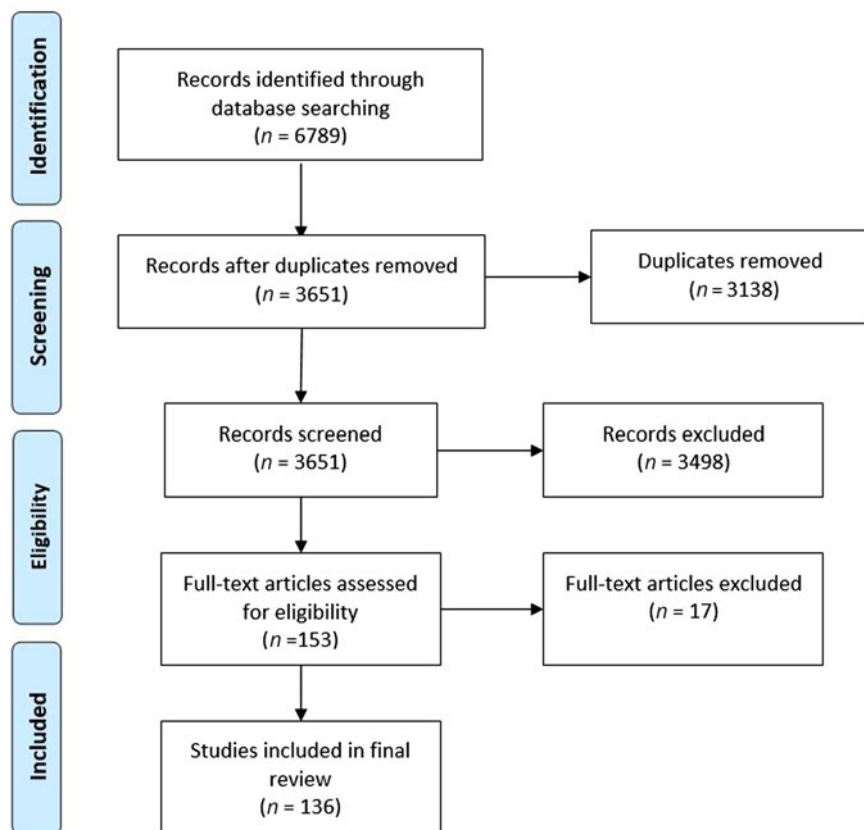


Fig. 1. PRISMA flow diagram for the selection of studies.

Analysis

The countries where DOHaD investigations took place were the primary outcome of interest for this review. A total response method, commonly used in New Zealand ethnicity categorisation, was used to ensure that each different country identified within a particular study's data set was given a single count.²² Although this meant that some studies were counted more than once if they were based on cross-country data sets, it allowed a representative overview of all the locations where DOHaD research occurred and ensured that no countries were missed. The total response method was also applied to explore age groups and country income classifications.

Results

Study selection

Fig. 1 outlines a flow diagram for the process of selecting studies. Based on the search criteria, a total of 6789 records were identified through the three databases. Internal and external duplicates ($n = 3138$) were removed via the Endnote software. Remaining records were screened for eligibility by title and abstract using the PICOS criteria outlined in Table 1, which resulted in the exclusion of 3498 records. Full-text articles were then assessed for the remaining records, with a final number of 136 studies included in this review (Supplementary Table S1).

Study characteristics

Table 2 outlines the main characteristics of the final 136 studies included in this review. It shows that DOHaD-related publications are steadily increasing over time, with the majority published in the

last 5 years. Most studies in this review had sample sizes greater than 1000. The smallest study had a sample size of $n = 31$, while the biggest study included data from 2,133,504 people. To be eligible for this review, studies had to have explored NCD-related outcomes in participants at least 2 years of age. A total response method was used to categorise each study's population into different age groups: children 2–9 years, adolescents 10–19 years and adults >19 years. Studies were allocated a single count for each group that included their study population's age range. Table 2 shows that a higher proportion of DOHaD studies included data on children, followed by adults and then adolescents.

Location of DOHaD studies

This review found a total of 41 different countries across the final 136 articles, with a frequency of 157 countries studied. The highest frequency of DOHaD investigations occurred in the United Kingdom ($n = 22$), followed by China ($n = 17$), the United States ($n = 16$) and the Netherlands ($n = 14$). The 157 country frequencies were then categorised by region, as shown in Table 3. This review found that 49.7% of DOHaD investigations exploring relationships between the early-life environment and later-life NCDs were based on populations within Western Europe. And 15.9% included data from East Asia, 12.7% in North America, 8.3% in Latin America and the Caribbean, 5.1% in Australasia, 3.2% in South Asia, 1.9% in both the Middle East and the Africas, and 1.3% in Central Asia. Fig. 2 presents a map of this information, highlighting the regions with the most DOHaD research using darker green shades and regions with fewer investigations in lighter green shades. The countries in grey indicate countries where no DOHaD research was found.

Table 2. Characteristics of the final studies included in the review

Study characteristics		Number of studies	%
Year of publication	2013–May 2018	73	53.7
	2007–2012	34	25
	2001–2006	18	13.2
	1995–2000	11	8.1
	<1995	0	0
Sample size	0–250	12	8.8
	251–500	17	12.5
	501–1000	31	22.8
	1001–2000	25	18.4
	>2000	51	37.5
Age group	Children (2–9 years)	65	37.1
	Adolescents (10–19 years)	50	28.6
	Adults (>19 years)	60	34.3

Table 3. Distribution of countries and regions where DOHaD investigations have taken place

Regional grouping	Frequency of countries	%	Countries with DOHaD investigations
Western Europe	78	49.7	United Kingdom, the Netherlands, Finland, Sweden, Germany, Spain, France, Italy, Norway, Belgium, Denmark, Poland, Cyprus, Greece, Hungary, Ireland and Portugal
East Asia	25	15.9	China, Singapore, Hong Kong, Japan, Philippines and South Korea
North America	20	12.7	United States and Canada
Latin America & the Caribbean	13	8.3	Brazil, Chile, Guatemala, Jamaica and Mexico
Australasia	8	5.1	Australia and New Zealand
South Asia	5	3.2	India and Bangladesh
Middle East	3	1.9	Israel and Iran
Africas	3	1.9	Nigeria, South Africa and Seychelles
Central Asia	2	1.3	Estonia and Russian Federation
TOTAL	157	100	

Income classification of countries with DOHaD research

To identify the proportion of studies that included countries across each income bracket, the World Bank classifications based on gross national income (GNI) per capita were used.²³ High-income economies were defined as having a GNI per capita of \$12,376 or more, upper-middle-income economies were those between \$3996 and \$12,374, lower-middle-income between \$1026 and \$3995 and low-income economies as \$1025 or less.²³ Table 4 shows that out of the 157 frequencies of countries studied, 76.4% were high-income countries, 19.1% were upper-middle-income and

Table 4. Classification of countries by income

World Bank income classification	n	%
High income	120	76.4
Upper middle income	30	19.1
Lower middle income	7	4.5
Low income	0	0

4.5% were lower-middle-income countries. This review found no DOHaD research, relating early-life factors during pregnancy and at birth to later NCD development, in low-income countries.

Discussion

This systematic review aimed to identify where DOHaD research was conducted and whether, given the burden of NCDs in LMICs, this breadth of current research was appropriate. The findings showed that the majority of DOHaD research has been based on populations within Western Europe. This contrasts with the regions experiencing the greatest burdens of NCDs, as identified previously, South-East Asia, Africa and the Western Pacific.⁴ This review found that only 19.1% of DOHaD research occurred across the East Asia and South Asia regions, 5.1% in Australasia and only 1.9% across Africa. Additionally, given that much of the NCD burden in the Western Pacific region occurs in Pacific Island countries, it is concerning that no DOHaD research has been conducted in these nations. This imbalance between the regions that produce the most research versus the regions with the greatest need has been previously identified in the literature.^{16,24–26} A study by Rahman and Fukui explored a global profile of biomedical research and found that North America, Australia and Europe overwhelmingly had the highest number of publications per million population per year, with other regions falling far behind.²⁴ Patel and Sumathipala corroborated this idea in their study, finding that only 6% of psychiatry literature was published from regions outside Euro-American countries.¹⁷ This gap needs to be addressed as data should not be directly transferred from Western countries to inform on interventions in other nations without local data, as research needs to account for contextual factors, differences in population and availability of resources. DOHaD research must be prioritised in settings with high disease burdens if evidence is to inform effective interventions and policies.

Similar imbalances were found in this review regarding income level, with a high proportion of DOHaD research found in high-income countries (76.4%) and no studies based in low-income countries despite 80% of global NCD-related deaths occurring in LMICs.¹ This disconnect has been identified across many disciplines, including a study on publications within general psychiatry journals.²⁷ They found that from 2002 to 2004, only 3.7% of published psychiatry research originated from LMICs, and acceptance of submissions from these countries was significantly lower than high-income countries.²⁷ Increased research in a setting creates a greater evidence base from which public health strategies, policies and improvements in clinical practice can result. The lack of DOHaD research in LMICs, as found in this study, may limit the development of local interventions and thus the potential to reduce the NCD burden. Guindon and colleagues explored the use of research-based evidence in clinical practice within LMIC

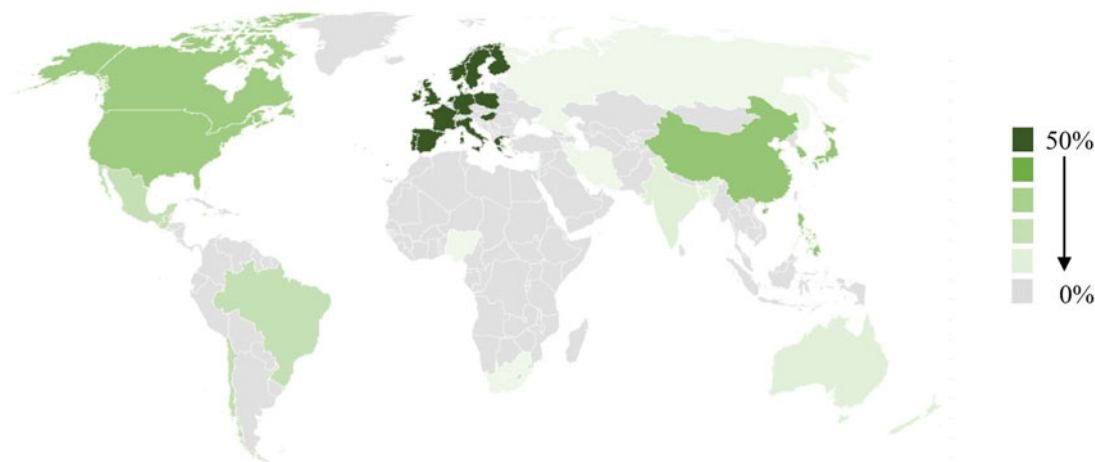


Fig. 2. Location of DOHaD studies by region.

health care providers.²⁸ They found that 84.6% of respondents were likely to change clinical practice if the research was performed in their own country, 66.4% if the research was performed somewhere in the region and only 55.8% if the research was performed in a high-income country.²⁸ These findings indicate that research conducted and published locally are more likely to influence changes in practice and interventions. There must be an increase in research in LMICs that considers contextual factors, to ensure the uptake and success of health interventions.

The DOHaD paradigm is centred on the influence of environmental exposures on later health; therefore, research must acknowledge the heterogeneity of environments. Upstream environmental drivers of place-based health inequities, such as historical factors and broader ecosystems, have been identified in the literature as ecological justice issues that need to be addressed.²⁹ This review identified that DOHaD research shows a clear preference to Western European settings, and thus, the potential for exploring heterogeneity of environmental contexts and upstream factors is limited. The lack of DOHaD research found in Pacific Island countries, for example, is concerning due to their unique environmental context and resulting health challenges. Past histories of colonisation and globalisation have influenced a rapid nutrition transition from traditional diets based on seafood and crops, to a predominance of imported, processed foods high in fat and sugar.^{30,31} Thus, the high proportion of research in Western European settings and lack of focus on LMICs found in this review demonstrates that current DOHaD research does not adequately address the breadth of environmental challenges faced across the globe. From a social justice standpoint, DOHaD research within LMIC settings must be prioritised as these populations contend with challenging environments influenced by broader upstream and historical factors.

There are many challenges to conducting and publishing important research from LMICs. While research from Western societies is often deemed worthy in its own right, some authors have discussed the tendencies of high-impact journals to only consider research from other countries if the findings indicate something unusual to that setting.¹⁷ Difficulties can also arise with sample size issues and perceived rigour of data from non-Western countries.³² Many reviews of academic journals have found that papers from LMICs are less likely to be submitted, and, when they are, these papers are more likely to be rejected.^{17,27} Such challenges need to be more widely recognised and addressed if there is to

be increased DOHaD research in LMICs and regions with a high NCD burden. In order to encourage more DOHaD research and build capabilities within LMICs, there is great potential in bringing together collaborators from multiple LMIC settings. The Consortium of Health-Orientated Research in Transitioning Societies group is an existing example which brings together researchers and data from DOHaD cohort studies based in five LMICs: Brazil, Guatemala, India, the Philippines and South Africa.³³ This collaboration has enabled data to be pooled to enhance statistical power, further exploration into contextual factors common amongst LMIC environments, and has contributed to the development of DOHaD research within these settings.³³ Encouragement by institutions and funders to engage in similar international collaborations in other high needs areas, such as the Pacific, would be highly beneficial to develop research capacity, capabilities and, in the future, positive outcomes for these communities.

Academic journals have an obligation in ensuring research from LMICs is prioritised and promoted because, as Sumathipala, Siribaddana, and Patel (2004) outline, 'their international success brings responsibilities to the global community they serve and profit from'.^{16,34} Considerations could be given to implementing systems that support this notion, such as fee waivers for open access and further developing and mentoring of authors from LMICs.³⁵ Governments, funders and universities in high-income countries also have a key role in encouraging the development of collaborations with researchers and leaders in LMICs, in order to strengthen capabilities and ensure that solutions are locally led.³⁵ In addition to promoting exposure of LMIC research in international journals, it also important to consider where this research could be published to have the greatest potential for community impact, for example, publishing locally in regional and national journals. This would also require institutions and universities to shift their preferences for researchers to publish within high-impact journals, to also considering where research might be best placed for relevancy and influencing practice. Improving research capacity in LMICs is crucial, not only for improving global health burdens and achieving publication equity, but also for advancing medical science.¹⁶

Strengths and limitations

While this review allowed exploration into global research gaps, a limitation was that this potentially masks research within countries

that address high needs populations, for example, indigenous communities in high-income nations. Future research and reviews could explore this further and identify whether gaps exist in regard to the proportion of research conducted on vulnerable communities within countries. Another limitation of this review was the absence of supplementary search methods, such as backward citation searching. Previous systematic reviews have explored the usefulness of checking reference lists and found the evidence to be weak, identifying that in many cases it may not be the best use of time and resources.^{36,37} Although this means it is possible some eligible studies have been missed from this review, the large number of articles included in the final analysis likely provide a reasonable representation of the literature. The main strength of this study was the broad nature of the systematic search, and although preconceptional health and paternal influences were not included, the search still allowed a comprehensive overview of where DOHaD research occurs globally. This approach also enabled the inclusion of studies that may fit the DOHaD paradigm, but that do not explicitly identify with it.

Conclusion

The DOHaD paradigm identifies relationships between adverse early-life environmental influences and later-life NCD risk, emphasising the importance of a healthy start to life to optimise future health. However, it is not a 'one size fits all' and therefore it is crucial that LMICs and regions with high NCD burdens, such as South-East Asia, Africa and the Pacific, have local DOHaD research that can inform policy and practice. At present, the wealth of DOHaD research taking place does not correspond to where the NCD burden exists. Strengthening health research capacity in LMICs is critical for increasing local research, influencing evidence-based interventions and thus contributing to reducing the global burden of disease.

Supplementary material. To view supplementary material for this article, please visit <https://doi.org/10.1017/S2040174420000276>

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Conflicts of Interest. None.

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