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Pre-gestational overweight and polyunsaturated fatty acids in human milk: theoretical causality model

Yasmin Notarbartolo di Villarosa do Amaral (https://orcid.org/0000-0001-8159-0564)
Daniele Marano (https://orcid.org/0000-0001-6985-941X) [1]
Mariza Miranda Theme Filha (https://orcid.org/0000-0002-7075-9819) [2]
Maria Elisabeth Lopes Moreira (https://orcid.org/0000-0002-2034-0294) [1]

Abstract *A number of studies have focused on the evaluation of the relationship between pre-pregnancy overweight and polyunsaturated fatty acids content in human milk. However, given the complexity of potentially confounding risk factors, the use of graphical tools is recommended to identify possible biases. This article aims to propose a theoretical model of causality using the directed acyclic graph between pre-pregnancy overweight and polyunsaturated fatty acids content in human milk. Methods: An extensive literature review was performed to identify variables with causal relationships with exposure and/or outcome. The choice of variables for adjustment followed the graphic algorithm that comprises six criteria for selecting a minimum set of potentially confounding variables. Socioeconomic conditions, interpartum interval, maternal age and food consumption pattern were the variables that would have to be adjusted in order to estimate the total effect of pre-pregnancy overweight on polyunsaturated fatty acids content in human milk. The minimum set of variables found in the present study can be used in the analysis of other studies that evaluate this association.*

Key words *Body weight changes, Fatty acids, omega-3, Fatty acids, omega-6, Directed acyclic graph*

[1] Instituto Nacional de Saúde da Mulher, da Criança e do Adolescente Fernandes Figueira Fundação Oswaldo Cruz. Av. Rui Barbosa 716, Flamengo. 22250-020 Rio de Janeiro RJ Brasil. yasminamaral@hotmail.com
[2] Escola Nacional de Saúde Pública Sergio Arouca, Fundação Oswaldo Cruz. Rio de Janeiro RJ Brasil.

Introduction

The high prevalence of deviations in pre-gestational nutritional status (overweight and obesity) have been the focus of several studies due to their determining role in negative outcomes both for the fetus (bleeding, macrosomia, asphyxia) and for the woman (gestational diabetes mellitus, gestational hypertensive syndromes, greater postpartum weight retention)[1].

In addition to the negative effects mentioned, studies reveal that overweight is considered a determinant in the nutritional composition of human milk; overweight increases human milk lipid content and changes the profile of polyunsaturated fatty acids and the balance between omega-6 and omega-3[2-5].

However, a recent systematic review on the topic revealed inconsistent results regarding this association. The authors highlighted limitations in the methods for identifying potential confounding or mediating factors, which would jeopardize the establishment of causal relationships between these two variables[6]. Failure to identify confounding factors can threaten the findings validity; on the other hand inappropriately identifying other variables as being confounding factors, can also affect estimates.

Investigations into the causal effects in health observational studies, the use of Directed Acyclic Graphs (DAG) has stood out as the most appropriate approach for identifying confounding variables, selection bias (colliders) and mediators. It is a visual and qualitative tool for selecting adjustment variables in multiple models, identified from a theoretical causality model. A fundamental characteristic of the DAG is that it is based on an *a priori* knowledge and not on study data, explaining the role of each variable in the relationship between exposure and outcome[7].

DAGs are non-parametric diagrammatic representations of the data generation process in a specific context. They provide a flexible framework for exploring the multidimensional determinants and complex causal mechanisms that support hypothesized relationships between variables[8], identifying those that need to be controlled to obtain an unbiased effect estimate[9]. However, causality studies involving human milk composition using DAG are still scarce in the literature and this can be partially explained by the lack of knowledge and limited practical guidance available on the use of this tool.

In order to collaborate with studies on the relationship between pre-gestational overweight and the omega-6/omega-3 ratio in breast milk, a DAG was proposed based on a review of the literature on the subject; the set of the minimum number of adjustment variables to be used in multiple models to estimate the causal effects between these two variables was identified.

Methods

The DAG consists of three main elements: nodes or vertices that represent variables; edges or arrows that represent the relationships between variables and also, the absence of arrows that indicates a strong assumption that there is no direct causal effect[10,11]. Predecessor variables are called parents and their descendants are called daughters. Between these variables there are direct paths - arrow pointing from the first to the second vertex and indirect paths - those that are intercepted by variables called mediators[12].

There are three possible structures (chain, fork and inverted fork) representing, respectively, causation, confounding and collision. A variable on a path where two arrowheads meet (inverted fork) is called a collider and no intervention should be performed (variables should not be considered in the analysis). On the other hand, when we are faced with a fork structure (confounding) it will be necessary to condition for the common cause[9].

The paths in a DAG can go through the front door, which may or may not be causal, or through the back door, which are not causal and can convey spurious associations[10]. Front-door paths are those in which arrows lead from the exposure to the outcome, while back-door paths are defined as a path from the exposure to the outcome that begins with an arrow pointing to the exposure[13]. A path between two variables is said to be blocked if all paths through the back door are closed. On the other hand, a path between two variables is said to be unblocked when there is at least one path open between them through the back door, which leads to a spurious statistical association, not a causal one. This may be caused by a common cause or by intervention by the investigator by unnecessarily adjusting a collider or descendant of the collider and opening a path through the previously closed back door[10].

The process of choosing variables for adjustment followed the graphical algorithm[14] and comprised six criteria until the selection of a minimum set of potentially confounding variables[15].

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The criteria are described as follows: (1) covariates chosen to reduce bias must not be downstream of the exposure; (2) exclusion of all variables: (a) non-ancestors of the exposure, (b) non-ancestors of the outcome, and (c) non-ancestors of the covariates that were selected for the model to reduce bias; (3) deletion of all lines starting from the exposition; (4) connection, through dotted lines, of two parents who share a common child (variable); (5) removal of all arrowheads; (6) deletion of all lines between the covariates in the model (selected variables) and any other covariates.

The causal diagram was created using the DAGitty program (in the public domain, available at www.dagitty.net) developed to create, edit and analyze causal models[16,17]. DAGitty follows the strict DAG rules to identify the minimum sufficient fit for the given DAG. First, all covariates directly caused by exposure are detected. Then closed cycles are detected on the graph. If a closed loop is found, the program will stop (such a graph violates a necessary assumption of causal diagrams). If the graph is acyclic, the backtracking algorithm identifies all backdoor paths and then identifies those that are blocked and unblocked. The adjustment set for potentially confounding variables is derived such that all backdoor paths are blocked. The sufficient adjustment set with the smallest number of covariates is called the minimum set of potentially confounding variables[14].

To construct our study's DAG, a broad bibliographical survey was carried out, which resulted in a systematic review in 2020[6], in order to establish the causal relationship between pre-gestational overweight (exposure) and the omega6/omega3 ratio in human milk (outcome) and possible covariates.

From this bibliographical survey, variables that predicted exposure were detected, such as: **pattern of food consumption** (intake of large amounts of ultra-processed foods categorized as No and Yes); **pregnant woman's age** (categorized as over 35 or under 35); **education** (categorized as primary education, secondary education or higher education); **income** (continuous variable); **parity** (categorized in terms of number of children greater than or equal to 3); **physical activity** (categorized as No and Yes); **menarche** (continuous variable); **marital status** (categorized as single, married, separated/divorced or widowed); **use of contraceptives** (categorized as No and Yes); **skin color or race** (self-reported and categorized as white, brown, black, yellow or indigenous); **genetics** (genetic factors have an impact on overweight categorized as No and Yes); **weight gain greater than recommended in other pregnancies** (categorized as adequate, insufficient, excessive based on the pre-gestational body mass index) as well as outcome predictor variables: **maternal nutritional status** (categorized as low weight, adequate weight, overweight or obesity); **age of the pregnant woman** (categorized as over 35 or under 35); **education** (categorized as primary education, secondary education or higher education); **income** (continuous variable); **parity** (categorized number of children greater than or equal to 3); **gestational age at birth** (categorized as greater or lesser than 37 weeks); **mothers with current or previous asthma/asthmatic or inhalant allergies** (categorized as No and Yes); **regionality** (categorized into coastal regions No and Yes); **food consumption pattern** (intake of large amounts of ultra-processed foods categorized as No and Yes); **maternal blood stocks** (continuous variable); **supplementation of omega 3 sources** (categorized as No and Yes); mother height (continuous variable); **lactation period** (categorized as colostrum, transition or mature); **ALEX classification** (categorized as small for gestational age – SGA, suitable for gestational age – AGA large for gestational age); **gestational nutritional status** (categorized as adequate, insufficient, excessive based on pre-gestational body mass index) (Table 1).

The predictor variables for both exposure and outcome are described in Table 2.

Results

Twenty-two covariates formed four possible causal paths (Figure 1). After applying the DAG rules, a minimum set of five potential confounders was identified to be used in the adjustment of the causal relationship between pre-pregnancy overweight and the omega6/omega3 ratio in breast milk including interpartum interval, socioeconomic conditions (income and education), age, food consumption pattern and parity. These variables met the back door criteria, blocking all open paths between exposure and outcome (Figure 2).

Discussion

Causal diagrams have been increasingly used as a unified technique for dealing with a range of is-

Table 1. Predictive variables of exposure (pre-gestational excess weight) and outcome (omega 6/omega 3 ratio in human milk), 2021.

Factors that impact exposure		Factors that impact the outcome	
Food Consumption Pattern	↑ Consumption of Ultra-Processed Foods ↑ Overweight	Maternal nutritional status	↑ BMI ↑ w6
Age of the pregnant woman	Age > 35 years ↑ Overweight	Age of the pregnant woman	↑ age ↑ w6
Socioeconomic conditions *Education* *Income*	↑ Education ↑ Overweight Classes C, D and E ↑ Overweight	Socioeconomic conditions *Education* *Income*	↑ education ↑ w3 ↑ income ↑ w3
Parity	Having more than three children and/or shorter intrapartum intervals ↑ Overweight	Parity	↑ number of children ↑ w3
Physical activity	↓ Physical activity ↑ Overweight	Gestational age at birth	Breast milk in mothers of premature babies ↑ w3
Menarche	Menarche <12 years ↑ Overweight	Mothers with current or previous asthma/asthmatic or inhalant allergies	Mothers with current or previous asthma/asthmatic or inhalant allergies ↓ w3
Marital status	Woman in common law m. ↑ Overweight	Regionality	Coastal regions ↑ w3
Use of contraceptives	Use of contraceptives ↑ Overweight	Food Consumption Pattern	↑ w3 font consumption ↑ w3
Skin color or race	Black color or race ↑ Overweight	Maternal stock (blood)	↑ stock ↑ w3
Genetic	Certain genetic factors impact the ↑ Overweight	W3 source supplementation	↑ supplementation ↑ w3
Weight gain > recommended in other pregnancies	Weight gain > recommended in other pregnancies impacts the ↑ Overweight	Maternal height	Maternal height - 1% increase in w3 per 1 cm
		Lactation period	Mature milk ↑ w3
		ALEX Classification	Breast milk in mothers of babies born SGA ↑ w3
		Pregnancy nutritional status	↑ BMI ↑ w6

w3 – omega 3; w6 – omega 6; SGA – Small for gestational age; IMC – Body mass index

Source: Authors.

sues in epidemiological research[18]. These graphical models have provided new formalizations for some important epidemiological concepts, such as the notion of confounding[9] and selection bias[19,20], allowing researchers to use relatively simple and systematic graphical criteria to identify a set of confounding variables that need to be adjusted[9].

The use of the criteria proposed by Pearl[14] in the construction of this DAG allowed the identification of the causal and non-causal structures of the relationship between pre-gestational overweight and the omega6/omega3 ratio in breast milk. The variables socioeconomic conditions (education and income), interpartum interval, maternal age and food consumption pattern were selected as the minimum adjustment set to estimate the total effect of pre-pregnancy overweight on the omega6/omega3 ratio in human milk. Lower education and income, reduced interpartum interval, maternal age greater than or equal to 35 years, food consumption pattern high in ultra-processed foods and parity (number of children greater than or equal to 3) are risk factors described in the literature that can cause both the exposure and the outcome studied and,

Table 2. Predictive variables of both exposure (pre-gestational overweight) and outcome (ratio of omega 6 to omega 3 in human milk), 2021.

Factors that impact exposure and outcome	
Age of the pregnant woman	↑ age ↑ w6
	Age > 30 years ↑ Overweight
Socioeconomic conditions	↑ Education ↑ w3
Education	↑ Education ↑ Overweight
Income	
	↑ Income ↑ w3
	Classes C, D and E ↑ Overweight
Parity	↑ number of children ↓ w3
	Having more than two children ↑ Overweight
Interpartum interval	Shorter interpartum interval ↑ Overweight ↓ w3
	Shorter interpartum interval ↑ Overweight
Food consumption pattern	↑ Ultra-processed ↑ Overweight
	↑ w3 source consumption ↑ w3

w3 – omega 3; w6 – omega 6

Source: Authors.

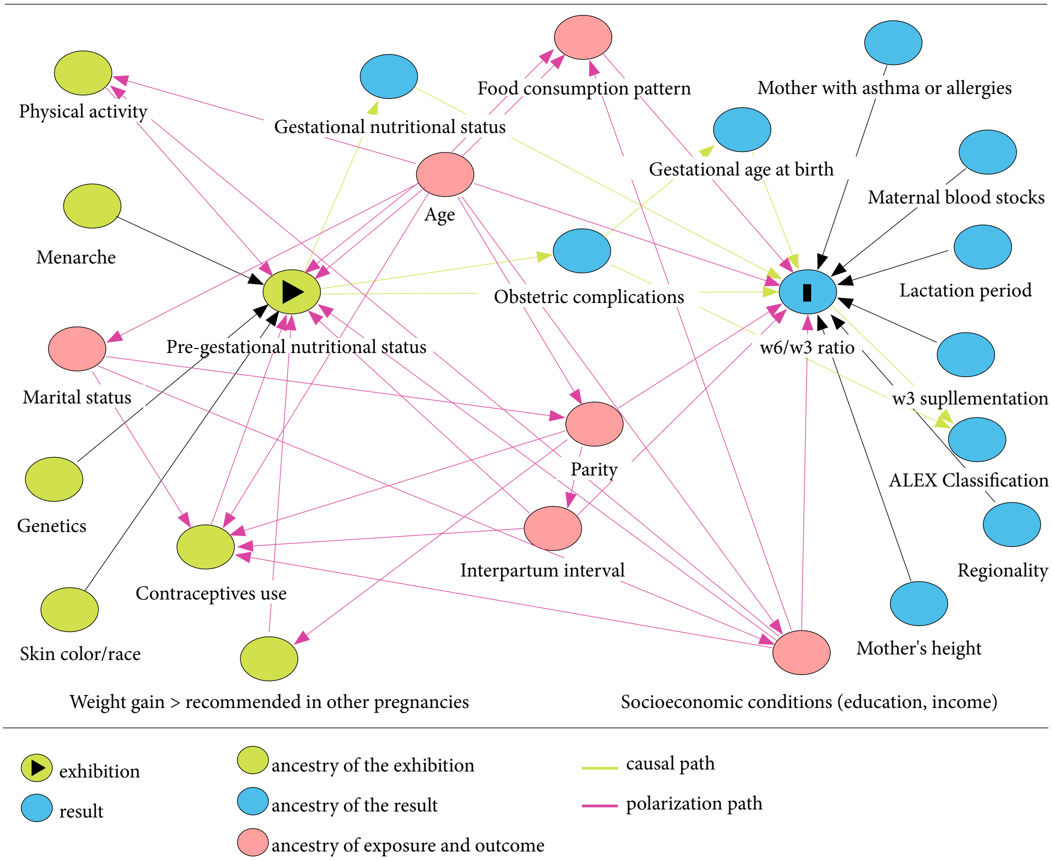

Figure 1. Causal diagram between pre-pregnancy overweight and omega 6 /omega 3 ratio.

Note: Pre-pregnancy nutritional status = exposure variable; omega6/omega 3 ratio = outcome variable; green node = exposure ancestor; blue node = result ancestor; red node = ancestor of exposure and outcome (confounding variables).

Directed Acyclic Graphics (DAG) Code (Chart1).

Source: Authors.

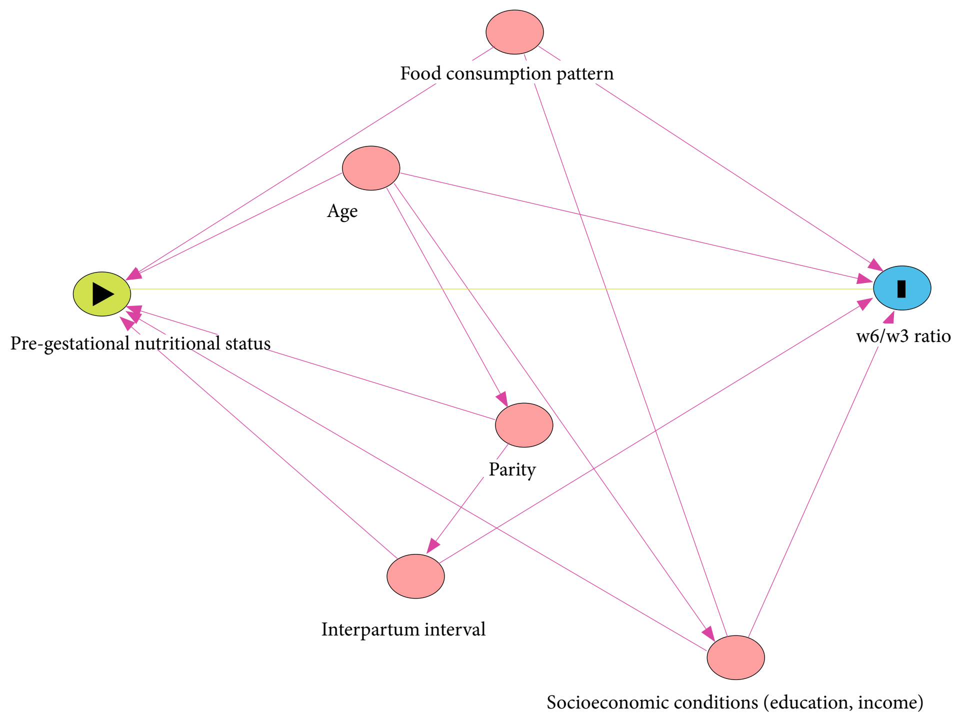

Figure 2. Minimum set of potential confounders to be used in adjusting the causal relationship between pre-pregnancy overweight and omega 3/omega 6 ratio in breast milk.

Source: Authors.

therefore, confuse the investigation of interest[6].

If we chose multiple analysis methods, such as Mantel-Haenszel estimators, logistic regression or modified Cox regression to assess the causal relationship between pre-pregnancy overweight and the omega6/omega3 ratio, several confounding factors, such as weight gain, gestational weight, gestational age at birth, regionality (place of residence), maternal blood stocks, mother's height, lactation period and ALEX classification would be controlled and could underestimate or overestimate the relationship between exposure and outcome. For example, weight gain above the recommended level[21] is an intermediate variable (mediator) in the causal relationship between pre-gestational overweight and the omega6/omega3 ratio in human milk. If conditioning or adjustment were carried out using this variable, the results would be biased, since part of the total causal effect of the relationship of interest would not be considered. Therefore, this DAG identified the variables that actually need to be controlled to obtain an unbiased effect estimate.

Although causal diagrams have been increasingly used in epidemiological research applied to health, a recent systematic review of observational studies that used the DAG highlighted some problems, such as the lack of explanation of the DAG construction, the relationships between variables, and the inclusion of variables not measured. It is important to note that the DAG, when graphically representing causal relationships, must not be limited to the variables measured in the study, but should include all relevant variables of the theoretical causality model that underlies this relationship[7]. Therefore, constructing a DAG is a challenging exercise, given that the causal structure between an exposure and outcome is the essential step when we wish to know whether the inclusion of a covariate can reduce or increase bias in the effect estimate[12].

As previously stated, DAG are used to describe three possible sources of statistical association between two variables: cause and effect, confounding and selection bias. Confounding occurs when the association between exposure

Chart 1. Directed acyclic graphic code (DAG)-Dagitty

```
dag {
bb="0,0,1,1"
"Physical Activity" [pos="0.080,0.083"]
"ALEX Classification" [pos="0.897,0.606"]
"Socioeconomic conditions (education, income)" [pos="0.736,0.905"]
"Skin color/race" [pos="0.070,0.848"]
"Gestational nutritional status" [pos="0.362,0.101"]
"Pre-gestational nutritional status" [exposure, pos="0.273,0.400"]
"Mother's height" [pos="0.844,0.836"]
"Maternal blood  stocks" [pos="0.907,0.206"]
"Weight gain > recommended in other pregnancies" [pos="0.251,0.917"]
"Gestational age at birth" [pos="0.684,0.170"]
"Interpartum interval" [pos="0.512,0.731"]
"Mother with asthma or allergies" [pos="0.822,0.051"]
"Food consumption pattern" [pos="0.539,0.044"]
"w6/w3 ratio" [outcome, pos="0.744,0.400"]
"Marital Status" [pos="0.076,0.483"]
"W3 Supplementation" [pos="0.888,0.487"]
"Contraceptives use" [pos="0.193,0.758"]
"Obstetric complications" [pos=""0.539,0.345"]
"Genetics" [pos="0.055,0.665"]
"Lactation period" [pos="0.903,0.335"]
Age [pos="0.412,0.234"]
Menarche [pos="0.090,0.281"]
Parity [pos="0.549,0.587"]
Regionality [pos="0.929,0.725"]
"Physical Activity" -> "Pre-gestational nutritional status"
"ALEX Classification" -> "w6/w3 ratio"
"Socioeconomic conditions (education, income)" -> "Physical Activity"
"Socioeconomic conditions (education, income)" -> "Pre-gestational nutritional status"
"Socioeconomic conditions (education, income)" -> "Food consumption pattern"
"Socioeconomic conditions (education, income)" -> "w6/w3 ratio"
"Socioeconomic conditions (education, income)" -> "Contraceptives use"
"Skin color/race" -> "Pre-gestational nutritional status"
"Gestational nutritional status" -> "w6/w3 ratio"
"Pre-gestational nutritional status" -> "Gestational  nutritional status"
"Pre-gestational nutritional status" -> "w6/w3 ratio"
"Pre-gestational nutritional status" -> "Obstetric complications"
"Mother's height" -> "w6/w3 ratio"
"Maternal blood stocks" -> "w6/w3 ratio"
"Weight gain > recommended in other pregnancies" -> "Pre-gestational nutritional status"
"Gestational age at birth" -> ""w6/w3 ratio"
"Interpartum  interval" -> "Pre-gestational nutritional status"
"Interpartum interval" -> "w6/w3 ratio"
"Interpartum interval" -> "Contraceptives use"
"Mother with asthma or allergies" -> "w6/w3 ratio"
"Food consumption pattern" -> "Pre-gestational nutritional status"
"Food consumption pattern" -> ""w6/w3 ratio"
"Marital Status" -> "Socioeconomic conditions (education, income)"
"Marital Status" -> "Contraceptives use"
"Marital Status" -> Parity
"W3 Supplementation" -> "w6/w3 ratio"
"Contraceptives use" -> "Pre-gestational nutritional status"
"Obstetric complications" -> "ALEX Classification"
"Obstetric complications" -> "Gestational age at birth"
"Genetics" -> "Pre-gestational nutritional status"
"Lactation period" -> "w6/w3 ratio"
Age -> "Physical Activity"
Age -> "Socioeconomic conditions (education, income)"
Age -> "Pre-gestational nutritional status"
Age -> "Food consumption pattern"
Age -> "w6/w3 ratio"
Age -> "Marital Status"
Age -> "Contraceptives use"
Age -> Parity
Menarche-> "Pre-gestational nutritional status"
Parity -> "Pre- gestational nutritional status"
Parity -> "Weight gain > recommended in other pregnancies"
Parity -> "Interpartum interval"
Parity -> "w6/w3 ratio"
Parity -> "Contraceptives use"
Regionality -> "w6/w3 ratio"
}
```

Source: Authors.

and disease includes a non-causal component attributable to a common uncontrolled variable. Selection bias materializes when the association between exposure and disease includes a non-causal component determined by the levels of a common effect of exposure and disease. In both cases, the exposed and unexposed in the study are not comparable or interchangeable, which is the ultimate source of bias. Therefore, statistical criteria are insufficient to characterize confusion or selection bias[22]. The use of statistical resources alone can lead to errors, since different types of variables, such as mediators or colliders, can behave as confounding variables that, according to the traditional definition, must be associated with both the exposure and the outcome and not be a step intermediary in the investigation of interest[12].

The results found in this causal model emphasize that this minimum set has an important impact on the causal relationship between exposure and outcome. However, it is important to highlight that studies involving causal relationships with human milk are complex and challenging, as milk ought to be understood as a dynamic system susceptible to the influence of individual and maternal biological factors, and environmental and external factors, which are difficult to control in their completeness and the DAG is not capable of evaluating the quality of the information collected, and limitations may persist in the measures used to adjust differences[12].

Among the strengths of this proposal is the extensive research into the most up-to-date literature on predictors of exposure, outcome and both, and the interrelationship between these variables, allowing a clear graphical approach to the variables that should be collected in empirical research for the appropriate confounding adjustment. Despite all the challenges of causal research, this DAG proposal can be an important step for studies that intend to estimate the causal effect of gestational weight gain on the Omega6/Omega3 ratio in breast milk in observational studies.

Final considerations

Estimating causal effects is one of the main objectives of applied health research. Therefore, the use of causal diagrams that contain rigorous epidemiological concepts is a way of using observational data for causal inference in a safer way.

The DAG proposed in the present study resulted in the minimum adjustment set composed of the variables including socioeconomic conditions (education and income), interpartum interval, maternal age and food consumption pattern to estimate the total effect of pre-pregnancy overweight on the omega-6/omega-3 ratio in human milk.

It is worth highlighting that the findings of this causal diagram are extremely important so that it can be used in other studies to evaluate the causal relationship between pre-gestational overweight and the omega6/omega3 ratio in human milk.

Collaborations

All authors made substantial contributions to the conception and design of the study, acquisition, review and interpretation of data and preparation of the manuscript. All authors approved the final manuscript version to be presented.

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