Health effect of nutrition development policies: The case of wheat flour fortification in South America[1]

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Abstract Developing countries implement food fortification policies to combat the effects of poverty and the health effects of inadequate micronutrient intake. With this objective, different strategies have been proposed, mandatory food fortification being widely used in South America due to its simplicity of application, supervision and cost effectiveness. A particular case is fortification with folates due to its effect on congenital malformations (closure of the neural tube or heart disease) among children under 1 year of age. The previous literature for this region evaluates these effects with comparative studies before - after from medical records. This paper explores the effect of these laws in South America through differences-in-differences for 1997-2015. It is estimated that the mortality rate among children under 1 year of age is reduced by between 15% and 25%. Furthermore, when economic, educational and health level controls are included, it turns out that a change between 33 and 44% can be explained. The estimated values are stable at various compositions of the data panel and tests of exogeneity of the treatment, because the origin of the effect is in the temporal comparison between cases that apply early and those that do it late.

Key words: Health, Nutritional Policies, Development

JEL: I12; I18

1 Introduction

A common issue in developing countries is the negative effect of poverty associated with inadequate food intake with respect to those levels that allow full development in health and cognitive terms. Thus, under-height, birth weight, obesity, etc. are expressions that have been incorporated into public, national and global policies. To eradicate the negative effects of poverty, governments implement nutrition policies (FAO (1996), Ravallion (1992), Drèze and Sen (1989) ONU (2015)), which tend to include the common idea that approximately one third of the population suffers from micronutrient deficiencies (Allen et al. (2006)). In developed countries there is also concern about the effects of the inadequate quality of nutritional intake, but in this case with greater emphasis on health problems.

For this reason, all over the world, food strengthening programs are implemented so that the population acquires the micronutrients considered adequate. These policies can have a greater impact when they are generalized to the entire population, without distinguishing by socioeconomic conditions, as is the case with the fortification of foods for mass consumption. A clear example is the fortification of flours with iron and folates to improve anemia levels and reduce congenital malformations in children. While iron has effects on maternal health and the development of children; folates have a direct impact in relation to mortality due to malformations in children under one year of age and their individual and social consequences of surgical interventions and/or rehabilitation in less severe cases.

Malformations lead to pregnancy loss, early death, or disability. It is estimated that some 300,000 children die each year from this cause (WHO (2016)) and some 16,700 children under one year of age die in 2015 in South America, according to the author's estimates based on PAHO data. In addition, the burden of disease from congenital diseases is 6% among neonates and post-neonates and 2.5% among children between 1 and 4 years old. In the global ranking of causes of death, it ranks 23rd in terms of quantity but, as most deaths occur in the first years of life, when the burden for years lost is computed, it rises to 17th place (Lozano et al. (2012), Murray (2012)).

If nutritional fortification policies have the expected effects, they could contribute to the reduction of infant mortality, a central objective of public policies both in traditional terms and because of their centrality in the global processes of seeking development (Goal 3 of the SDGs) ONU (2015)). This rate is in a global process of convergence towards the levels of developed countries, around 6%, so it is essential to identify policies that favor and accelerate this process. In this context, it is important to note that DALY's (disability-adjusted life years) associated with congenital malformations have decreased by 44.8% between 1990 and 2010, with the decrease in the burden of disease from the two main causes of this group: tube defects neural and heart disease (Murray (2012)).

There are several strategies that can be adopted to include folate intake in the first three months of pregnancy, the only time when it can help to prevent malformations. One possibility is the weekly consumption of supplements, which requires a medical care system developed with great complexity and the ability to plan and predict pregnancies with precision (WHO (2018a)). Another alternative is the fortification of flour, which is usually considered a success as an instrument of public policy since it achieves great effectiveness at a very low cost (Običan et al. (2010)), at the same time that it allows to solve the organizational problems typical of developing countries and the inability to achieve improvements in the voluntary intake of folic acid as a supplement (Pachón (2015), Botto et al. (2006)).

Despite this positive outlook on this type of policy, from the perspective of world nutrition policy, there are still spaces to expand it, either because there are still gaps between the consumption and fortification of foods that provide the necessary micronutrients (Keats (2019)) and the number of countries that have not yet adopted micronutrient policies. By 2008, 52 countries have adopted flour fortification (Centers for Disease Control and Prevention (2008)) while by 2018 there are 71 countries that fortify flour in a context where twice as many cases are implementing other types of programs such as iodine in salt or nutrition training (World Health Assembly (2019)).

The central objective of folate fortification is to contribute to the reduction of malformations associated with neural tube closure, with an estimated 4% reduction in the prevalence of neural tube defects (Blencowe et al. (2010)). However, there is evidence (Modell et al. (2016)), which is not definitive, that they also improve other malformations such as heart disease (Shaw et al. (1995), Botto et al. (1996), Blencowe et al. (2018b), Leirgul et al. (2015), Liu et al. (2016)). In addition, the effects are not only in children but also in mothers since the fortification of flour has a positive effect on anemia, one of the main causes of maternal mortality (Sanghvi, Harvey, and Wainwright (2010)), in addition to reducing the premature mortality, preeclampsia, intrauterine growth restrictions, etc. (Običan et al. (2010)).

It is important to note that despite this optimistic view on the effect of fortification on malformations, the expected effects are small since it is estimated that the proportion of malformations that cannot be explained is 65% (Rojas and Walker (2012), Običan et al. (2010)), which is evidenced by the fact that even when a correct ingestion occurs, they do not disappear (Običan et al. (2010)). This fact suggests that there are factors such as genetics or other types of co-morbidities, such as diabetes, that could be at work. There are several studies for developed or developing countries that show a step-like decline in the incidence rate of live birth defects. In the case of the United States, the effect is estimated in a reduction of about 1,000 live births per year (Williams et al. (2015), Centers for Disease Control and Prevention (2004)). For South America, the evidence is mixed. On the one hand, López Camelo (2010), based on medical records, reports the presence of a positive effect for Chile and Argentina but not for Brazil. When this analysis is extended to analyze the types of malformations, they conclude that fortification with folates would have improved only the condition of mortality from neural tube defects. Using a similar methodology, Sanabria Rojas et al. (2013) found similar results for Peru. For Argentina, Calvo and Biglieri (2010) found that there is better absorption of folates and a reduction in mortality from neural tube defects, although there appears to be a downward trend prior to the enactment of the law.

A weakness of all these studies is that they are usually retrospective based on clinical records of live births for a single geographical area, so they cannot carry out controls on issues such as genetic predisposition, context of the health system, access to healthy foods, etc. In this way, the traditional weaknesses of before versus after studies include the lack of control elements when trying to compare results between areas. Just as an example, it is necessary controls that allow understanding what happens in cases where the effect of fortification is not observed due to weaknesses in implementation or the action of other factors affecting only one country, such as Zika in Brazil (WHO (2016)). In this sense, the application of quasiexpermental methods to this problem can be considered novel although it is not for the study of the determinants of infant mortality. It is applied in various studies such as Alderman et al. (2009) for growth monitoring policies; Galiani, Gertler, and Schargrodsky (2005) or Anttila-Hughes et al. (2018) for the link to water availability; Kotsadam et al. (2018) to analyze the effect of international aid and; Keats (2018) or Breierova and Duflo (2004) for the effect of education.

This work aims to carry out an evaluation of the impact size of mandatory flour fortification on congenital malformations. In particular, the case of the laws implemented in South America and their effect on mortality due to malformations among children under 1 year of age will be evaluated. For this, data by country from the Pan American Health Organization for the period 1997-2015 (circa) will be used. With this data structure, we seek to identify with differences-in-differences techniques what is the size of this effect and its sensitivity to the various forms of application, both in content of the fortification and in the implementation. The target population is children under 1 year of age, who report the highest levels of mortality due to malformations, so the "effect" sought to identify in this work is only on the most severe case of them: those that they carry mortality. A potential weakness of this study is the long-term negative effects of excess folates, such as cancer (Johansson et al. (2008)) or neurological changes in old age (Miller et al. (2009)), which cannot yet be identified by the short time since implementation. Also, controls are included that attempt to distinguish how much genetic and environmental factors contribute, and how much remains to be identified.

It is concluded that the implementation of the mandatory fortification of flour has a positive and significant effect on the reduction in the mortality rate, even though in certain cases the *a priori* analysis would not show an effect, but it does not seem to have a significant effect on the amount of flour cases. This result arises from the use of quasi-experimental methods of differences-in-differences, a novel application in the literature of the quantification of the effects of the application of these norms, which is usually based on before - after studies based on medical records. The estimated values of the impact coefficient are notoriously stable at different compositions of the data panel and tests of exogeneity of the treatment, because the origin of the effect occurs in the temporal comparison between the cases that apply the law early and those that do so late. It is estimated that the implementation of the law reduces the mortality rate among children under 1 year of age by between 15 and 25%. Furthermore, when economic and educational factors and anemia levels are included, it turns out that between 33 and 44% of the variability of the results can be explained. Other factors such as access to water, exposure to pollutants or conditions of poverty or inequality, considered relevant in the literature, were not significant. Finally, it is emphasized that there is some evidence in the literature on a higher prevalence of these pathologies in the Hispanic population, a hypothesis that could not be evaluated here. Given the stability of the coefficient of change, achieving additional progress in reducing mortality due to malformations could require reformulations in the effective micronutrient content in the flours, provided that there are no improvements in other dimensions that contribute to this objective. One hypothesis that remains open in this document is whether this stability is not associated with changes in nutritional preferences, beyond those captured by the improvement in the average income level, against the consumption of flour, which would weaken the transmission channel of this policy.

The rest of the document is organized as follows. The next section characterizes the malformations from two perspectives. One, regarding the factors with which the presence of malformations is usually associated and; the other, on what has been its quantitative evolution in population terms. In the following section, the nutritional policies developed to combat these pathologies are analyzed and, especially, the application of the flour strengthening law in South America is discussed. The section 4 presents the estimation methodology and the results obtained. The last section, Conclusions, makes a broad reading of the document, which ends with the usual References sections and the appendix of Tables and Figures.

2 Congenital malformations

This section does not intend to carry out a detailed analysis of the origin and causes of congenital malformations, there is even an important part of their origin that still remains unknown, but rather to provide a framework to be able to understand and evaluate the possibilities and limitations of the methodology of proposed evaluation and the quantitative results it produces in the section 4.

Folates are mainly found in vegetables, legumes and some fruits, but their effective intake is usually reduced by the cooking process: between 50 and 80% are destroyed by it. Brito et al. (2012) present the biochemical details of them and the characteristics of the metabolization process. Insufficient intake of micronutrients, specifically folates, is usually associated with a series of congenital anomalies. These are not the only causes as there are also genetic and environmental issues that operate in the period of conception and/or pregnancy (IOM (2003), De-Regil et al. (2015), Običan et al. (2010)). These malformations, details of which can be seen in Botto et al. (1999), are structural or functional and can be detected during pregnancy, at birth or the rest of his life (WHO (2016), Murray and Lopez (1997)).

One of the most studied effects in relation to folate is the closure of the neural tube, the severity of which ranges from complete non-closure (craniorachischisis) through anancephaly to spina bifida. Neural tube defects can be diagnosed prenatally by ultrasonography, screening techniques such as maternal serum alpha-fetoprotein examination in the second trimester of pregnancy and alpha-fetoprotein measurements in amniotic fluid using amniocentesis performed for other indications (López-Camelo et al. (2010)). These effects can be significantly prevented through daily folate intake during conception and the first trimester of pregnancy. This fact is what reinforces the policy of universal and permanent intake of fortified foods. The effects of them can be both immediate, such as abortions, prenatal or child deaths, but also have long-term effects with lasting disabilities and a strong negative impact on individuals, families, and health care systems (Blencowe et al. (2018b), WHO (2016), Assembly (2010)).

For South America this situation is especially relevant because there is some evidence that in the population of Hispanic origin the incidence is higher while it seems that non-Hispanic African Americans have the lowest incidence, with the difference between them being about 2 to 3 points. This difference is due to the food basket and how they metabolize FA (Centers for Disease Control and Prevention (2004)). But also, given the region's development shortcomings, the fact that there is extensive literature that begins with Mosley and Chen (2003) on the need to include socioeconomic determinants to understand children's health processes is relevant (Hill (2003). By case, Pridmore and Carr-Hill (2011) reviews 58 evaluations of nutritional programs carried out between 2000 and 2010 with the aim of drawing conclusions about the origins of malnutrition. They conclude that the causes are: lack of access to nutritious food, health services, water and sewers and poor health care practices for children.

2.1 Quantification

Various population health indicators are available to study the relevance of malformations in a population. On the one hand, the widely used retrospective incidence studies based on medical records[1], as López Camelo (2010). The disadvantage of this type of study is that it is difficult to identify and control for differences in socio-environmental factors.

Another possibility is to use the data on mortality and its causes available from health records of the national health systems, easily obtainable, with a known degree of homogeneity between countries but with more limited content since they reflect cases whose severity is such that they end in death. The advantage of this approach is that it is able to relate these indicators to macro variables that reflect the interaction of public policies with socio-environmental conditions. In addition, it can be adjusted by the disabilities that the pathologies generate, as in Murray (2012), but that richer approach, in the case of malformations, is limited by the amount of data and the period of time[2].

Congenital malformations cause 11.3% of neonatal deaths, about 303 thousand newborns (WHO (2016)). In 2015, children in South America lost a total of 11 million years of life with disabilities, to which malformations contributed 33.7%. If we order the countries by their contribution to malformations in relation to their population participation, the diagrams in Figure 1 show, for the year 2000 and 2015, three relatively stable groups: one, those that contribute less malformations with respect to of its population size such as Chile, Argentina and Venezuela; a second group contributes in the same proportion made up of Brazil, Colombia, Paraguay, Peru and Uruguay and finally, the group of those who participate more in the burden of malformations with respect to the population of children, Bolivia and Ecuador.

The participation of the main types of malformations for children aged 0 to 4 can be seen in Table 1 which exposes certain facts, already known in the literature, such as the preponderance of congenital heart disease that explains 43.2% of the total DALYs lost due to malformations, while neural tube defects explain only 7.2% of them. It is interesting to note that both have tended to reduce their participation since 2000 despite the fact that the total number of malformations increases with respect to the total loss. A somewhat different perspective can be obtained when analyzing how this participation is in relation to the total of DALYs, Figure 2, the participation of malformations by type is not related to global health levels (total of DALYs) but it does the total of congenital malformations. This result is important because it is often argued that the organization of the health system and the more or less healthy behavior of people could affect malformations, which although inconclusively, this figure would be disproving provided that DALYs are accepted as a synthetic indicator of these relationships.

If we wanted to evaluate the effects of fortification laws in the region on DALYs, it would be quite complicated since we could only have the specific situation in three years, which do not cover all countries (e.g., Chile). As an approximation, the changes between 2000 and 2010 could be analyzed, Table 1, for the countries that sanction the law in that period: in all cases, Argentina, Brazil, Peru and Uruguay, the importance of the charge due to the closure of the neural tube and congenital heart disease decreases (in the latter case, participation increases only in Argentina).

An alternative source is the mortality rate due to malformations that emerges from the population records of the National Statistical Systems and compiled by PAHO. Of these data, two facts are particularly relevant. The first refers to the incidence by age of deaths due to malformations. From the PAHO data search engine, a graph emerges with the age structure by

[1]In the last 10 years the implementation of specific malformation registries has expanded in South America `https://www.paho.org/hq/index.php?option=com_content&view=article&id=15352:birth-defects-registries-expanding-in-latin-america&Itemid=1926&lang=es`

[2]Details are shown later in this same section

malformations for each country, Figure 3, which reveals that indeed the problem of malformations in relation to mortality is concentrated in children under 1 year, eventually it is extended to the following age group of children under 4 years of age, and without substantial differences by gender. The second characteristic fact that emerges from these data is that not all countries have a reduction in deaths between 1997 and 2015 (circa), Figure 4, which happens only in Argentina, Chile, Peru and Uruguay. The remaining countries[3] increase with two modalities: a soft one, Brazil and Venezuela with an increase of 20% and the other intense, Colombia, Ecuador and Paraguay, with an increase of twice the base value.

3 Micronutrient policies: the case of folic acid in flours

The previous section reflects the relevance of malformations for the countries of South America. That is why certain terms and/or dimensions, such as short stature, birth weight or obesity, have been incorporated into national and global development policies. Although these situations are associated with conditions of poverty, they are not the only limitation since developed countries are also concerned about these issues but with another perspective related to the quality and timeliness of food intake.

In response, food strengthening programs have been implemented so that the population acquires the appropriate micronutrients (Shamah and Villalpando (2006))[4]. Allen et al. (2006) presents a complete review of the topics associated with micronutrients which include iron, vitamin A, iodine, zinc, folates, vitamin B, vitamin C, vitamin D, calcium, selenium and flour. The list is long because in general it is usually cost effective to incorporate these supplements into food compared to other strategies, such as supplementation.

A central situation in public health policy is the coverage of the necessary micronutrients during the pregnancy and delivery process, because the mother and the child are compromised; whether due to unanticipated abortions, maternal deaths or infant mortality, as well as the long-term effects of disabilities on children. A case that is usually considered successful is the incorporation of folates (FA) into food[5] which affect the embryo development process (Običan et al. (2010)). That is why the incorporation of reinforcements in the nutritional intake is recommended to compensate for the shortcomings.

A characteristic of folate in relation to malformations is that its intake, in order to achieve the objective of reducing them, must be at the beginning of pregnancy, the first 12 weeks. This circumstance generates various considerations. The first is that it can be a significant portion of women who do not know or intuit if they are pregnant. De-Regil et al. (2015) shows that the vitamin supplementation strategy has no effect to prevent malformations but does achieve some protective effect on subsequent pregnancies. This fact, added to the problem of adherence to voluntary intake (Blencowe et al. (2018b)), lead to the design of proposals that achieve coverage by "forcing" intake on the grounds of the magnitude of the effects of these pathologies on people and the health system. The difficulties of identifying the population with deficiencies (Development Initiatives (2018)) as the intake of supplements at the wrong time

[3] With the exception of Bolivia for which there is data only for a short period (1995-2003) and therefore it is not considered.

[4] In Darnton-Hill et al. (2009) you can see the evolution of food strengthening policies until late 90's.

[5] In Običan et al. (2010) you can see the process by which FA went from being a laboratory study in mice to a public policy implementation in several countries.

(Holguín-Hernández (2013)) demand from the health services strategies that require different administrative and medical care processes (Blencowe et al. (2018a)).

One proposal is to promote actions for the permanent consumption of vitamin supplements. The WHO proposes to cover folate deficiencies with the intake, every other week, of vitamin supplements (WHO (2018b)). While this strategy may be useful, in the face of the experience of non-adherence (Običan et al. (2010), Blencowe et al. (2018b)), governments since the mid-90s have promoted food fortification. In this sense, the United States in 1998 (Običan et al. (2010)) and Chile in 2000, are the initial cases of this policy, to the point of being cited in the foundations of laws of other countries. In the case of the United States, Williams et al. (2015) carried out a review of the results of 19 surveillance programs between 1995 and 2011 with the aim of revising the estimate of a reduction of 1,000 annual cases of Centers for Disease Control and Prevention (2004). They find a decrease of the order of 20% post fortification to remain at the new levels for 12 years.

There are several reasons why fortification is successful (Darnton-Hill et al. (2009)). First, low cost, fortifying flours is less expensive than supplementing nutrient intake (Allen et al. (2006)). Also, fortifying flours with a combination of iron, vitamin B, niacin and folic acid is less than 0.5% of the sale price. Second, the food industry tends to add elements for its preservation, they have the machinery and are used to quality controls. In addition, there are a few mills which provide supervision and monitoring of the implementation of the policies. Finally, globalization motivates to be competitive and this includes healthy food. Additionally, this process is stimulated when governments agree to prevent the entry of unfortified flour.

In this context, the question is about the evidence regarding the capacity of public policies to solve these micro nutrient deficiencies. The evidence on the effects of FA supplementation is not conclusive in terms of its ability to reduce prevalences. On the one hand, some studies find evidence of a positive effect of PA obligation (Atta et al. (2016), Williams et al. (2015), Zaganjor et al. (2016)) while voluntary supplementation or fortification would have little effect (De-Regil et al. (2015); Khoshnood et al. (2015)).

3.1 Laws of mandatory fortification of flours with folic acid in South America

Based on Chile's experience in 1999, the application of laws that force the fortification of flours for consumption by the entire population has expanded in South America. It would appear that these laws are successful in reducing the incidence of malformations in some countries but without achieving complete elimination or a sustained reduction path. This is due, in part, to the fact that not all malformations are affected by the consumption of FA and also because the amounts of the supplement may require an adjustment in the face of changes in consumption preferences that could lead to a reduction in the intake of flours. That is why this work will not only review the effect of applying the law but also the intensity of its application, but the changes in consumption channels are left for a later study.

López Camelo (2010) from the study of clinical records in 77 hospitals for 1982-2007 concludes that they have a significant effect for Chile and Argentina, while for Brazil no change is noted. When this analysis is extended to analyze the types of malformations, they conclude that fortification with folates would have improved only the condition of mortality from neural tube defects. For Argentina, Calvo and Biglieri (2010) evaluate folate intake from the National

Nutrition and Health Survey, from which they conclude that there is an improvement in folate intake after the application of Law 25630/2002 and concomitantly there is a significant reduction in mortality from neural tube closure defects as well as public hospital discharges. Also for Peru, Sanabria Rojas et al. (2013) reviewed 88,236 clinical records of newborns with the aim of evaluating the effects on neural tube malformations due to flour fortification. What is interesting about this study is that it shows a marked decrease in incidence after the application of the law, but in the four subsequent years the process stabilized at a new level of around 7 per 10,000 live births. In the analysis by type, it is observed that the great change in incidence, 63%, is in anencephaly, while for spina bifida the change is relatively small, 19%. This result is compared with the decrease in Chile from 17 to 10 per 10,000 live births and in Costa Rica from 9.7 to 6.3, in both cases after the flour fortification law and studies with similar methodologies.

In this context, it is interesting to know how is the application of the strengthening laws in the region. For the region, this decision is not minor since there is some evidence for the USA that Latinos have a greater tendency to this type of pathologies while the reverse is true for African Americans (Centers for Disease Control and Prevention (2004)). Table 4 shows, from left to right, for each country which is the standard with which the obligation to fortify wheat flours with FA is established, in which year it is sanctioned and from when it is in force; the following columns show two measures of intensity of the policy given by the specific amount to be incorporated per kg of flour according to the current standard and, based on a compilation of studies, the analysis of compliance with the median of samples[6]. In it you can see that between 1999 and 2006, 6 laws were enacted, all of which are currently in force. Although Bolivia and Colombia promulgated the norm in the mid-1990s, no evidence has been found on its effective implementation, not even as a case reference in other studies at the same time as studies have been found, such as Holguín-Hernández (2013), who analyze the intake of FA without mentioning the laws. The case of Venezuela is interesting because although it has a flour fortification law, it does not include FA, so it is explicitly the only country that does not include FA among micronutrients.

Two noteworthy situations arise from the last two columns of that table. The first is that the column "Content" reflects what policy makers estimate that the population will ingest given the consumption structure at the time of enactment of the law. But, if later events such as changes in food intake preferences arise either for taste or medical or technological reasons, these values should be adjusted, which does not happen. That analysis is beyond the scope of this document and remains for a future study. The second issue is that the degree of effective content, measured by the last column, varies over time but it has not been possible to construct a series of temporal values, rather it was only possible to obtain one per country, which implies that the results of the analysis with this variable are valid as long as it is accepted that these coefficients are representative of a certain permanent behavior over time.

Since their implementation at the beginning of this century, these standards have not been adjusted either to take account of changes in consumption or by auditing the actual content, or by fears of the adverse effects of excessive consumption. This is why analyzing the evolution of infant mortality due to malformations in the last 25 years would allow us to analyze some dimensions for which it might be necessary to review its parameters. For example, Argentina and Chile decrease the mortality rate after implementing the law but it was a previous trend (see Figure 4). As a general matter, it can be seen that there are three groups of countries: one, made up of Argentina, Chile and Uruguay, where the rate of malformations drops after

[6]These cases are always data from a single year.

the law; a second group, Brazil, Ecuador, Paraguay, in which said rate shows an increasing trend while a third group, Peru and Venezuela, do not seem to show a clear trend. It is also observed that in the group of those where there is a decrease, it culminates after a few years to remain stable. It should be noted that this analysis is also true when analyzing exclusively the number of deaths due to malformations (see Figure 4). In any case, the regional balance from a current perspective shows a stable trend in 2 out of 3 countries, while in the rest there is a growing trend.

Additionally, it is also relevant to know how the temporal dynamics of these effects has been in order to assess whether they generate a continuous downward trend or whether it is a change in level. It can be seen that it seems that in some countries, as the antecedents suggest, the implementation of the law causes a change in the trend in mortality from congenital causes, but that this is not fulfilled in all cases (see Figure 4). The second fact that can be corroborated is that after the implementation of the law the effect disappears, that is, it would seem that there is a step effect.

4 What is the effect of fortification of flours with folic acid on mortality from malformations?

The previous section discusses the enactment of mandatory flour folate fortification laws in South America. Their objective is to reduce congenital malformations in the closure of the neural tube and the heart. A common strategy for analyzing the effects of these laws is by the evolution of the incidence of these pathologies in medical records, as in López Camelo (2010) or Calvo and Biglieri (2010), which can make it difficult to control by other related determinants with aspects not included in said registries such as social determinants of health (Chen et al. (2017)). For example, López Camelo (2010) concludes that the law has had no effect in Brazil but without taking into account other effects such as the presence of Zika or other socio-environmental issues such as the quality of nutritional intake, access to health or drinking water, or the deficiency of environmental regulation on fertilizers. In general, it is difficult to understand why in some countries mortality from malformations is reduced after the law and in others it increases.

In this study, the methodology of differences-in-differences at the country level is applied, which allows considering these characteristics, not always observable, in relation to a particularly severe case of these malformations, that of those that culminates in death. In addition, the criterion is to study the group of children under one year of age, which is identified in the section 2 as the one that suffers the most cases. Focusing on this group increases the relevance of the case for health policy in terms of its effect on the monitoring and fulfillment of the objectives regarding the infant mortality rate in children under one year of age, but also in terms of the policies for monitoring the pregnancy. In what follows, the methodology for estimating this effect and the results of its implementation are presented in detail. The basic statistics of the data panel can be seen in Table 5.

4.1 How to estimate the effect?

The data structure of this problem suggests the implementation of the differences-in-differences methodology[7]. Although its application to congenital malformations is novel, this methodology is applied in various studies of effects on infant mortality such as, just to name a few cases, Alderman et al. (2009) for growth monitoring policies; Galiani, Gertler, and Schargrodsky (2005) or Anttila-Hughes et al. (2018) for the link to water availability; Kotsadam et al. (2018) to analyze the effect of international aid and; Keats (2018) or Breierova and Duflo (2004) for the effect of education.

In this case, there is a group of countries (P_{it}^{L}) that at a certain moment (t) apply a law (L) while others do not (P_{it}^{NL}). It is expected that it will have some effect on the presence of birth defects, in particular, the most extreme case of them, which are those that culminate in death (M_{it}). Thus, the effect of applying these laws would be:

$$\alpha_{DID} = [M_{post}^{L} - M_{pre}^{L}] - [M_{post}^{NL} - M_{pre}^{NL}] \tag{1}$$

Thus, according to this equation, the effect of the strengthening laws will arise from the difference between the change in mortality between the countries that adopt them (first term) and the change that occurs at the same time between those countries that do not (second term).

Following Cameron and Trivedi (2005), the value of α_{DID} can be estimated using the panel methodology with country fixed effects with:

$$M_{it} = \gamma + \alpha * T_{it} + \delta_t + \epsilon_{it} \tag{2}$$

where M_{it} is a mortality indicator that can be the rates per 1,000 live births (Table 2) or the cases (Table 3); T_{it} is the application of the law that is identified with 4 indicators (Table 4) and α is the estimate of α_{DID}; δ_t is a dummy variable per year and ϵ_{it} is the typical error. Since this is a long-term approach (20 years, approx.), certain conditions such as food production processes or the relative costs of obtaining them may change. These effects will be controlled in the estimate by means of the time fixed effects.

Bertrand, Duflo, and Mullainathan (2004) argue that in this structure it is relevant to establish that the application of the law is random conditional on the fixed effects of time and country. Given that the implementation of these laws can be associated with nutritional issues such as anemia or poverty levels and, therefore, there is a certain degree of endogeneity, a simple model of determinants of the application of the laws is estimated:

$$T_{it} = \alpha + \theta * X_{it} + \epsilon_{it} \tag{3}$$

where X_{it} is: anemia in children under 5 years of age, poverty gap and income level. The estimates, Table 6, show that only in the case of enactment of the law and with per capita income, the sign is positive and significantly different from zero. Therefore, when these laws are enacted, countries do not do so because they assess situations, such as anemia, that could affect the intensity of treatment. In this test of exogeneity of the treatment, we are going to include a second one, which is the variability of the value of α_{DID} when other determinants are introduced and when the time interval is modified.

[7]Since this methodology is widely used, different types of presentations can be found, among which the survey of Lechner (2010) or the intuitive presentation of Gertler et al. (2017).

The question in this structure is how is the value of $\hat{\alpha}_{DID}$ interpreted? The problem being analyzed is one in which one country is part of the control group at one point but is part of the treatment group at another[8]. For example, Uruguay goes from being a control group to being a treatment group in 2006 while Argentina shares with Uruguay being part of the control group for Chile and Colombia until 2002, at which time it changes to the treatment group being Venezuela the only one that is always part of the control group. As Theorem 1 of Goodman-Bacon (2018) shows, the effect estimated by the equation (2) is actually a weighting of effects resulting from all possible cases, which arises from considering the permanence and relevance quantitative of each country in the total time interval.

This result is important since in estimates like the one implemented here, the value of $\hat{\alpha}_{DID}$ can be decomposed into: i. the comparison between countries that apply the law first (like Chile or Colombia) and countries that apply later (like Uruguay) while they are not treated; ii. the comparison between those that apply first and those that apply last when the former are treated and, finally, iii. the comparison between all treated and those that are never treated (Venezuela in our case). The problem is that, to carry out this evaluation requires restricting the panel to be balanced, with which the years in which Chile, Colombia, Ecuador and Paraguay do not apply the law are mainly lost. This is why the exercise[9] is considered descriptive of the results that should actually be obtained if the original panel were balanced. To the extent that the $\hat{\alpha}_{DID}$ values that arise from this restricted exercise are similar to those of the free panel, the results of the first could be extrapolated to the latter.

To complement the analysis, the temporal extension of the panel will also be modified as follows. The lower limit is not modified to be able to have observations without validity of the law of those that apply early, but the upper limit as of the year 2009 in order to be able to visualize how the changes in the composition of the two groups, treated and untreated, affects the estimated value of the impact of the law. Narrowing the time interval further is not advisable given the loss of observations. This second exercise also allows us to analyze to what extent the effect of this law, on which the previous experience outlined in the section 3.1 indicates that it is one-time or step-shaped, is maintained over time. To the extent that the value of $\hat{\alpha}_{DID}$ for this time iteration is constant, we could think of that moment as the one in which additional actions are required. Finally, it will also allow us to evaluate the value of $\hat{\alpha}_{DID}$ as the data changes from the cross section scheme to one of multiple time series.

Finally, it is important to note that all the models will be estimated in semi-elasticities, the result variable in logarithm and the treatment variable or the controls in levels. This specification allows us to consider that each of the coefficients will tell us how M changes in percentage when it changes in one unit T or X. This is the best way to treat the different definitions of T in a similar way: when it comes to the sanction or validity of the law, it would be the change from not sanctioning it to sanctioning it and, when the case of the content is analyzed, it would be the effect of increasing the folate content by 1 mg/kg.

[8] Figure 1 of Goodman-Bacon (2018) shows the structure for a generic case of this problem.

[9] It is carried out in STATA (15) by means of the BACONDECOMP module of Goodman-Bacon, Goldring, and Nichols (2019) that allows computing the decomposition of Goodman-Bacon (2018).

4.2 Compulsory laws affect mortality from malformations?

The results of estimating the equation (2) for panel data with fixed effects by country and year according to robust methods[10] are synthesized in Table 7. It shows, for the two outcome measures levels and rate, the values adopted by $\hat{\alpha}_{DID}$ for men, women and the total population in each of the four indicators considered for T. The first general result is that the simple sanction or enforcement of a rule would not be generating changes: of the 12 estimated values (all of the expected negative sign) only 3 are significantly different from zero and at 90% significance. In these cases the value of $\hat{\alpha}_{DID}$ is close to 25%. Note that this value is similar to the one the CDC has identified for the US (Centers for Disease Control and Prevention (2004).

The reverse side of this result is what happens when the folate contents that each kilogram of flour should have, Content and Adjusted Content are taken into account (it arises from multiplying the column "Content" with the column "Compliance" from Table 4, which although they reflect the implementation of the law, what they show is the importance of the dose in fortification). In this sense, the last row of that table shows that both for the quantities and for the rate, the effective quantity of folates that is transferred to consumption would have a positive impact: for each unit that is added to fortification there is a decrease in between 12% for the number of cases and 15% for the rate, with slight differences by gender. This result suggests that, if the effect were linear, making the average of the countries go from 0.94 to 2.3 (similar to the levels of Argentina, Uruguay or Chile) would imply a significant reduction in both the number of cases and the rate.

One characteristic of malformations is that, as shown in section 2, they are not only related to micronutrient deficiency but also to other characteristics of individuals or the context in which they develop, such as access to water or fertilizers and pesticides but also educational or income levels. That is why the equation (2) is reformulated as follows:

$$M_{it} = \gamma + \alpha * T_{it} + \omega * X_{it} + \delta_t + \epsilon_{it} \tag{4}$$

The models include the following controls, X_{it}: anemia among children under 5 years of age ($anemia < 5$), real GDP per capita ($GDPpc$), use of $fertilizers$ and *pesticides*; access to potable water (*potable water*); the ratio of births to human resources ($Nac - HR$), the Gini index (*Gini*), the poverty gap with respect to a value of 3.2U$S PPP ($PG32$) and the expected years of primary education for women (*Years Educ. Esp. Prim.*).

With these indicators, three sets of estimates are constructed for the different treatment measures, except for "Validity" since it has been seen that it has no effect for the mortality rate among children under one year of age. These estimates were also made by gender, but just to keep the presentation simple, the results are not presented since, in general, they do not present large differences between them. These estimates have two objectives: one, to establish the degree of exogeneity of the treatment variables and the other, to study to what extent other variables co-determine health outcomes. Regarding the first point, when comparing the tables 8 to 10 it can be seen that the value $\hat{\alpha}_{DID}$ changes slightly when the additional controls are introduced. However, it is highlighted that the changes when the sanction of the law is used are greater than when either of the two content measures is analyzed. Also, in the case of the sanction of the law, the degree of statistical significance increases while in the other cases the change is not present or is very slight.

[10]Correcting the estimates with robust variance is a standard technique from Bertrand, Duflo, and Mullainathan (2004).

In each of these tables, the first column is presented again, the estimates are with the treatment variable, "DID" and a simple model that is established as a base, "Basic", which includes income, anemia and educational level of women. Then, different indicators of situations such as contamination by agrochemicals, access to drinking water, access to the health system, and conditions of inequality and poverty are individually introduced. From all these models the following facts emerge. First, from the basic model, only the income level and the educational level are significant, while anemia is significant only when the treatment variable is the one that reflects the effective content (Table 10). The remaining variables are not significant, except for "Fertilizers" for men (the estimates are not presented in this work but are available) and considering the effective content treatment. A second issue is that this basic model has a great joint explanatory capacity since the R^2 goes from 50 to 60%, with the explanatory capacity of the law of the order of 20 to 40%. This could indicate the relative relevance of improvements in nutritional intake to other explanations.

A usual recommendation for this type of pathology, as well as others related to pregnancy and birth, is to include controls on access to appropriate health coverage, which in this case implies having information on controls carried out, studies, etc. This last variable is not available, so the proportion of deliveries attended by trained personnel is used as a proxy. It is important to recall that of the usual determinants in studies of malformations, those associated with other conditions, such as race or the Zika epidemic in Brazil, have not been expressly included in this study, although to the extent that this characteristic is typical of each country will be subsumed in the respective fixed effect.

Finally, Table 11 shows a comparison of the three models only for the basic model. There the magnitude of each of the coefficients can be viewed and compared. It can be seen that an additional year of education improves mortality due to malformations by at least 13.5%, while the effect of an additional thousand dollars of income is just over 2%, a value similar to that generated by a 1 point reduction in the incidence of anemia. The joint effect of these determinants, together with the application of the law, would lead to a reduction in mortality between 33.1 and 44.2%. The question that this table leaves, which obviously escapes the objectives of this work, is the cost-effectiveness of each action, but if the evaluation history of fortification policies is considered, it clearly seems to be by far the one with the best cost-effectiveness ratio. A second issue to take into account is that these estimates only allow establishing causality in the case of the effect of the laws, leaving the coefficients on the other variables as simple correlations.

Before continuing, it is important to make some relevant caveats regarding the limitations of these estimates due to the combination of the complexity of the case to be studied with the capabilities of generating indicators from the national information systems. A typical case is that of exposure to pollutants, Borja-Aburto et al. (1999) analyze the difficulties when carrying out a study of malformations in this dimension since there is a temporal profile that depends on the transmission vector: if the father is the transmission vector, the process is before gestation, while if it is the mother it occurs in the period of organogenesis. This opening of information at the aggregate level is not only difficult but it would be almost impossible to obtain. Rojas and Walker (2012) show various cases where environmental issues associated with contamination by chemicals lead to malformation processes in births and Borja-Aburto et al. (1999) assesses questions such as whether the mother works in risky activities such as nursing, close to solvents, ionizing radiation and anesthetic gases, while in the case of the father they refer to agricultural activities, solvents, pesticides, ionizing radiation, mercury and cleaning products. Additionally, the moment of exposure of each one of them is also relevant.

Also, it is possible that these results are affected by changes in people's habits or by doctors' prescription on the incorporation of vitamin supplements in women. This variable is difficult to include as a control, mainly due to the lack of information on these consumptions. But, if this type of decision is strongly influenced by educational levels, income or health access, its presence will be considered in the results.

Finally, a question that emerges from the previous evaluation literature is the temporal form of α_{DID}. The answer is important since, as we have seen, adding an additional mg causes a 15% reduction in the mortality rate when the entire panel is taken into account. If this value were to hold for different doses and previous levels, doubling the doses would reduce the mortality rate by 28% compared to current levels. In countries with high incidence it may happen that the combined effort of supplementation with fortification is required (De-Regil et al. (2015)). It is important to note that countries with mandatory fortification have managed to reduce the prevalence of neural tube defects, but the effect depends on the baseline level: the reductions are smaller the lower the starting point (Heseker et al. (2009)). If this were the case, it would require modifying the estimation methodology towards dynamic panels, but as can be seen in Table 5 the average levels of the rate per 100 thousand live births, in the cases studied here, are similar.

4.3 Are the results sensitive to the temporal structure of the panel?

One issue that we must consider is how the results change when the composition of the panel changes between treated and untreated countries (Goodman-Bacon (2018)) and the symmetry regarding the number of pre and post treatment periods (Chabé-Ferret (2010); Lechner (2010)). For this, two exercises are carried out only for the sanction of the law and its effective content. The first, presented in Table 12 and 13, is to shorten the time interval of the panel so that the last country that applies micronutrients (Uruguay in 2006) has a few years of implementation and then be added one year to the panel. The results for both measures show a change in the coefficient after 2009, but that in the case of the sanction leads to a continuous sequence of staggered increases, while for the effective content it seems that the changes disappear after this. Therefore, this would be a first indication that the value of 15% could be considered structural. This exercise also reflects that the estimated coefficient does not change as the time dimension tends to move away from the units dimension.

The second exercise is to force a balanced panel for which the time interval is restricted to 1998-2011. The results of these estimates are presented in columns (1) and (3) of the Table 14 and next to it the respective exercise without restricting the time interval. As can be seen, the impact coefficient is slightly reduced in both cases and is no longer significant (it was at 10%) for the sanction of the law. It is important to note that there is a significant loss of observations, of the order of 30%. This exercise would be a second validation of the results that have been obtained: a low relevance of the enactment of the law but not of its content, which is around 15%.

Finally, in this balanced panel, the STATA module is applied (Goodman-Bacon, Goldring, and Nichols (2019)) that allows evaluating Theorem 1 of Goodman-Bacon (2018). This module allows to compute the decomposition by treatment and control groups; and also with or without other determinants X_{it} but in any case only for the sanction of the law since it requires that the treatment variable go from 0 to 1. When it is computed with this module, the value of $\hat{\alpha}_{DID}$ arises to introduce or not controls does not substantially change the estimated values, which is

-18.5%. One of the weaknesses of this exercise is that the no-treatment group ends up being a single country. However, when the origin of the effect is estimated, it appears that it proceeds in 73.6% of the difference between those treated and those who were always treated and 18% between those who were treated late compared to the initial ones. In Figure 5 it can be seen that these comparisons are the ones with the highest value. When estimating this composition including the controls, the weights change a bit but the structure remains the same.

5 Conclusions

This paper aims to explore the size of the impact of mandatory flour fortification on congenital malformations. In particular, with data by country from the Pan American Health Organization for the period 1997-2015 (circa), the case of the laws implemented in South America and their effect on mortality due to malformations among children under 1 year of age is evaluated. The choice of this region is due to the fact that there is some evidence that shows a higher prevalence of this type of pathology among the Latino population.

The motivation to carry out this study, in addition to the traditional concerns about the poverty-nutrition-infant mortality link, arises from several aspects. On the one hand, evidence for some South American country of the non-reduction of cases after the application of the law, which would not be expected given the extensive literature that argues otherwise. Another motivation is that the previous literature uses clinical history studies of the before - after type that do not control for the effects of other variables. Also, that less than half of all countries have implemented this type of laws, which suggests the need to advance in studies that justify or not the sanction of these norms. Finally, the existence of certain ignorance about the mechanisms underlying the relationship between folic acid and the risks of malformations, which is usually estimated to be around 65%.

It is concluded that the implementation of mandatory fortification of flour has a negative and significant effect on the mortality rate, even though in certain cases the *a priori* analysis would not show an effect, but it would not seem to have a significant effect on the number of cases. This result can be identified from the use of quasi-experimental methods in panels, a novel application in the literature of the quantification of effects of the application of these norms, which is usually based on before - after studies based on medical records. The estimated values of the impact coefficient are notoriously stable at different compositions of the data panel and tests of exogeneity of the treatment, because the origin of the effect occurs in the temporal comparison between the cases that apply the law early and those that do it late. The estimate is that the implementation of the law reduces the mortality rate among children under 1 year of age by between 25 and 15%. Furthermore, when economic and educational factors and anemia levels are included, it turns out that a change between 33 and 44% can be explained. Other factors such as access to water, exposure to pollutants or conditions of poverty or inequality, considered relevant in the literature, were not significant. Given the stability of the coefficient of change, achieving additional progress in reducing mortality due to malformations could require reformulations in the effective micronutrient content in the flours, provided that there are no improvements in other dimensions that contribute to this objective.

It should be noted that there is some evidence in the literature on a higher prevalence of these pathologies in the Hispanic population compared to the population of African American origin, a hypothesis that could not be evaluated here. Given the value of the differences found between these groups and the population compositions of South America, a study that includes these dimensions could shed light on relevant factors for the organization of health systems in the search to reduce infant mortality.

It is also important to note that this study cannot distinguish why these reductions in the mortality rate in malformations are due. That is, the available information does not allow to discriminate between the cases associated with the closure of the neural tube, congenital heart disease and other cases. Clearly, being able to advance in studies that consider this distribution would allow not only to advance in estimating the effects, but also in the channels of action and the policies required to achieve health objectives.

Finally, this study suggests that other socioeconomic factors may continue to contribute in a long-term perspective. Therefore, advancing with the improvements in the mortality of children from these causes requires a reformulation of these policies, either with their strengthening or with the search for actions in the health system that complement them in the style of the National Program for Congenital Heart Disease of Argentina (Porto, Crosta, and Pedraza (2014), Crosta and Porto (2009)). In this sense, it is possible to establish as a hypothesis to prove that recent changes in consumption patterns in certain population groups towards reducing the consumption of flour reduce the power of these policies. Thus, if this were true, other channels should be sought through which to improve nutritional quality.

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Tables and Figures

Table 1: Disability Adjusted Life Years

DALYS total malformations (%. DALYs total)

					Country						
Year	*Argentina*	*Bolivia*	*Brazil*	*Chile*	*Colombia*	*Ecuador*	*Paraguay*	*Peru*	*Uruguay*	*Venezuela*	*Total*
2000	22.9%	8.6%	13.8%	31.1%	14.8%	21.5%	14.1%	12.8%	24.9%	14.5%	17.9%
2010	26.5%	12.1%	19.5%	32.6%	23.5%	22.9%	18.5%	20.3%	30.3%	18.7%	22.5%
2015	27.4%	13.7%	22.1%	34.8%	23.6%	23.7%	20.0%	21.9%	34.6%	19.1%	24.1%
Total	25.6%	11.5%	18.5%	32.8%	20.6%	22.7%	17.6%	18.3%	29.9%	17.4%	21.5%

DALYS total Neural Tube Defects (%. DALYs Malformations)

					Country						
Year	*Argentina*	*Bolivia*	*Brazil*	*Chile*	*Colombia*	*Ecuador*	*Paraguay*	*Peru*	*Uruguay*	*Venezuela*	*Total*
2000	10.8%	10.7%	10.6%	10.4%	6.4%	5.4%	10.3%	8.7%	5.5%	8.0%	8.7%
2010	6.0%	9.7%	9.1%	9.1%	4.0%	5.4%	9.7%	6.3%	2.9%	5.4%	6.8%
2015	5.6%	8.5%	7.9%	8.9%	3.4%	4.9%	9.2%	5.6%	2.3%	5.6%	6.2%
Total	7.5%	9.6%	9.2%	9.5%	4.6%	5.2%	9.7%	6.9%	3.6%	6.3%	7.2%

DALYS total Congenital Heart Disease (%. DALYs Malformations)

					Country						
Year	*Argentina*	*Bolivia*	*Brazil*	*Chile*	*Colombia*	*Ecuador*	*Paraguay*	*Peru*	*Uruguay*	*Venezuela*	*Total*
2000	40.6%	41.9%	44.6%	33.6%	52.0%	50.0%	47.2%	39.8%	45.0%	49.2%	44.4%
2010	41.5%	40.6%	41.8%	31.4%	51.3%	45.8%	45.1%	39.8%	42.9%	47.1%	42.7%
2015	40.1%	41.0%	41.7%	31.1%	50.9%	46.2%	44.4%	40.7%	44.4%	45.8%	42.6%
Total	40.7%	41.2%	42.7%	32.1%	51.4%	47.3%	45.5%	40.1%	44.1%	47.3%	43.2%

Note. These data are for children 0 to 4 years
Source: Own elaboration based on GLOBAL HEALTH ESTIMATES 2016 SUMMARY TABLES (2018) `http://www.who.int/healthinfo/global_burden_disease/en/`

Table 2: **Mean mortality rate due to malformations in children under 1 year***

Country	Male	Var	Female	Var	Total	Var
Argentina	333.1	-23.2	304.0	-26.0	318.8	-24.5
Brazil**	247.4	20.1	225.9	25.9	236.8	22.8
Chile	298.9	-12.9	286.7	-22.0	292.9	-17.4
Colombia	292.0	14.7	251.4	14.0	272.2	14.4
Ecuador	164.4	74.9	147.7	82.9	156.2	78.5
Paraguay**	215.2	206.4	189.1	73.2	202.4	133.1
Peru**	138.2	-5.3	126.9	-10.9	132.7	-8.1
Uruguay	291.0	-35.5	252.1	-38.9	272.0	-37.2
Venezuela**	279.6	31.4	250.7	13.8	265.5	22.9

Note *Per 100 thousand children. **Brazil 1976-2015; Peru 1999-2015; Paraguay 1996-2014 and Venezuela 1996-2013. The "Var" column reflects the variation over the available time interval for each country

Source Own elaboration based on OPS https://www.paho.org/data/index.php/es/

Table 3: **Mean mortality due to malformations in children under 1 year***

Country	Male	Var	Female	Var	Total	Var
Argentina	1219.6	-15.6	1074.0	-18.7	2293.3	-17.1
Brazil	4119.2	11.0	3609.4	16.1	7728.6	13.4
Chile	370.3	-19.8	342.4	-28.4	712.6	-24.1
Colombia	1183.2	2.5	975.1	1.7	2158.2	2.1
Ecuador	264.1	86.6	227.3	93.6	491.4	89.7
Paraguay	149.9	193.3	126.6	65.1	276.5	122.7
Peru	424.8	-2.4	375.8	-8.5	800.5	-5.4
Uruguay	75.8	-43.7	62.8	-46.2	138.6	-44.9
Venezuela	829.4	42.3	710.1	23.0	1539.6	33.0

Note *Brazil 1976-2015; Peru 1999-2015; Paraguay 1996-2014 and Venezuela 1996-2013.The "Var" column reflects the variation over the available time interval for each country

Source Own elaboration based on OPS https://www.paho.org/data/index.php/es/

Table 4: Flour fortification laws in South America

Country	Law	Enactment	Validity	Content*	Compliance
Argentina	Law 25630	2003	2004	2.2	94,00%
Bolivia	Biministerial Res. 008/97	1997		1.5	
Brazil**	Decree 291	2002	2005	1.5	45,20%
Chile	Decree 475	1999	2000	2.2	72,70%
Colombia***	Decree 1944	1996		1.5	35,00%
Ecuador	Decree 4139	1996	2006		
Peru	Law 28314	2004	2006	1.2	47,80%
Paraguay	Decree No. 20830	1998	2001		21,00%
Uruguay	Decree No. 130	2006	2006	2.4	95,80%
Venezuela**	Norm COVENIN 217	2001	2001		

Notes. *mg/kg, ** Brazil and Venezuela they also fortify cornmeal. ***Colombia: the degree of compliance is on rice flour.
Source: Own elaboration based on López Camelo (2010) for Argentina, Brazil and Chile; Pereira Fukuoka (2012) for Paraguay; Peru from Sanabria Rojas et al. (2013); Venzuela following Pachón (2015) and David. L (2004), Russo et al. (2014) for Uruguay y Bolivia, Ecuador and Colombia based on David. L (2004)

Table 5: Panel: Descriptive statistics

Variables	N	Mean	Sd	Min	Max
Country code	167	5.820	2.784	1	10
Male Mortality	167	989.6	1,228	42	4,446
Rate Male Mortality	167	251.8	73.22	106.7	405.2
Female Mortality	167	860.3	1,075	39	3,946
Rate Female Mortality	167	226.8	66.07	92.23	352.9
Total Mortality	167	1,850	2,302	81	8,269
Rate Total Mortality	167	239.5	68.73	104.8	364.7
GDP pc	167	8.103	3.521	3.135	14.92
Anemia <5	167	27.69	8.285	18.20	52.40
Nac-HR	136	94.92	7.515	56.40	99.90
Potable water	167	91.17	6.763	71.52	99.71
PG32	133	6.508	5.088	0.100	22.90
Gini	133	50.24	4.912	39.90	59.90
Fertilizers	167	243.5	2,864	3.208	37,038
Pesticides	167	3.854	2.740	0.340	14.07
Years Educ. Esp. Prim.	156	6.379	0.505	4.988	7.475
Enactment	167	0.790	0.408	0	1
Validity	167	0.599	0.492	0	1
Content	129	1.163	0.935	0	2.400
Compliance	129	0.778	0.806	0	2.299

Source: All information about mortality by malformation is extracted from PAHO. The remain data is taken from World Bank Open Data

Table 6: Endogeneity of the Flour Fortification Law

Variables	Enactment	Content	Compliance
Anemia <5	-0.0104	-0.131	-0.0969
	(-0.489)	(-1.027)	(-1.022)
PG32	0.00981	0.0393	0.0568
	(0.542)	(0.898)	(1.344)
GDP pc	0.158***	0.342**	0.325**
	(5.366)	(3.689)	(3.493)
Constant	-0.181	1.167	-0.00842
	(-0.333)	(0.356)	(-0.00375)
Observations	133	100	100
R-squared	0.268	0.424	0.405
Number of countries	9	7	7
Country FE	YES	YES	YES

Notes: (i) Robust country fixed effects estimates (ii)* p<.1 ** p<.05 *** p<.01. (iii) Robust t-statistics in parentheses.

Table 7: Impact of flour fortification on mortality (under 1 year) due to malformations

Mortality	Cases			Rate			Obs
Malformations	Male	Female	Total	Male	Female	Total	
Enactment	-0.204	-0.245*	-0.223	-0.208	-0.250*	-0.227*	
	(-1.72)	(-1.89)	(-1.82)	(-1.83)	(-1.99)	(-1.92)	167
Validity	-0.0274	-0.0322	-0.0304	-0.0144	-0.0174	-0.0165	
	(-0.27)	(-0.32)	(-0.31)	(-0.15)	(-0.18)	(-0.18)	
Content	-0.111*	-0.102**	-0.107*	-0.114**	-0.106**	-0.110**	
	(-2.285)	(-2.619)	(-2.435)	(-2.822)	(-3.175)	(-2.993)	111
Compliance	-0.146**	-0.133**	-0.140**	-0.160***	-0.148***	-0.154***	
	(-2.631)	(-3.331)	(-2.913)	(-4.170)	(-5.928)	(-4.851)	

Notes: (i) Fixed country and year panel data estimates (ii)* p<.1 ** p<.05 *** p<.01. (iii) Robust t-statistics in parentheses.

Table 8: Determinants of the total mortality rate: sanction of the law fortification of flours with FA

Variables	(1) **DID**	(2) **Basic**	(3) **Pollutans**	(4) **Water**	(5) **Health Access**	(6) **Inequality**	(7) **Poverty**
(log) Tasa Def. Totales							
Enactment	-0.227*	-0.175***	-0.175***	-0.180**	-0.173**	-0.154***	-0.142***
	(-1.919)	(-3.555)	(-3.597)	(-3.136)	(-2.997)	(-3.608)	(-3.358)
GDP pc		-0.0545**	-0.0536**	-0.0501*	-0.0567**	-0.0593***	-0.0519**
		(-2.897)	(-2.703)	(-1.898)	(-2.568)	(-3.782)	(-3.095)
Years Educ. Esp. Prim.		-0.191**	-0.188**	-0.178*	-0.150	-0.220***	-0.229***
		(-2.386)	(-2.523)	(-2.083)	(-1.557)	(-4.465)	(-3.489)
Anemia <5		-0.0216	-0.0205	-0.0221	-0.0114	-0.0220	-0.0236
		(-1.360)	(-1.292)	(-1.395)	(-0.516)	(-1.308)	(-1.340)
Fertilizers			-7.01e-07				
			(-0.470)				
Pesticides			0.00423				
			(0.326)				
Potable Water				0.00297			
				(0.246)			
Nac-HR					0.00119		
					(0.222)		
Gini						-0.0216	
						(-1.634)	
PG32							-0.00702
							(-1.180)
Constant	5.250***	7.537***	7.464***	7.172***	6.775***	9.134***	8.129***
	(60.80)	(12.41)	(14.84)	(4.828)	(5.550)	(10.74)	(15.79)
Observations	167	156	156	156	126	125	125
R-squared	0.231	0.449	0.451	0.450	0.414	0.515	0.481
Number of countries	9	9	9	9	9	9	9
Country FE	YES	YES	YES	YES	YES	YES	YES
Year FE	YES	YES	YES	YES	YES	YES	YES

Notes: (i) Fixed country and year panel data estimates (ii)* p<.1 ** p<.05 *** p<.01. (iii) Robust t-statistics in parentheses.

Table 9: Determinants of the total mortality rate: sanction of the law fortification of flours with FA

Variables	(1) DID	(2) Basic	(3) Pollutants	(4) Water	(5) Health Access	(6) Inequality	(7) Povert
(log) Rate Total Mortality							
Content	-0.110**	-0.121***	-0.124***	-0.121***	-0.126***	-0.110***	-0.105**
	(-2.993)	(-5.383)	(-5.325)	(-5.529)	(-4.476)	(-7.093)	(-6.874
GDP pc		-0.0268***	-0.0247**	-0.0272*	-0.0191	-0.0379**	-0.0346*
		(-4.636)	(-2.840)	(-2.260)	(-1.569)	(-3.272)	(-6.432
Years Educ. Esp. Prim.		-0.184**	-0.181**	-0.186*	-0.194**	-0.195**	-0.200**
		(-3.150)	(-3.339)	(-1.945)	(-2.450)	(-3.670)	(-4.962
Anemia <5		0.0254*	0.0258**	0.0255	0.0255*	0.0266*	0.0321*
		(2.278)	(2.701)	(1.884)	(2.102)	(2.093)	(2.523
Fertilizers			0.00317				
			(1.573)				
Pesticides			0.00499				
			(0.785)				
Potable Water				-0.000327			
				(-0.0493)			
Nac-HR					-0.000196		
					(-0.0475)		
Gini						-0.00943	
						(-0.749)	
PG32							-0.0071
							(-1.242
Constant	5.483***	6.309***	6.192***	6.353***	6.437***	7.056***	6.486**
	(75.13)	(33.62)	(35.13)	(6.720)	(9.200)	(12.73)	(37.09
Observations	129	120	120	120	104	94	94
R-squared	0.308	0.512	0.531	0.512	0.508	0.579	0.577
Number of countries	7	7	7	7	7	7	7
Country FE	YES	YES	YES	YES	YES	YES	YES
Year FE	YES	YES	YES	YES	YES	YES	YES

Notes: (i) Fixed effect estimates (ii)* p<.1 ** p<.05 *** p<.01. (iii) Robust t-statistics in parentheses.

Table 10: Determinants of the total mortality rate: sanction of the law fortification of flours with FA

Variables	(1) **DID**	(2) **Basic**	(3) **Polutants**	(4) **Water**	(5) **Health Access**	(6) **Inequality**	(7) **Poverty**
(log) Rate Total Mortality							
Cont. Ajst.	-0.154***	-0.147***	-0.148***	-0.146***	-0.152***	-0.133***	-0.129***
	(-4.851)	(-6.330)	(-6.080)	(-6.838)	(-4.945)	(-5.886)	(-5.711)
GDP pc		-0.0234**	-0.0211**	-0.0275**	-0.0185	-0.0324**	-0.0295***
		(-3.433)	(-3.014)	(-3.301)	(-1.280)	(-2.870)	(-4.236)
Years Educ. Esp. Prim.		-0.135**	-0.132**	-0.155*	-0.148*	-0.150**	-0.156***
		(-2.512)	(-2.674)	(-1.949)	(-2.231)	(-3.059)	(-3.828)
Anemia <5		0.0255**	0.0263**	0.0267*	0.0251*	0.0269*	0.0317**
		(2.685)	(3.259)	(2.238)	(2.434)	(2.309)	(2.899)
Fertilizers			0.00260				
			(1.791)				
Pesticides			0.00584				
			(0.977)				
Potable Water				-0.00306			
				(-0.563)			
Nac-HR					-0.00123		
					(-0.290)		
Gini						-0.00810	
						(-0.827)	
PG32							-0.00613
							(-1.391)
Constant	5.497***	5.948***	5.824***	6.360***	6.209***	6.592***	6.111***
	(120.9)	(31.15)	(32.59)	(8.431)	(9.440)	(15.07)	(32.97)
Observations	129	120	120	120	104	94	94
R-squared	0.441	0.567	0.582	0.569	0.567	0.617	0.616
Number of countries	7	7	7	7	7	7	7
Country FE	YES	YES	YES	YES	YES	YES	YES
Year FE	YES	YES	YES	YES	YES	YES	YES

Notes: (i) Robust country fixed effects estimates (ii)* p<.1 ** p<.05 *** p<.01. (iii) Robust t-statistics in parentheses.

Table 11: Relative size of the coefficients: effect on the mortality rate of the entire population

Variables	(1) **Enactment**	(2) **Content**	(3) **Compliance**
(log) Rate Total Mortality			
Enactment	-0.175***		
	(-3.555)		
GDP pc	-0.0545**	-0.0268***	-0.0234**
	(-2.897)	(-4.636)	(-3.433)
Years Educ. Esp. Prim.	-0.191**	-0.184**	-0.135**
	(-2.386)	(-3.150)	(-2.512)
Anemia <5	-0.0216	0.0254*	0.0255**
	(-1.360)	(2.278)	(2.685)
Content		-0.121***	
		(-5.383)	
Compliance			-0.147***
			(-6.330)
Constant	7.537***	6.309***	5.948***
	(12.41)	(33.62)	(31.15)
Observations	156	120	120
R-squared	0.449	0.512	0.567
Number of countries	9	7	7
Country FE	YES	YES	YES
Year FE	YES	YES	YES

Notes: (i) Robust country fixed effects estimates (ii)* p<.1 ** p<.05 *** p<.01. (iii) Robust t-statistics in parentheses.

Table 12: Sensitivity to the composition of the panel: sanction of the law

Variables	(1) **2009**	(2) **2010**	(3) **2011**	(4) **2012**	(5) **2013**	(6) **2014**	(7) **2015**
(log) Total Mortality							
Enactment	-0.161*	-0.184*	-0.189*	-0.198*	-0.205*	-0.219*	-0.227*
	(-1.898)	(-1.866)	(-1.896)	(-1.920)	(-1.899)	(-1.878)	(-1.919)
Constant	5.307***	5.290***	5.279***	5.269***	5.262***	5.252***	5.250***
	(90.45)	(81.96)	(76.11)	(72.15)	(67.30)	(60.75)	(60.80)
Observations	117	126	134	143	152	160	167
R-squared	0.165	0.170	0.190	0.211	0.227	0.234	0.231
Number of countries	9	9	9	9	9	9	9
Country FE	YES	YES	YES	YES	YES	YES	YES
Year FE	YES	YES	YES	YES	YES	YES	YES

Notes: (i) Fixed country and year panel data estimates . (ii)* p<.1 ** p<.05 *** p<.01. (iii) Robust t-statistics in parentheses.

Table 13: Sensitivity to the composition of the panel: Effective content of the law

Variables	(1) **2009**	(2) **2010**	(3) **2011**	(4) **2012**	(5) **2013**	(6) **2014**	(7) **2015**
(log) Rate Total Mortality							
Compliance	-0.128***	-0.148***	-0.149***	-0.150***	-0.148***	-0.154***	-0.154***
	(-4.847)	(-3.932)	(-4.070)	(-4.556)	(-5.014)	(-4.724)	(-4.851)
Constant	5.522***	5.518***	5.510***	5.504***	5.500***	5.499***	5.497***
	(192.0)	(152.6)	(139.6)	(138.6)	(139.0)	(127.0)	(120.9)
Observations	90	97	103	110	117	123	129
R-squared	0.426	0.441	0.435	0.443	0.430	0.435	0.441
Number of countries	7	7	7	7	7	7	7
Country FE	YES	YES	YES	YES	YES	YES	YES
Year FE	YES	YES	YES	YES	YES	YES	YES

Notes: (i) Fixed country and year panel data estimates (ii)* p<.1 ** p<.05 *** p<.01. (iii) Robust t-statistics in parentheses.

Table 14: Sensitivity to panel composition: Effective content of balanced panel law

Variables	(1) **Balanced**	(2) **All**	(3) **Balanced**	(4) **All**
(log) Tasa Def. Totales				
Sanción	-0.185	-0.227*		
	(-1.445)	(-1.919)		
Cont. Ajst.			-0.139**	-0.154***
			(-3.215)	(-4.851)
Constant	5.464***	5.250***	5.583***	5.497***
	(70.49)	(60.80)	(112.4)	(120.9)
Observations	108	167	84	129
R-squared	0.162	0.231	0.403	0.441
Number of countries	9	9	7	7
Country FE	YES	YES	YES	YES
Year FE	YES	YES	YES	YES

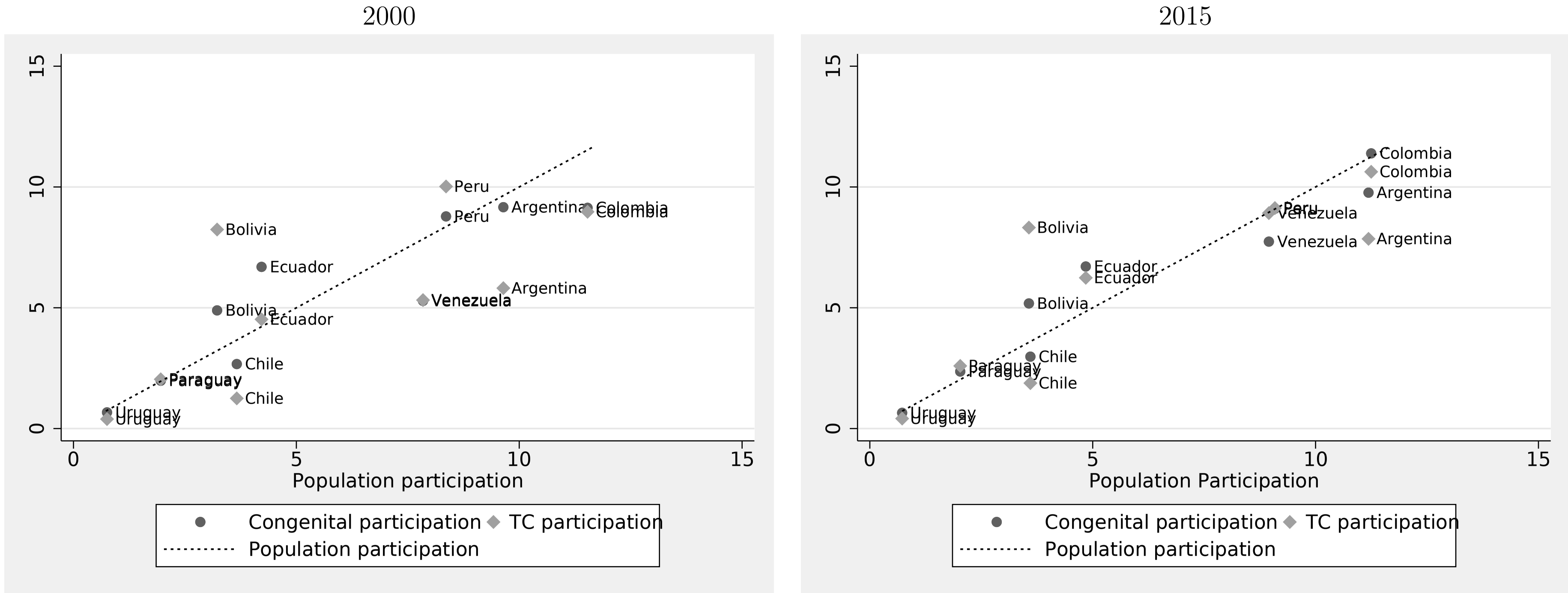
Notes: (i) Fixed country and year panel data estimates (ii)* p<.1 ** p<.05 *** p<.01. (iii) Robust t-statistics in parentheses.

Table 15: Decomposition for the sanction of the law by treatment-control group (Goodman-Bacon (2018))

DD Comparison	Weight	Avg DD Est
Earlier T vs. Later C	0.085	0.042
Later T vs. Earlier C	0.179	-0.238
T vs. Already treated	0.736	-0.198

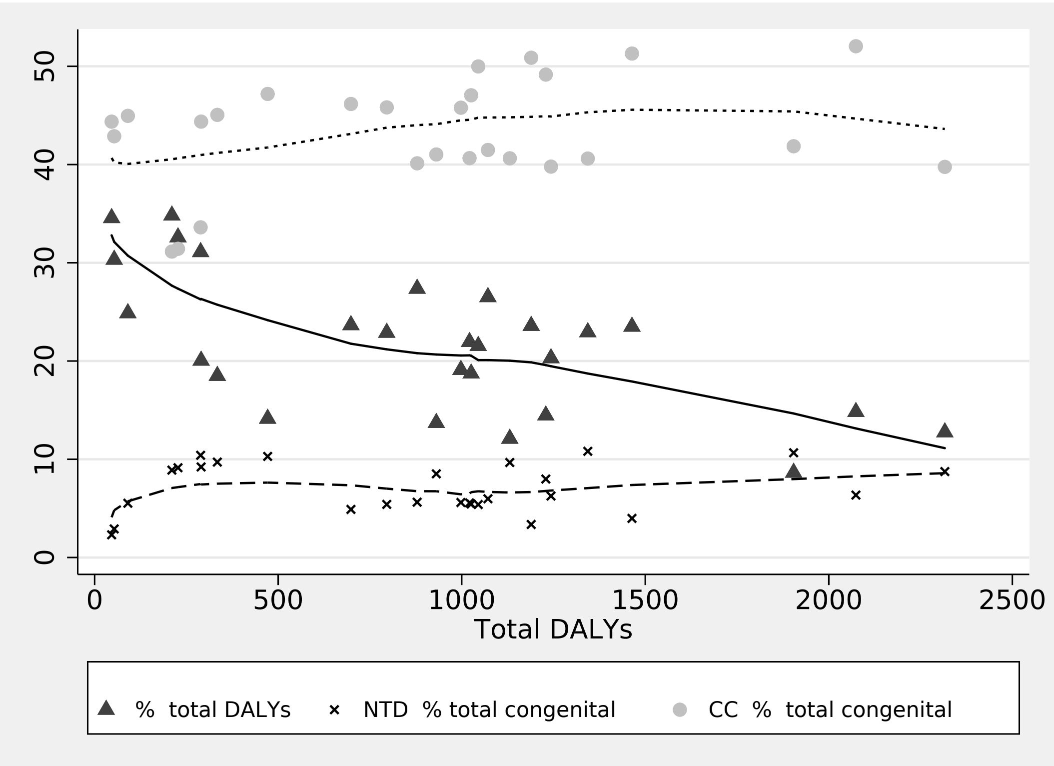
Notes: Estimates from the BACONDECOMP module (Goodman-Bacon, Goldring, and Nichols (2019))

Figure 1: Participation in regional DALYs per year



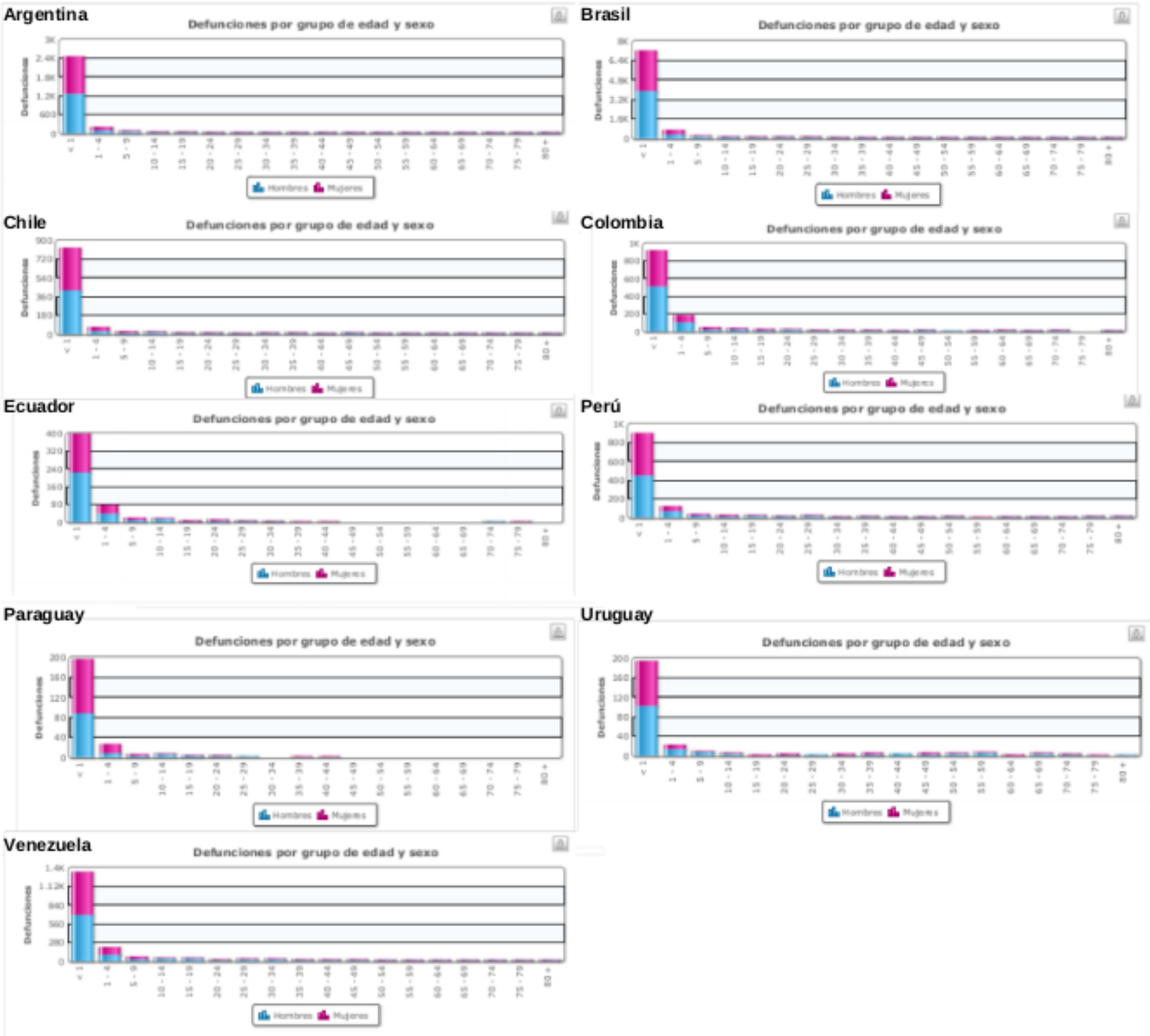
Notes: These figures are for children 0 to 4 years.
Due to its large size, Brazil is excluded, whose percentages are similar to those of the population (44,8%).
Source: Own elaboration based on GLOBAL HEALTH ESTIMATES 2016 SUMMARY TABLES (2018) `http://www.who.int/healthinfo/global_burden_disease/en/`

Figure 2: Participation of malformations and total DALYs



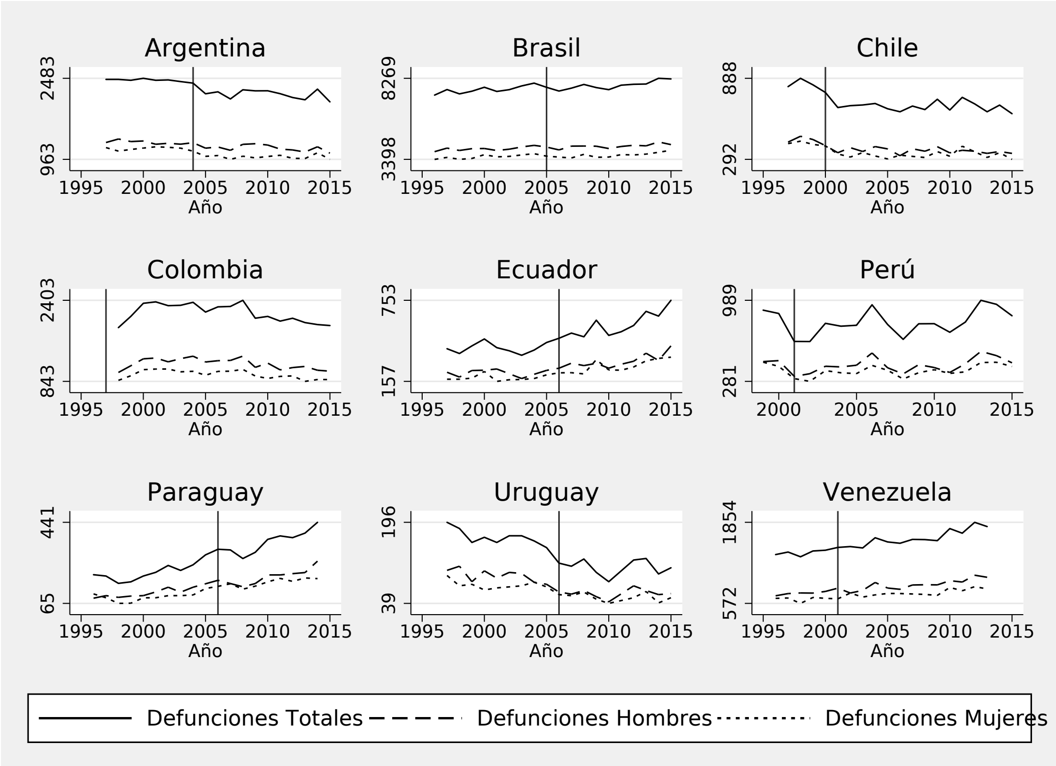
Source: Own elaboration based on GLOBAL HEALTH ESTIMATES 2016 SUMMARY TABLES (2018) `http://www.who.int/healthinfo/global_burden_disease/en/`

Figure 3: Age structure of mortality due to malformations



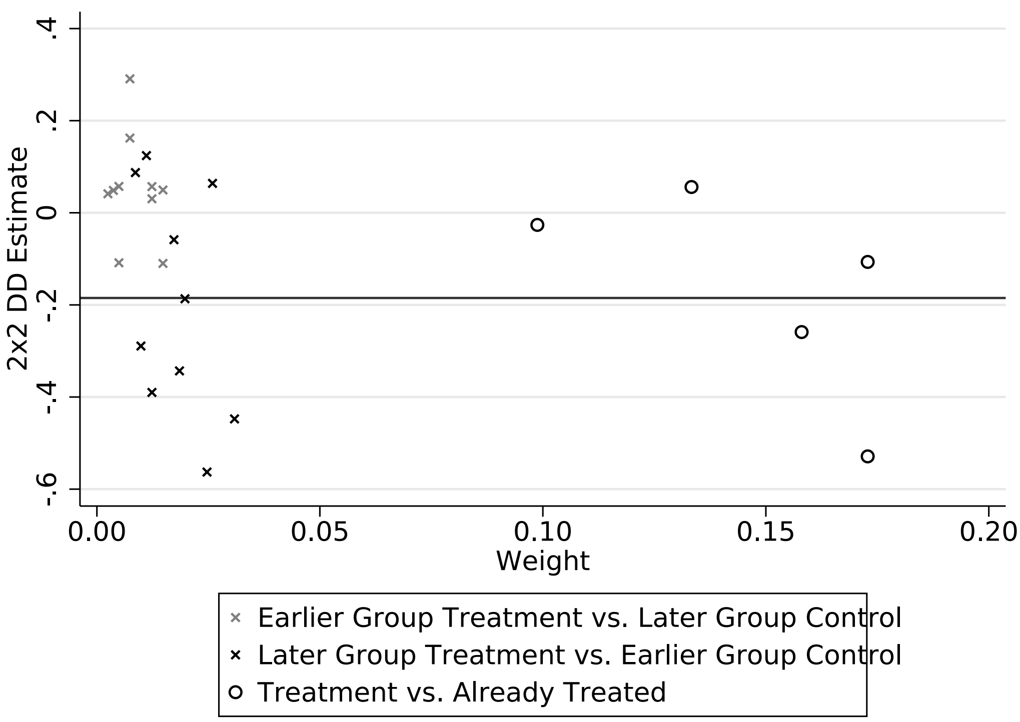
Source: https://hiss.paho.org/pahosys/grp.php

Figure 4: Mortality under one year and validity of the flour fortification law



Source: https://hiss.paho.org/pahosys/ and Table 4.

Figure 5: DID: Decomposition of α_{DID} by groups



Note: This graph arises from estimating the equation (4) without controls and only for the effect of implementing the law with the STATA BACONDECOMP module (Goodman-Bacon, Goldring, and Nichols (2019))