



## Nutrition and Health of Women in Chile

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### Abstract

The objective of this study was to diagnose the nutritional and health status of Chilean women of reproductive age by conducting a literature review. Chile is in an advanced stage of nutritional transition, which means that there is an increased prevalence of obesity in addition to the health problems commonly caused by underweight, especially in pregnancy. Availability and intake studies show that intakes of ultra-processed foods are on the rise. Several micronutrients and omega-3 fatty acids are cited as deficient. Pregnancy complications including anemia, diabetes, hypertension, cesarean section and inadequate fetal growth are frequently found in malnourished women. New health policies have been implemented that include, distribution of a micronutrient fortified food supplement to pregnant women, food labeling changes, taxes on sugar sweetened beverages, and a secondary prevention program for overweight non-pregnant girls and women. Other proposed policies include the use of a more accurate weight chart during pregnancy, improvements in the current fortified food supplement, and inclusion of overweight pregnant and nursing women in the secondary prevention program.

**Keywords:** Nutritional status; Adult women; Pregnancy; Lactation

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### Introduction

Chile is currently in an advanced stage of economic, demographic, and nutritional transition [1]. Over the last 25 years, the country has done much to improve per capita income and to bring relief from the conditions of extreme poverty that lead to malnutrition and disease [2]. However, this success has also created new problems. Chile now finds itself in the midst of an obesity epidemic with rising risk factors for chronic disease. This trend indicates the need to modernize existing programs and policies to emphasize prevention for nutrition-related chronic diseases [1,2]. Many indicators of both the benefits and detriments of this transition can be seen in the status of women's nutrition and health [3]. The objective of this study was to diagnose the nutritional and health status of Chilean women of reproductive age by reviewing the current literature with the goal of finding ways to improve current health policies.

### Methods

The methodology used in this study follows guidelines set by the "Nutriplanet" Project, whose overall goal is to develop a database of dietary, nutrition, and health data from various cultures and communities. The methodology called 'NutriPlanet' describes the nutritional and health situation of specific population groups (e.g. children, pregnant women, seniors) within a country. Understanding the current health and nutritional status in a setting is the first essential step in adapting regimes to each local context. It pretends to map local food consumption patterns and nutrient intakes in different population groups and to evaluate its link to health outcomes [4]. Over the last 10 years, the analysis has been implemented in 52 countries worldwide, 15 of which are European countries. The analysis consists of two complementary approaches. Firstly, an extensive literature review covering all published and grey literature in the context of health and nutrition (e.g. nutritional deficiencies, breast-feeding practices, vaccination regimes) is performed. Secondly, this review is enriched by the opinions and experiences of different local experts from academia, hospitals and institutions.

This study was based on a literature review, including both indexed and non-indexed reports published between 2003 and 2013, dealing with the health and nutritional status of non-pregnant, pregnant, nursing women and children of up to 3 years of age. A total of 34 criteria were used in the search. The research team, including an expert librarian from the Pontificia Universidad Católica de Chile, created a set of search terms used for the literature review. The databases from LILACS (Latin American Literature in Health Sciences), IBECs (Index Bibliographic Spanish in Health Sciences), MEDLINE, the Cochrane Library, SciELO (Scientific Electronic Library Online), PAHO (Pan American Health Organization), and WHOLIS (World Health Organization Library Information System) we searched using the aforementioned criteria. Other sites were searched including 19 non-indexed web sites belonging to the Chilean government and various international sites such as research societies and NGOs devoted to maternal and child health.

This search produced a list of 46 documents, which were published between 2003 and 2013. Additionally, 39 other documents were also considered in order to complement and provide context for the information provided by the selected papers. Four specialists, whose names are listed in the Acknowledgements section, were consulted about the literature included in the study. Ethical approval for this study was not required by Chilean law, as there were no human subjects involved.

## Results

### Maternal and child health in Chile

The Chilean Ministry of Health has historically been committed to maternal and child health and has implemented nutrition programs that have been widely accepted as successful [5]. According to the National Health Survey (NHS) 2009-2010, 77.5 percent of the population is eligible to receive some or all of the various services provided by the Ministry of Health [6]. This survey found that 30.6 percent of the population has low education levels of less than 8 years of formal education, 55.6 percent have 8-12 years of formal education, and 13.8 percent have more than 12 years of formal education. The public health services provided by the Ministry of Health focus mostly on the population in the low and middle educational categories [6] covering 91.5 percent of the population with low education levels, 82.4 percent of the population at the middle education levels, and 55.2 percent of those with a high education level.

Over the last decades, birth rates have dramatically declined in Chile. In 1964, the mean fertility rate was 5.4 live births per 1,000 women of reproductive age. By the year 2000, it had dropped to 2.1 live births per 1,000 women of reproductive age [7]. This rate is lower than replacement level for the Chilean population.

In Chile nearly all deliveries receive professional care [8,9] and babies are registered with the Civil Registry Office within the first week after birth [10]. The cesarean section rate at the national level has increased from 30 percent in 2001 to 37 percent in 2010 [11]. This figure is considerably higher than the WHO recommendation that no more than 15 percent of all deliveries be by cesarean section [12]. The average figures for cesarean section rates in Chile hide considerable differences between the private and public medical care systems, as 71.8 percent of the total number of these births occur in patients seeking private care [13].

Maternal mortality has also undergone a dramatic decline over the last 60 years, from 270.7 per 100,000 live births in 1957 to 18.2

**Table 1:** Prevalence of obesity in child-bearing age women (18-44 years), according to educational level (< 8 years: low; 8 to 12 years: medium; 13 years and more: high) in two Health National Surveys: 2003 and 2010, Chile [6,42].

Year	Obesity (%) by education			Total
	Low	Medium	High	
2003	28.6	19.8	14.9	20.8
2010	48.0	22.5	17.7	22.8

per 100,000 live births in 2007. In the Americas, only Canada exhibits a lower maternal mortality rate than Chile [14]. However, over the last decade, maternal mortality rates have not continued to decline, a fact that could be explained by an increase in the percentage of gravidas over 40 years of age, a group with a higher risk of maternal and perinatal complications [15]. The current maternal mortality rate associated with abortion, of any kind, excluding ectopic pregnancy, is 0.4 per 100,000 live births [16].

Gestational diabetes was reported in 11.2 percent of subjects participating in a study of 234 pregnant women, and was associated with maternal overweight [17]. Obesity in Chilean women has been also found to be associated with higher rates of induced labor and caesarian sections, as well as a higher percentage of macrosomic infants [11,17-20]. Obesity before and during pregnancy is associated with greater risks for pregnancy complications, increased birth weight, and perinatal morbidity and mortality [21-23]. The international literature also highlights the association of obesity with an increased frequency of hypertensive disorders of pregnancy, congenital malformations, recurrent abortions, macrosomy, instrumental delivery, thromboembolism, puerperal infections, maternal mortality and fetal mortality [3,21].

Underweight women also have a greater risk of pregnancy and perinatal complications. Women who are underweight at the beginning of pregnancy and do not have adequate weight gain during pregnancy are at a higher risk for fetal growth restriction, low birth weight, and cesarean section [18-20]. Anemia in early pregnancy has been the subject of three studies [24-26]. Two of them reported an average prevalence ranging between 11 percent and 15 percent [24,25]; 29% of underweight women were anemic according to the WHO standard in the most recent study (Table 1) [26,27].

High blood pressure, a severe complication in pregnancy, affects 7-10 percent of Chilean gravidas [28]. After septic abortion, it is one of the major causes of maternal mortality (16.7 per 100,000 live births in 2002). In addition, it is an important cause of fetal growth restriction, low birth weight, prematurity and perinatal morbidity and mortality [28].

Smoking during pregnancy has been reported by 7 percent of gravidas [6]. By contrast, alcohol consumption is considerably more common; 57.4 percent of women reported some ingestion of alcoholic beverages during pregnancy, 3.7 percent reported intake levels considered to put a fetus at risk (12 g per day of alcohol), and 1.1 percent reported levels of intake considered to put the fetus at very high risk ( $\geq 48$  g per day of alcohol) [29].

Deaths from infectious diseases have significantly declined and those caused by chronic diseases have proportionally increased [30]. Currently, the five main causes of death in women are: diseases of the circulatory system, cancer, diseases of the respiratory system, diseases of the digestive system, and diseases of the endocrine system. All of these causes combined accounted for more than 76 percent of 2012

total deaths.

The National Health Service (NHS) was founded in 1952 [31]. Since then, the country has experienced major advances in social medicine, particularly in the field of maternal and child health [5,31-33]. For example, maternal mortality has drastically decreased since the implementation of a family planning program in 1965 [34]. A new development is the obesity epidemic stemming from improvements in income, increased food intakes, a change in eating habits, and other factors [1-3,35].

The frequency of high-risk births, especially in obese and underweight women, has not decreased in the last 10 years. Low birth weight babies (< 2,500 g) accounted for 10 percent of all live births in the 1960's, a value that fell to 6-7 percent during the 1980's and 5-6 percent of all live births during the 1990's [23]. However, between 2000 and 2014 this proportion has remained unchanged reaching 6.2 percent [36]. Another indicator that has remained rather constant during the 2000-2013 period, although with a slight tendency to increase, is birth weight less than 3,000 g [36]. In the year 2000, babies classified in this category made up 20.3 percent of all live births, while in year in 2014 the proportion increased to 22.1 percent.

The national incidence of birth weight  $\geq$  4,000 g in 1987 was 6.1 percent and reached 9.7 percent in 2000 while at the same time the proportion of overweight and obese pregnant women increased from 31.7 percent to 54.3 percent [23]. The rather weak association between those two categories of maternal nutritional and the incidence birth weight  $\geq$  4,000 g continued until recent years when it reached just 8.5 percent in Chile for the year 2014 [36]. However, recent analyses have shown that another macrosomy category of birth weight  $\geq$  4,250 g, is closely associated to maternal nutritional status [20]. The national incidence for this category was 3.0 percent in the year 2014 [36].

The frequency of babies with birth length less than 50 cm has also proven to be an increasing trend. In 1994 babies in this category were 44 percent, a value that remained rather constant between 1994 and 2004 and began to rise after 2005 [36]. In 2014 newborns with a body length less than 50 cm comprised 50.3 percent of all live births. Studies in school age Chilean children have found an association with obesity, metabolic syndrome factors and impaired school performance in children with birth length of less than 50 cm [37-40]. Prematurity, defined as live birth with less than 37 weeks of gestation, represented 5.5 percent of all births in 1990. In 2003 the prematurity rate was at 6.4 percent and in 2014 it was at 7.9 percent [36]. Health risks associated with high and low birth weight or prematurity are well known, both during the perinatal period and in the long term [3,10,37-40].

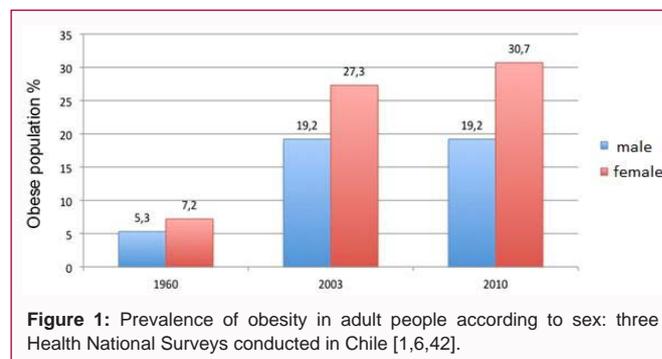
### Anthropometric assessment of non-pregnant and pregnant women

The National Health Survey (NHS) 2009-2010, a national representative study on body mass index (BMI) of adult women and men the obesity prevalences were 30.7% and 19.2%, respectively [6]. The same survey found that the prevalences of total cholesterol > 200 mg/dl in adult women and men were similar and rather high: 38.1% and 39.0%, respectively. Obesity in Chilean women was slightly lower than recent prevalences observed in the USA and Mexico: 35.5% and 32.4%, respectively [41].

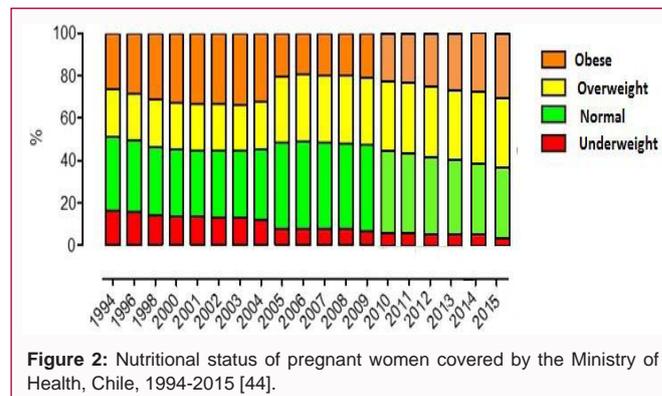
Other results from the NHS showed that in the specific sample of non-pregnant women of reproductive age (18-44 years) 43 percent of women had a normal BMI, 31 percent were overweight, 20 percent

**Table 2:** Anemia prevalence in pregnant women according to maternal nutritional status, Concepción, Chile [26]. WHO criteria to diagnose maternal anemia [27].

Nutritional Status	Anemia (%)
Underweight	28.9
Normal	14.4
Overweight	11.6
Obesity	12.4
Total	14.5



**Figure 1:** Prevalence of obesity in adult people according to sex: three Health National Surveys conducted in Chile [1,6,42].



**Figure 2:** Nutritional status of pregnant women covered by the Ministry of Health, Chile, 1994-2015 [44].

obese, 2.8 percent morbidly obese, and 3 percent were underweight [6]. When compared with the 2003 NHS, there was a modest increase in obesity from 20.8 percent to 22.8 percent. However, in women with less than 8 years of formal education, obesity increased from 28.6 percent to 48.0 percent (Table 2) [42]. A study conducted in 1,223 nulliparous pregnant women who were overweight or obese before pregnancy indicates that these gravidas have significantly higher risk factors for cesarean section and induced labor [43]. Figure 1 shows female obesity prevalence in 1960, before the beginning of the obesity epidemic, and in 2003 and 2009-2010, illustrating in three national surveys the marked increase in the prevalence of obesity among women [1,6,42]; which is considerably higher than in men.

The Chilean Ministry of Health carries out an assessment, based on BMI, of nutritional status during pregnancy in all women enrolled in the public maternal care service. This group represents about 80 percent of all pregnant women in Chile. The data is reported annually. As shown in Figure 2, in the year 2015 obesity and underweight frequencies were 29.9 percent and 4.5 percent, respectively [44]. In the year 2005 there was a sharp drop in the frequencies of obese and underweight pregnant women. This change coincided with a change in the measurement standard or classification criteria of maternal nutritional status adopted that year by the Ministry of Health. Since 1986 and until 2004 maternal nutritional status was measured using a chart developed by Rosso and Mardones [18]. This instrument was

replaced in 2005 by a modified Rosso-Mardones' chart introduced by Atalah et al. [45]. Both of these charts are also used in other Latin American countries [21]. The Atalah et al. [20] instrument has a wider range for normal measurement and consequently many women who would be considered either underweight or obese by the Rosso-Mardones' chart are classified as "normal" by the Atalah chart. The implications of this change are obvious. As seen in Figure 2, approximately 35 percent of pregnant women were classified as obese in the year 2004 using the Rosso and Mardones chart whereby only 20 percent were classified as obese in year 2005 and only 29.9 percent were classified as obese in year 2015 using the Atalah chart. On the other hand, using the Rosso and Mardones chart, approximately 14 percent of pregnant women were classified as underweight in the year 2004, while with the Atalah chart only 7 percent were classified as underweight in the year 2005 and 4.5 percent were classified as underweight in the year 2015. A recent study in a cohort of more than 28,000 pregnant women showed that the Rosso and Mardones chart is more sensitive than the Atalah chart for detecting mothers with a higher risk of delivering high and low birth weights and reduced birth length babies [20].

### Availability and intake of macronutrients

A study of the changes in food availability in Chile between 1964 and 2003, based on the Food and Agricultural Organization of the United Nations (FAO) balance sheets, shows an increase in energy availability from 2,630 kcal/day/person in 1965 to 2,872 kcal/day/person in 2003 [46,47]. Between 1995 and 2003, the availability of meat increased 20.6 percent, the availability of fish and seafood decreased 33 percent, and the availability of fruits decreased 22.1 percent. These trends are confirmed in other recent reports [48-51].

Between 1987 and 1997 spending on food increased at all socio-economic levels of the Chilean population, but there was a proportionally greater increase in low-income groups [48]. The largest increases in food spending were for sugar-sweetened beverages, alcoholic beverages, processed fruit juices, pre-prepared meals, and food consumed outside the home. Expenditures on processed foods, as a percentage of total food expenditure, increased from 42 percent to 57 percent in the average Chilean home [48]. Similar trends were observed in studies reported between 1997 and 2007 [49,50].

Data indicates that intakes of dairy products and calcium rich foods are lower than international recommendations. By contrast, intakes of added sugars are greater than international recommendations [50]. Information collected in 2006-2007 indicates that the average Chilean diet includes many ready-to-use foods with high caloric content and low nutritional value [51]. A PAHO/WHO study on the sales of ultra-processed foods between 2000 and 2013 reported a steady rise in the consumption of these foods in Chile and in other 12 Latin American countries [52]. Between 2000 and 2013 sales of carbonated soft drinks in Chile increased 63.3 percent, from 104 to 170 liters per capita per year. These increases in sales of ultra-processed food products have been associated with obesity [52]. A recent publication found a significant association between sugar-sweetened beverage intake and high BMI in Chilean children [53].

The Chilean National Survey of Food Consumption (NSFC), conducted in a nationally representative sample, found a high prevalence of overweight and obesity among the population 2 years old and older. This survey also found that obesity is mostly concentrated in low-income groups and rural areas [54]. These populations had a higher consumption of high calorie foods and a lower consumption

**Table 3:** Intake frequency of milk, cheese, cottage cheese, yogurt, milk desserts, butter or margarine, according to the National Health Survey 2010 [6].

Frequency distribution (%)	Men	Women	Total
three times or more a day	6.2	8.3	7.3
Less than three times a day	14.3	14.6	14.4
Once a day	31.7	36.3	34.1
Every other day	17.2	13.2	15.1
At least once a week	18.4	14.9	16.6
At least once a month	5.8	5.9	5.9
Never	6.4	6.9	6.6
Total	100	100	100

**Table 4:** Intake frequency of fish or seafood, according to the National Health Survey 2010 [6].

Frequency distribution (%)	Men	Women	Total
More than once a week	10.2	11.1	10.7
Once a week	29.6	27.9	28.7
Less than three times a month	26.6	26.1	26.3
Less than once a month / never	33.6	34.9	34.3
Total	100	100	100

of protective foods.

1) In addition, NSFC findings indicated the following: Total nutrient intakes are generally adequate in relation to standards for age and sex.

a. Approximately one third of those surveyed reported excessive caloric intake, especially preschool children, 14-30 year old women and middle-aged men. Higher values found in rural areas, mainly in the Southern part of the country, and in the low-income population.

b. Protein intakes were below recommended levels in 5 percent of the population of all ages. In rural areas and low-income groups, inadequate protein intakes were 4-5 times higher than in urban areas and higher income groups.

2) Nutritional status, determined by BMI, indicated the following:

a. Most cases of under nutrition are concentrated in the older adult population, rural areas, the Central-Southern zone of the country, and in low-income groups.

b. Approximately 70 percent of the population is classified as overweight or obese. Obesity was found more frequently in women, rural areas, the southern area of the country, and in middle to low-income groups. A very high abdominal obesity rate was found in women, especially in those over 65. Morbid obesity was found in 2.5 percent of the population, mostly in women.

The 2009-2010 NHS is another valuable source of information regarding dietary habits of the Chilean population. Data from this survey indicate that 41 percent of adult non pregnant women have very low daily intakes of dairy products and 61 percent have very low intakes of fish and seafood (Table 3 and 4) [6]. Recent information on daily intakes during pregnancy is lacking, but the results of a survey conducted in 1999 show similar patterns to those reported for non-pregnant women in the 2009-2010 NHS [55].

## Micronutrients intakes

Several studies focusing on micronutrient intakes were published during the period considered in this review. The first one conducted in 47 pregnant women from Temuco, a city located in the south of Chile with mostly low-income population, found that intakes of calcium, iron, zinc and vitamin C were less than 75 percent of recommended levels (acceptable range  $\pm$  25 percent) [56]. A larger study of daily intakes in 411 underweight pregnant women, based on two 24-hour recalls, found that up to 75 percent had daily intakes of vitamins A, C, E, B6 and of minerals such as calcium, iron, manganese, and zinc below recommendations, and intakes of omega-3 fatty acids were less than 20 percent of recommendations [57]. The findings of these studies are similar to those reported in a previous survey carried out in 1999 [58].

A study of post-menopausal women, with normal sun exposure and without vitamin D fortification, found a high frequency of low plasma levels of vitamin D [59]. There were two studies looking at plasma vitamin D levels in children living in the southern areas of Chile, where sun exposure is lower than in other areas due to long winters. The first study reported abnormally low levels of vitamin D in 65 percent of children, and the second reported abnormal levels in 93 percent of children [60,61].

Docosahexaenoic acid (DHA) has been supplemented to pregnant and nursing mothers through powdered milk [62]. This intervention increased daily intake of DHA from an average of 48.8 mg to 147.8 mg ( $p < 0.001$ ) and has shown an improvement in the fatty acid composition of red blood cells and breast milk. Another study evaluating a supplementation program using fortified powdered milk for omega 3 fatty acids, vitamins, and minerals in pregnant women, showed a positive impact on perinatal variables [63]. This intervention increased daily intake of Alpha-Linolenic Acid (ALA) from 570 mg to 900 mg ( $p < 0.001$ ). The results of these supplementation studies encouraged a study of acceptability of a dairy product fortified with DHA and micronutrients [64].

## Discussion

It can be concluded that more research is needed for a better assessment of the consequences of women's nutrition in Chile. In the meantime some interventions have been recently designed by Chilean authorities to improve it. Four important new policies are now being implemented. The first is a program designed to supply a micronutrient fortified milk-based supplement to pregnant women, the second is a food labeling law that requires warning labels on packaged foods containing levels of nutrients over a specified amount, the third imposes special taxes on sugar sweetened beverages, and the fourth is a secondary prevention program for overweight non-pregnant girls and women.

The new milk-based supplement program for pregnant women was designed by the Ministry of Health to address micronutrient deficiencies. Results from the literature suggested the idea since food intake surveys have revealed a trend to replace the intake of healthy foods with high calorie processed foods, especially in low-income groups [46-59]. Specifically, the most recent NSFC survey reported a low consumption of fish and dairy products in non-pregnant women aged 14 to 64 [54]; women also have reduced intakes of micronutrients such as calcium, iron, zinc, vitamins C and D, and omega-3 fatty acids, and 5 percent of women have a low protein intake. A few trials preceded the development of the fortified milk called "Purita

Mamá", containing omega-3 and micronutrient supplements [62-64]. Introduced in 2009, this product is distributed by the National Program of Complementary Feeding [65]. Unfortunately, reports show "Purita Mamá" has had acceptability problems: the number of women showing an interest in taking home this food product from their health clinic, notably decreased between years 2009 and 2012 [66]. The provision of adequate amounts of micronutrients in the diet would clearly help to increase both birth length and maternal height in the long run [3]. The 2010 National Health Survey (NHS) found a mean height of 156.1 cm (CI95%: 155.5-156.7) in women 15 years old and over [6]. Mean values are much higher in developed countries [23]. Fetal growth during the second half of pregnancy is largely dependent on the maternal supply of blood/nutrients. Maternal height and pelvic size are correlated and, in turn, pelvic size and the size of the uterus and its blood supply are also correlated with each other and with maternal size [3,67]. Thus, maternal size determines how much nutrition will receive the fetus.

A new law requiring front-of package labeling went into effect as of June 2016 [68]. Foods that exceed a certain level of energy, sugars, sodium, or saturated fat are required to place a warning on the front of the package that can be easily read by the consumer. It is expected that this measure will help inform the population so they can make better food choices.

The PAHO/WHO report on sales of processed foods reveals that Chile has had a marked increase of carbonated soft drinks consumption [52], meaning that between 2000 and 2013 sales of those drinks increased 63.3 percent, from 104 to 170 liters per capita per year. In this context, the Chilean parliament approved in 2015 a tax increase for those beverages and a tax reduction for low calorie drinks [69]. Tax increases were also applied to alcoholic beverages.

The obesity prevention program of the Ministry of Health, covering children from 2 years of age is a step in the right direction, strengthening secondary preventive actions in early life in those who are already overweight or obese [70]. Obesity in girls is a condition, which extends to adulthood [71]. The beginning of the epidemic of obesity in the population under 6 years has been well documented [72]. Using the NCHS anthropometric standard, a survey conducted by the Chilean Ministry of Education found a prevalence of obesity in 12.3 percent of youngsters [73]; however, the prevalence could be twofold higher using the WHO standard [74]. The literature indicates that obese adolescent girls can have an earlier menarche, a fact that has consequences ranging from a smaller final height to a more complex adolescence [67].

The presented available evidence may also allow to propose three other policies to improve present programs of the Ministry of Health: to diagnose malnutrition during gestation using a different chart, to develop a better accepted micronutrients fortified food supplement "Purita Mamá", and to include overweight pregnant and nursing women in the secondary prevention program.

The use of the Rosso and Mardones chart is supported with a new study showing its higher sensitivity to diagnose fetal growth problems than the Atalah et al. [20] chart. In addition, two recent publications on maternal nutrition have supported its use in developing countries [3,75]; however, another two charts could be also compared in their sensitivity values to assess fetal growth problems [23,76]. The modification of the fortified food supplement "Purita Mamá" is needed due to its low acceptability [66]. The inclusion of overweight

pregnant and nursing women in the secondary prevention program is justified because public primary health care services have done historically much to improve local nutrition and health [5]; overweight secondary prevention has been recently included as part of primary health care and pregnant and nursing women are in very much need as demonstrated in this review [70].

The presence of smoking and alcohol consumption in Chilean pregnant women represent a serious risk of fetal damage in only a very small percentage of women [6,29]. However, considering the deleterious consequences for the fetus these aspects must be carefully monitored and intervened when detected [77].

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## Declaration of Interest

Gabriela Olagnero, one of the coauthors, is Scientific Coordinator at Research and Development Department, DanoneNutricia Early Life Nutrition, Buenos Aires, Argentina. The sponsoring company was not involved in the design, analysis or writing of this document. Other coauthors have no relevant interests to declare.

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