Accepted manuscript

A simulation study to improve calcium intake through wheat flour fortification

Gabriela Cormick[1,2,3*], Iris Romero [3], María Bernardita Puchulu[3,4], Surya M. Perez[3], Miriam Sosa [5,6], Lorena Garitta[5,6] , Eliana Elizagoyen [5,6], Fernanda Gugole [5,7], José M. Belizán [1,2], Natalia Matamoros [8], Luz Gibbons [2]

[1]Centro de Investigaciones en Epidemiología y Salud Pública (CIESP - IECS), CONICET, Buenos Aires, Argentina; gabmick@yahoo.co.uk, belizanj@iecs.org.ar

[2]Instituto de Efectividad Clínica y Sanitaria (IECS – CONICET), Buenos Aires, Argentina; gabmick@yahoo.co.uk, belizanj@iecs.org.ar, gibbonsl@iecs.org.ar

[3]Universidad Nacional de La Matanza, San Justo, Argentina; gabmick@yahoo.co.uk, romeroiris.b@gmail.com, mariabpuchulu@gmail.com, suryaperez13@gmail.com

[4]Universidad de Buenos Aires, Facultad de Medicina, Departamento de Ciencias Fisiológicas, Buenos Aires, Argentina; mariabpuchulu@gmail.com

[5]Departamento de Evaluación Sensorial de Alimentos (DESA), Instituto Superior Experimental de Tecnología Alimentaria (ISETA), 9 de Julio, Buenos Aires, Argentina; lorena@desa.edu.ar, miriam@desa.edu.ar, eliana@desa.edu.ar

[6]Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Buenos Aires, Argentina; lorena@desa.edu.ar, miriam@desa.edu.ar, eliana@desa.edu.ar

This is an Accepted Manuscript for Public Health Nutrition. This peer-reviewed article has been accepted for publication but not yet copyedited or typeset, and so may be subject to change during the production process. The article is considered published and may be cited using its DOI 10.1017/S1368980024001228

[7]Instituto de Desarrollo E Investigaciones Pediátricas "Prof. Dr. Fernando E. Viteri" Hospital de Niños "Sor María Ludovica de La Plata (IDIP), Ministerio de Salud/Comisión de Investigaciones Científicas de La Provincia de Buenos Aires, La Plata, Argentina; natymatamoros@gmail.com

[8]Comisión de Investigaciones científicas de la provincia de Bs As (CIC), Buenos Aires, Argentina

Corresponding author: Gabriela Cormick gabmick@yahoo.co.uk

Short title: Flour fortification to improve calcium intake

Acknowledgements: we would like to thank the authorities of the Ministry of Health of Argentina for providing the data.

Financial Support: This work was funded by the Agencia Nacional De Promoción De La Investigación, El Desarrollo Tecnológico y la Innovación, Ministerio de Ciencia, Tecnología e Innovación, Proyectos de Investigación Científica y Tecnológica (PICT 2020), grant number 2769, by the Programa PROINCE-UNLaM-CyTMA SAL-077 and by the Bill & Melinda Gates Foundation grant no. OPP119082

Conflict of Interest: None

Authorship: G.C. had the original idea and wrote the first protocol and draft of this manuscript. L.G., I.R., and G.C. compiled the data and performed the statistical analyses. All authors reviewed and approved the last version of this manuscript.

Ethical Standards Disclosure: Not applicable.

Data Availability Statement: The data presented in this study are openly available in http://www.extensioncbc.com.ar/wp-content/uploads/ENNyS-2007.pdf.

https://doi.org/10.1017/S1368980024001228 Published online by Cambridge University Press

Abstract

Objective: to simulate the impact on calcium intake- effectiveness and safety- of fortifying wheat flour with 200, 400 and 500 mg of calcium per 100 g of flour.

Design: secondary analysis of cross-sectional data collected through repeated 24-hour dietary recalls using IOWA the Intake Modelling, Assessment and Planning Program.

Setting: urban cities in the National Health and Nutrition Survey of Argentina (ENNyS 2018 – 2019).

Participants: 21358 participants, including children, adolescents, and adults.

Results: Most individuals in all age groups reported consuming wheat flour. The prevalence of low calcium intake was above 80% in individuals older than 9 years. Simulating the fortification of 500 mg of calcium per 100 g of wheat flour showed that the prevalence of low calcium intake could be reduced by more than 40 percentage points in girls and women aged 19 to less than 51 and boys and men aged 4 to less than 71, while it remained above 65% in older ages. The percentages above the upper intake level remained below 1.5% in all age groups.

Conclusions: Calcium flour fortification could be further explored to improve calcium intake. Subnational simulations could be performed to identify groups that might not be reached by this strategy that could be explored in Argentina. This analysis could be used to advocate for a strategy to fortify wheat flour.

Keywords: calcium, micronutrient, fortification, flour, inadequate intake

1. Introduction

Calcium is the most abundant mineral in the human body with more than 99% stored in bone tissue as hydroxyapatite, a key structural function to the skeletal system. [1] The remaining 1% is found in soft tissues and in fluids, such as blood.[1] Calcium is involved in several vital functions, including blood coagulation, cardiac and skeletal muscle contraction, neuronal signalling, secretory activity, apoptosis, immune response, cell differentiation and enzyme activation. [1–3] All calcium necessary for growth and replenishment of daily losses, must be supplied via food sources as this essential nutrient is not synthesized by the human body. [3] Unfortunately, there are no practical population level markers of calcium status. Variations in calcium intake are typically not reflected in calcium serum levels. [3] Serum calcium concentration is tightly maintained at levels around 1.0–1.2 mmol/L by homeostatic mechanisms that regulate renal excretion and reabsorption, intestinal calcium absorption and bone formation. [3] Since there is a lack of reliable biochemical marker for calcium status, calcium adequacy is usually measured by comparing population dietary intakes with dietary reference values. [4] Calcium dietary reference values vary by age, gender and life stages (pregnancy and lactation), and also by reference guidelines.[3] The Food and Agriculture Organization and World Health Organization (FAO/WHO) suggests a Recommended Nutrient Intake (RNI) of 1000 mg calcium per day for young adults and 1300 mg/day for men over 65 years and for postmenopausal women. [4] The US Institute of Medicine (IOM) suggests a Recommended Dietary Allowance (RDA) of 1000 mg/day for most adults, but 1200 mg/day for postmenopausal women. [5] According to data from food balance sheets, approximately half of the world's population has inadequate access to appropriate foods to cover their dietary calcium needs. [6] A systematic review performed by International Osteoporosis Foundation Calcium Steering Committee, compiled available data on average national dietary calcium intake around the globe and found that calcium intake is low (averaging less than 400 mg/day) in many countries of Southeast Asia, and around 400 to 600 mg/day in countries of South America, including Argentina. [7] The study revealed a health inequity as the lowest calcium availability from foods and lowest calcium intakes are largely found in low and middle income countries (LMICs) of Asia, Africa, and Latin America. [8, 9]

Randomised controlled trials performed on children, adolescents, pregnant women, women of reproductive age, and postmenopausal women have shown the impact of improving calcium intake through calcium supplementation and calcium-fortified foods. [10] The impact was observed on health outcomes including height, bone mineral density and perinatal health. [10]

https://doi.org/10.1017/S1368980024001228 Published online by Cambridge University Press

Hypertensive disorders of pregnancy (HPD) cause around 50,000 maternal deaths and 500,000 neonatal deaths annually worldwide, making them one of the leading obstetric causes of maternal mortality globally.[11, 12] Calcium supplementation reduces the occurrence of HDP, and halves the occurrence of pre-eclampsia in populations with low calcium intake.[13] Maternal mortality ratio in Argentina is 45 deaths per 100000 live births with no clear decline in the last 10 years. [14] HDP represents the main obstetric cause of maternal mortality in Argentina and calcium is one of the most deficient micronutrients in the population, with little changes since 2005.[14, 15]

The World Health Organization recommends exploring calcium fortification of staple foods in populations with low calcium intake as it is an important public health intervention for the prevention of pre-eclampsia, as well as having additional benefits for the general population.[16]Food fortification is an effective strategy to improve micronutrient intake.[17] Calcium may be added to certain staple foods, such as wheat flour, maize flour or cornmeal, rice and dairy products. [9] However, few countries have official regulations and/or food standards for calcium fortification. [9, 17] Different analyses have modelled the impact of water and flour calcium fortification in LMICs and high-income countries (HICs). [15, 18–20]

A recent analysis from the second Nutrition and Health National Survey in Argentina (abbreviated as ENNyS2 in Spanish), found that the prevalence of low calcium intake was as high as 88% in girls and women.[21]

The objective of this study was to simulate the impact -effectiveness and safety - of fortifying wheat flour with 200, 400 and 500 mg of calcium per 100 g of flour using the ENNyS2 performed in Argentina between 2018 and 2019. [22] This would be the first step towards designing a strategy to fortify wheat flour with calcium at a population level.

2. Materials and Methods

This study is a simulation to assess the impact of wheat flour fortified at different calcium levels on overall calcium intake. We estimated the calcium intake in different age groups and then simulated the impact of fortifying white wheat flour with 200, 400 and 500 mg of calcium per 100 g of flour. This analysis was performed to determine which calcium level would be most effective in reducing low calcium intake in the population, defined as the proportion of individuals in the group with usual calcium intake below the age-specific

Estimated Average Requirement (EAR), while minimizing those at risk of excess in calcium intake, defined as the proportion of individuals who exceeded the tolerable upper intake level (UL).

Population

Data were obtained from the ENNyS2, a cross-sectional survey carried out in urban areas by Ministry of Health and Social Development of Argentina between 2018 and 2019, designed to extrapolate the results to the whole urban population of Argentina.[22] Participants were selected using a probabilistic complex sample design including small and large cities from all provinces of Argentina. A total of 21358 participants, 5763 infants, 8228 children and adolescents and 7367adults, were included in the sample. The ENNyS required 1200 participants by age and country region to be representative at regional level. The final sample was reached for all regions except greater Buenos Aires, which is the most populated region in the country. Age groups representativeness was reached by all age groups except children less than 2 years. [22]

Dietary assessment

Dietary assessment was performed in person by trained dietitians. [22] Data was collected using a standardised multiple pass 24-hour diet recall designed to capture all foods, beverages, supplements, and medicines consumed by participants in the previous day. A repeated 24-hour dietary recall was performed to 20% of the population at least 48 hours after the first dietary recall. A Digital Photographic Food Atlas was designed to estimate portion sizes. Primarily we used the local food chemical composition table (Sistema de Análisis y Registro de Alimentos 2, SARA2 in Spanish abbreviation) to estimate nutrient intake.[23] This food chemical composition table is a compilation of data from local sources such as ARGENFOODS. The SARA2 methodology describes that when local data were not available, chemical composition of similar foods from other countries´ chemical composition tables, like UK and USA were added to the local database.[24–26] In this way, if a food item is fortified in one composition table, but not in Argentina, it was not used. The SARA2 presents data of 1105 food items including mandatory and voluntary fortified foods and beverages as well as brand specific foods and beverages available in the local market. Data is presented in 26 food groups and 39 food components including energy, water, macro and micronutrients. [23] We used food labels when a food item was not available in the database.

https://doi.org/10.1017/S1368980024001228 Published online by Cambridge University Press

Analysis

All analyses were adjusted for the complex sample design weight. We used the Intake Modelling Assessment Program (IMAPP) developed by Iowa State University (IOWA), a computer program that allows running different simulation scenarios of nutrient intake using dietary intake information of population age-groups. We first calculated the calcium intake distribution of one single day and calculated the day-to-day variability of calcium intake using the repeated 24hour dietary recalls. This calcium intake distribution included calcium containing foods, beverages, supplements, and medicines reported in the ENNyS. We then adjusted calcium intake distribution with the day-to-day variability to obtain an estimated distribution of the usual calcium intake.

Afterwards, we calculated the baseline prevalence of inadequate calcium intake as the proportion of individuals in the group with usual calcium intake below the age-specific EAR, and risk of excess as the proportion of individuals with usual calcium intakes above the age-specific upper intake level (UL). We used the default harmonized dietary reference values that the IMAPP assigns to each population group. This reference values are mainly a compilation of EARs and ULs from IOM's RDAs, and RNIs from the FAO/WHO tables.[27] The calcium EAR and UL values used for this analysis are presented in Table 1.

We then performed a distribution of wheat flour and calcium intake and estimated the calcium required to decrease the population level of calcium inadequacy without exceeding the recommended calcium UL for each population group. [27] We calculated the "initial gap" defined as the estimated amount of calcium in flour to achieve the target prevalence of inadequate intakes. The initial gap was calculated as the difference in mg per day between the EAR for the target population group and the usual calcium intake for that group.

To perform the calcium fortification simulation, we used the ENNyS database to identify foods and beverages such as pizza, bread, cakes and milkshakes that might contain white wheat flour. We then calculated the percentage of white wheat flour in each consumed item to obtain the total wheat flour intake in grams. We used local recipes obtained from the Nutritionists Federation of Argentina (FAGRAN), websites, labels and documents showing standardised recipes such as the UK bread and flour regulations. [28] When an item contained a mix of flours, we calculated the amount of wheat flour in that item.

https://doi.org/10.1017/S1368980024001228 Published online by Cambridge University Press

Finally, using IMAPP, we estimated the potential impact of different calcium fortification levels in wheat flour. To assess the impact on inadequate calcium intake and risk of excess, we estimated the adjusted calcium intake distributions for each age group after simulating the addition of 200, 400 and 500 mg of calcium per 100 g of wheat flour. We measured effectiveness of each fortification level, as the percentage of individuals below the calcium EAR and measured safety or risk of excess as the percentage of individuals exceeding the calcium recommended UL of their corresponding age-specific population subgroup. [27]

3. Results

The number of participants, mean wheat white flour intake, mean calcium intake before and after simulation, prevalence of low calcium intake before and after simulation, and percentage of individuals exceeding the UL before and after simulation, are presented by age-sex categories in Table 1. Flour and calcium intake by country region is reported in Table 2. The prevalence of low calcium intake, defined as the proportion of individuals in the group with usual calcium intake below the age-specific EAR, was above 80%, in age groups older than 9 years (Table 1). Only 2.4% of participants reported taking any kind of supplements and less than 0.1% of participants reported taking calcium supplements.

Wheat flour intake was reported by more than 95% of individuals in all age groups (Table 1) and by more than 90% of individuals in all age groups from each region of the country (Table 2).

The highest levels of wheat flour intake were found in those aged 9 to 51 years. Mean wheat flour intake ranged from 101.8 to 110.0 g a day in men aged 19 to 51 years, wheat flour intake was lower in women. Women aged 51 and older showed the lowest wheat flour intake of the whole adult population with values ranging from 55.4 to 59.4 g a day (Table 1).

Changes in calcium intake after simulating wheat flour fortification with different calcium levels are presented in Table 1. The simulation with a fortification level of 200 mg of calcium per 100 g of flour showed that the prevalence of low calcium intake could be reduced from 20.3% to 12.4% in children aged 1 to less than 4 and from 53.2 % to 31.0 % in children aged 4 to less than 9. In girls aged 9 to less than 14, the prevalence of low calcium intake was slightly reduced, from 97.3 to 91.6%, whereas in boys of the same age it could be reduced from 94.4 to 82.8%. In adolescent girls and boys, the prevalence of low calcium intake

https://doi.org/10.1017/S1368980024001228 Published online by Cambridge University Press

remained around 80% after simulating a fortification of 200 mg of calcium per 100 g of flour (Table 1). A greater impact was observed with the adult population data. The prevalence of low calcium intake could be reduced from 91.0% to 55.5% in women aged 19 to less than 31 (representing a reduction of 35.5 percentage points), from 89.4% to 61.6% in women aged 31 to less than 51 (representing a reduction of 27.8 percentage points) and from 96.5% to 73.8% in women aged 51 to less than 71 (representing a reduction of 22.7 percentage points) (Table1). In men, the prevalence of low calcium intake could be reduced from 80.6% to 55.5% in those aged 19 to less than 31 (representing a reduction of 25.1 percentage points), from 88.4 to 61.6%. In those aged 31 to less than 51 (representing a reduction of 26.8 percentage points), from 88.1% to 73.8% in those 51 to < than 71 years (representing a reduction of 14.3 percentage points) (Table 1). The results of the simulation showed a smaller impact for those aged 71 years or older. The prevalence of low calcium intake could be reduced from 93.3% to 85.7% in women and from 92.2% to 85.7% in men. After the simulation of a wheat flour fortification with 200 mg of calcium per 100 g of wheat flour, none of the age groups studied showed more than 0.5% above the UL which was our cut off for safety (Table 1).

The simulation of a wheat flour fortification with 400 mg of calcium per 100 g of wheat flour, allowed greater reductions of inadequate calcium intake. The prevalence of low calcium intake could be reduced by more than 30 percentage points in girls and women aged 19 to less than 51 and boys and men aged 9 to less than 71. The prevalence of low calcium intake remained above 70% in older ages. With a fortification of 400 mg of calcium per 100 g of flour, percentages above the UL remained at 0.2% or lower in all age groups, except for men aged 71 or older where it reached 0.9%.

The simulation of wheat flour fortification with 500 mg of calcium per 100 g of wheat flour, allowed even greater reductions in the percentage of inadequate calcium intake. The prevalence of low calcium intake could be reduced by more than 40 percentage points in girls and women aged 19 to less than 51 and boys and men aged 9 to less than 71. The prevalence of low calcium intake remained high in older ages. With a fortification of 500 mg of calcium per 100 g of flour, percentages above the UL remained at 0.5% or lower in all age groups, except for men aged 71 or older where it reached 1.3%.

https://doi.org/10.1017/S1368980024001228 Published online by Cambridge University Press

The original distribution of calcium intake and distribution of calcium intake after the simulating a fortification with 400 mg of calcium per 100 g of wheat flour for women and men are shown in Figures 1 and 2, respectively.

4. Discussion

In this simulation, we show that it is effective and safe to improve calcium intake in Argentina through fortifying wheat flour at levels of 200 mg, 400 mg, and 500 mg of elemental calcium per 100 g of wheat flour. With a fortification of 200 mg of calcium per 100 g of flour, the prevalence of low calcium intake would be reduced by more than 20 percentage points in women aged 19 to less than 71 and men aged 19 to less than 51. At this fortification level, it was more difficult to reduce the prevalence of low calcium intake in individuals aged 9 to less than 19, women older than 51 years and men older than 71 years, due to their higher EAR values. The simulation of a wheat flour fortification with 400 mg and 500 mg of calcium per 100 g of flour showed reductions in the prevalence of low calcium intake of 40 percentage points or more in children aged 4 to less than 9, women aged 19 to less than 31, and men aged 19 to less than 71.

Our analysis using the ENNyS2 shows that the prevalence of low calcium intake in Argentina is high, reaching above 80% in all groups 9 years or older.[22] The calcium intake we report for women and children in this analysis is similar to a previous analysis that used data from the first national survey in Argentina (ENNyS 1), indicating that calcium intake remains low, with minimal changes since 2005.[18] In this analysis we show that the prevalence of low calcium intake is also high in adolescent boys and adult men, both of which were groups not included in the ENNyS 1. [18] Adolescent boys and adult men are important to take into consideration as they usually have a higher food intake than the rest of the population and are prone to reach the UL more easily with the introduction of fortified foods. Groups with higher food intake may limit the maximum level that can be recommended for a large-scale food fortification policy, which needs to be effective for the most vulnerable populations, yet safe for whole population. [4]

The UL is the highest level of calcium intake that is likely to pose no risk of adverse health effects [29]. In our analysis the risk of exceeding the UL, defined as the proportion of individuals in the group with usual calcium intake above the age-specific UL, started to

https://doi.org/10.1017/S1368980024001228 Published online by Cambridge University Press

increase in men aged 71 years or more with the simulation of a fortification level with 400 mg of calcium per 100 g of wheat flour, however it only reached 0.9%. The simulation of wheat flour fortification with 500 mg of calcium per 100 g of flour produced further reductions in the prevalence of low calcium intake while the risk of exceeding the UL remained low, reaching 1.3% only in men aged 71 years or more. In Argentina the use of micronutrient supplements is low, so the risk of exceeding the UL is low. However, even in countries like the US, where micronutrient supplement intake is common, risk of exceeding the calcium UL was also reported to be low, at around 3%. [30] In our simulations we used the default IMAPP harmonized dietary reference values, with an UL of 2000 mg of calcium a day for those aged 71 or older. This level is still under discussion, and it is considerably lower than the 2500 mg of calcium a day used by other standards.[31] For individuals aged 71 or older, the European Food Safety Authority (EFSA) panel recommends 2500 mg of calcium a day, the same UL as younger groups, as data from population-based studies indicate that calcium intake can be close to this level without posing any health risks.[31] The EFSA panel based their recommendation on the results of long-term clinical trials in which individuals received a daily supplement containing 2500 mg of calcium, besides their habitual food calcium intake. 31] These clinical trials found no evidence of increased risk of hypercalciuria, nephrolithiasis, cardiovascular disease, or prostate cancer.[31] ~~In this way,~~ Running this simulation with a higher UL of 2500 mg of calcium a day, would produce a fortification level that yields greater reductions of low calcium intake without increasing older adult`s risk of exceeding the UL.

Our analysis is limited to the population data included in ENNyS2, the latest national survey available in Argentina. The ENNyS2 includes only urban population, as most of the population of Argentina lives in urban areas (92.5 %). Further studies should estimate the impact of wheat flour fortification in rural populations.[32] Results from children under 2 years of age and the region of Greater Buenos Aires should be taken with caution and confirmed by further studies as samples did not reach representativeness.

Low calcium intake is common worldwide, however the percentage of the population with low calcium intake differs widely between age groups and populations. [7] In our previous simulation analysis using a fortification of 156 mg of calcium per 100 g of flour, we showed reductions in the percentage of population with low calcium intake in LMICs such as Argentina, Uganda, and Zambia. However, in HICs, a population-based strategy could be

https://doi.org/10.1017/S1368980024001228 Published online by Cambridge University Press

limited by the risk of men exceeding the calcium intake UL at this fortification level. [18] Despite having an average calcium intake higher than in LMICs, data from the United States National Health and Nutrition Examination Survey (NHANES) 2009-2010 indicated that 42% of Americans did not meet their IOM-EAR for calcium. [33, 34] A study using a large national survey performed in Canada, modelled a mandatory calcium fortification of food products with levels from 55 mg to 165 mg of calcium per serving. The results show that the fortification would be effective in reducing the prevalence of low calcium intake in Canada, however despite being beneficial for most population age groups, the risk of excess would increase in men, reaching 7% of individuals above the UL. [20] On the other hand, evidence from the United Kingdom's long-term experience of mandatory calcium fortification with levels between 94 and 156 mg of elemental calcium per 100 g of white wheat flour, demonstrated that calcium fortification increases calcium intake and has a positive impact on bone health with no adverse effects.[35] It is estimated that calcium fortified wheat flour contributes to 13–14% of the total calcium intake in the United Kingdom, and without this policy, an additional 10–12% of adolescents would not meet the recommended intake. [17] Since the implementation of mandatory calcium fortification of wheat flour in the United Kingdom, few countries have adopted mandatory or voluntary wheat flour fortification, mainly with levels between 125 and 312.5 mg of calcium per 100 g of flour. [17] In Germany calcium fortification of bread was shown to improve bone mineralization, contributing to significant reductions in health cost of bone fracture treatment. [36]

It is important to consider the selection of the fortification vehicle within the legal framework. Food fortification can either be mandatory, designed to address certain inadequate intakes and their health consequences, or voluntary, which depends on food manufacturer´s and consumer´s demand. [4, 17] Mandatory food fortification programs require minimal behaviour change and, if well implemented, can be a cost-effective public health intervention.[17] The food vehicle selected for a food fortification policy should be consumed regularly by the target population and ideally be industrially produced to facilitate effective fortification. [17, 37] A review that assessed food fortification in 72 countries, showed that most countries (n=55, 76%) had mandatory wheat flour fortification with at least one nutrient, and that mandatory maize (n=11, 15%) or rice flour fortification (n=6, 8%) with at least one nutrient was less common [38]. Argentina has had mandatory wheat flour fortification with iron, folate, riboflavin, niacin and thiamine since 2002, a policy designed to reach the whole population. [39] A pre and post fortification study showed reductions in

https://doi.org/10.1017/S1368980024001228 Published online by Cambridge University Press

Neural Tube Defects attributed to mandatory folate fortification of wheat flour. [40] The study shows that the prevalence of anencephaly, bifid spine and encephalocele per 10000 births decreased between pre and post fortification periods from 6.92 (5.80-8.20) to 2.33 (1.99-2.72); from 8.16 (6.94-9.54) to 4.34 (3.86-4.85) and from 2.12 (1.52-2.87) to 0.73 (0.54-0.95), respectively. [40]

Argentina has no mandatory calcium fortification of wheat flour, however, the country has regulations for voluntary calcium fortification of staple foods [17]. This regulation allows for fortification of 20%–50% of the Recommended Nutrient Intake, which represents 200–500 mg of elemental calcium per food serving. Despite these regulations, the industry does not fortify wheat flour with calcium voluntarily. [17] Dairy products are voluntarily fortified with calcium in Argentina; however, the high levels of low calcium intake indicate that these products are insufficient to reach the recommended calcium intake levels.

The existing laws of wheat flour fortification in Argentina would facilitate the incorporation of calcium fortification, as mills and wheat flour production infrastructure are already equipped to include micronutrients into the premix. [39] According to Argentina`s 2005 Food and Household survey, the main intake of flour is in the form of bread and pasta. The survey also shows that lower income quintiles have higher flour intake and lower dairy product intake when compared with higher income quintiles. Given this discrepancy, large-scale flour fortification would benefit the lowest quintile (poorest) which consume less calcium rich products such as dairy products.[41] Wheat flour seems to be an appropriate vehicle for this population, as it is widely consumed in Argentina, it was reported by most individuals of all age groups and country regions. [4] Our simulations show that wheat flour could be a good and effective fortification food vehicle to improve calcium intake in Argentina and could help decrease the high prevalence of low calcium intake without placing risk of calcium intake excess. These results show that wheat flour intake increased up to the age of 14 to less than 19 years and then decreased with age. Despite having higher flour intake, those aged 9 to less than 19 also have the highest recommended calcium intake (EAR=1100 mg of calcium a day), part of the reason why greater impacts on reducing low calcium intake were not observed in this group.

The information from this simulation is the first step towards designing a fortification strategy, as it assesses current calcium intake levels, wheat flour intake and the theoretical

https://doi.org/10.1017/S1368980024001228 Published online by Cambridge University Press

impact of different calcium fortification levels in all population age groups. This, together with the existing legal framework that allows food fortification with calcium and the current legislation of mandatory wheat flour fortification with other minerals, could facilitate a policy change from voluntary to mandatory calcium fortification. The final food fortification level will depend on several criteria, including industrial feasibility and organoleptic acceptability of wheat flour food derivatives such as bread and pasta. Future studies should assess the industrial feasibility of fortifying flour at higher levels such as 400 or 500 mg of elemental calcium per 100 g of flour. Assessments of physicochemical and rheological characteristic of flour and flour derived products such as bread, cakes, and pastas should be performed. The available infrastructure, capacities for food processing and production systems, cost and access to calcium salts and other industrial inputs such as changes in labels and monitoring regulations need to be analysed. [4, 37]

The population organoleptic acceptability of calcium fortification should be assessed before deciding the fortification levels and should continue once the fortification is implemented as this would ensure adherence and success of the proposed intervention. [4] Previous experiences usually refer to the use of calcium carbonate to fortify wheat flour, however, depending on the type of product, other salts such as calcium citrate, calcium phosphate and calcium lactate could be selected. [42, 43]

Monitoring and evaluation strategies should be designed and implemented as part of a food fortification programme. Regulatory monitoring should ensure flour production and end-product fortification processes work effectively. Wheat and its main derivative, flour are domestically produced on a large scale in Argentina, which is the eleventh biggest wheat producer and exporter worldwide [44]. Monitoring strategy implementation is feasible as 88% of wheat is grown in three provinces of Argentina and more than half of the flour is produced and commercialized by 11 mills. [45]

Regular population surveys should be administered to monitor food consumption, especially the amount and type of flour consumed and calcium rich foods intake, as their changes could impact in the result of the fortification strategy. [46] Population surveys should also assess health outcomes in the population, mainly bone health and hypertensive disorders. National and regional maternal mortality and its causes such as hypertensive disorders of pregnancy are reported annually by the Ministry of Health in Argentina. [47] To better monitor the impact of the fortification strategy, additional vital statistics could include incidence of pre-

https://doi.org/10.1017/S1368980024001228 Published online by Cambridge University Press

eclampsia, eclampsia, preterm birth as well as death and health loss from osteoporotic fractures.

Future research is needed to understand the possible interactions of fortification with multiple nutrients on iron and calcium status, and assess the magnitude of the interaction to inform multiple nutrient fortification. [48] Short-term studies and single meal studies have assessed that calcium from fortified foods or supplements inhibits the bioavailability of iron; however, this constraint is still under debate. [3, 4, 8] A recent systematic review suggests that this short-term effect does not translate to a long-term detriment of iron status. [49] Several food fortification programs around the world include iron and calcium simultaneously, like that of the United Kingdom which mandates the fortification of wheat flour with iron, calcium, and B-complex vitamins. [9]

Conclusion

Considering the magnitude of calcium intake inadequacy in Argentina and the widespread intake of wheat flour, calcium fortified flour could be further explored to improve calcium intake. Subnational simulations could be performed to identify groups that might not be reached by this strategy. As previous experiences have shown cost-effectiveness of wheat flour fortification with calcium in some countries, this strategy could be explored in Argentina, a country with high prevalence of low calcium intake and high wheat flour consumption. The analysis presented here could be used to advocate for a strategy to fortify wheat flour.

https://doi.org/10.1017/S1368980024001228 Published online by Cambridge University Press

References

[1] Shkembi B, Huppertz T. Calcium Absorption from Food Products: Food Matrix Effects. *Nutrients* 2021; 14: 180.

[2] Matikainen N, Pekkarinen T, Ryhänen EM, et al. Physiology of Calcium Homeostasis. *Endocrinol Metab Clin North Am* 2021; 50: 575–590.

[3] Cormick G, Belizán JM. Calcium Intake and Health. *Nutrients* 2019; 11: 1606.

[4] Allen L, Benoist B de, Dary O, et al. Guidelines on Food Fortification With Micronutrients. *Who, Fao Un* 2006; 341.

[5] Institute of Medicine. *DRI Dietary Reference Intakes Calcium Vitamin D*. 2011. Epub ahead of print 2011. DOI: 10.1111/j.1753-4887.2004.tb00011.x.

[6] Kumssa DB, Joy EJM, Ander EL, et al. Dietary calcium and zinc deficiency risks are decreasing but remain prevalent. *Sci Rep*; 5. Epub ahead of print 2015. DOI: 10.1038/srep10974.

[7] Balk EM, Adam GP, Langberg VN, et al. Global dietary calcium intake among adults: a systematic review. *Osteoporos Int* 2017; 28: 3315–3324.

[8] Bourassa MW, Abrams SA, Belizán JM, et al. Interventions to improve calcium intake through foods in populations with low intake. *Ann N Y Acad Sci* 2022; 1511: 40–58.

[9] Palacios C, Cormick G, Hofmeyr GJ, et al. Calcium-fortified foods in public health programs: considerations for implementation. *Ann N Y Acad Sci* 2021; 1485: 3–21.

[10] Gomes F, Ashorn P, Askari S, et al. Calcium supplementation for the prevention of hypertensive disorders of pregnancy: current evidence and programmatic considerations. *Ann N Y Acad Sci* 2022; 1510: 52–67.

[11] Karrar SA, Hong PL. *Preeclampsia*, http://www.ncbi.nlm.nih.gov/pubmed/34033373 (2022).

[12] Belizán JM, Gibbons L, Cormick G. Maternal mortality reduction: a need to focus actions on the prevention of hypertensive disorders of pregnancy. *Int J Equity Health* 2021; 20: 1–6.

[13] Kinshella MW, Sarr C, Sandhu A, et al. Calcium for pre-eclampsia prevention: a systematic review and network meta-analysis to guide personalised antenatal care. *BJOG An Int J Obstet Gynaecol*. Epub ahead of print 20 May 2022. DOI: 10.1111/1471-0528.17222.

[14] UNICEF. *World Bank Group and the United Nations Population Divisionv. Vol. Trends in Maternal Mortality 2000 to 2017: Estimates by WHO. 2. Washington, D.C:*

World Bank Group. Geneva, https://www.who.int/reproductivehealth/publications/maternal-mortality-2000-2017/en/ (2019).

[15] Knight F, Ferguson EL, Rana ZH, et al. Including calcium-fortified water or flour in modeled diets based on local foods could improve calcium intake for women, adolescent girls, and young children in Bangladesh, Uganda, and Guatemala. *Ann N Y Acad Sci* 2023; 1526: 84–98.

[16] *WHO recommendation: Calcium supplementation during pregnancy for the prevention of pre-eclampsia and its complications*. Geneva. Epub ahead of print 2020. DOI: CC BY-NC-SA 3.0 IGO.

[17] Cormick G, Betrán AP, Metz F, et al. Regulatory and policy-related aspects of calcium fortification of foods. implications for implementing national strategies of calcium fortification. *Nutrients* 2020; 12: 1022.

[18] Cormick G, Betran AP, Romero IB, et al. Impact of flour fortification with calcium on calcium intake: a simulation study in seven countries. *Ann N Y Acad Sci* 2021; nyas.14550.

[19] Cormick G, Gibbons L, Belizán JM. Impact of water fortification with calcium on calcium intake in different countries: a simulation study. *Public Health Nutr* 2022; 25: 344–357.

[20] Johnson-Down L, L'Abbé MR, Lee NS, et al. Appropriate Calcium Fortification of the Food Supply Presents a Challenge. *J Nutr* 2003; 133: 2232–2238.

[21] Cormick G, Romero IB, Matamoros N, et al. Calcium concentration of drinking water to improve calcium intake: A simulation study. *Ann N Y Acad Sci* 2023; 1524: 97–104.

[22] Ministerio de Salud de la Nación Argentina. Base de datos de la 2° Encuesta Nacional de Nutrición y Salud (ENNyS2) 2018-2019, http://datos.salud.gob.ar/dataset/ennys2 (2021).

[23] Ministerio de Salud de la Nación Argentina. Sistema de Análisis de Registro de Alimentos (SARA), https://datos.dinami.gov.ar/sara/ (2018).

[24] U.S. Department of Agriculture, Agricultural Research Service. USDA National Nutrient Database for Standard Reference, Release 24. *Database* 2011; 150.

[25] Universidad Nacional de Luján. Tabla de Composición de Alimentos de la Unlu. *2010*, http://www.argenfoods.unlu.edu.ar/Tablas/Tabla.htm.

[26] Public Health England. Composition of foods integrated dataset (CoFID) - Publications - GOV.UK. *online*.

https://doi.org/10.1017/S1368980024001228 Published online by Cambridge University Press

[27] Technology ISU of S and. Software for intake distribution estimation; intake monitoring assessment and planning program (IMAPP), http://www.side.stat.iastate.edu.

[28] Government of UK. The Bread and Flour Regulations 1998. 1998; 141: 1–10.

[29] (EFSA) EFSA. Scientific Opinion on Dietary Reference Values for calcium. *EFSA J* 2015; 13: 1–82.

[30] Fulgoni VL, Keast DR, Bailey RL, et al. Foods, Fortificants, and Supplements: Where Do Americans Get Their Nutrients? *J Nutr*. Epub ahead of print 2011. DOI: 10.3945/jn.111.142257.

[31] Scientific Opinion on the Tolerable Upper Intake Level of calcium. *EFSA J*; 10. Epub ahead of print July 2012. DOI: 10.2903/j.efsa.2012.2814.

[32] Ministerio de Salud de la Nacion. *Manual del Nutricionista. ENNyS 2*. Ciudad Autónoma de Buenos Aires, 2022.

[33] Wallace TC, McBurney M, Fulgoni VL. Multivitamin/Mineral Supplement Contribution to Micronutrient Intakes in the United States, 2007-2010. *J Am Coll Nutr*; 33. Epub ahead of print 2014. DOI: 10.1080/07315724.2013.846806.

[34] Hoy MK, Goldman JD. Calcium Intake of the U.S. Population, WWEIA/NHANES 2009-2010. *What We Eat Am NHANES 2009-2010*.

[35] Scientific Advisory Committee on Nutrition. Nutritional implications of repealing the UK bread and flour regulations. 2012; 1–30.

[36] Sandmann A, Amling M, Barvencik F, et al. Economic evaluation of vitamin D and calcium food fortification for fracture prevention in Germany. *Public Health Nutr* 2017; 20: 1874–1883.

[37] Olson R, Gavin-Smith B, Ferraboschi C, et al. Food Fortification: The Advantages, Disadvantages and Lessons from Sight and Life Programs. *Nutrients* 2021; 13: 1118.

[38] Marks KJ, Luthringer CL, Ruth LJ, et al. Review of Grain Fortification Legislation, Standards, and Monitoring Documents. *Glob Heal Sci Pract* 2018; 6: 356–371.

[39] ARGENTINA HCDLN. Ley 25.630, https://www.argentina.gob.ar/normativa/nacional/ley-25630-77088/texto (2022).

[40] Sargiotto C, Bidondo MP, Liascovich R, et al. Descriptive study on neural tube defects in Argentina. *Birth Defects Res Part A Clin Mol Teratol* 2015; 103: 509–516.

[41] Zapata ME, Rovirosa A, Carmuega E. Urbano y rural: diferencias en la alimentación de los hogares argentinos según nivel de ingreso y área de residencia. *Salud Colect* 2019; 15: e2201.

https://doi.org/10.1017/S1368980024001228 Published online by Cambridge University Press

[42] Affairs D for EF& R. Bread and Flour Regulations 1998 Consultation, www.defra.gov.ukwww.defra.gov.uk/corporate/consult/open (2013).

[43] Osler M, Heitmann BL. Food patterns, flour fortification, and intakes of calcium and vitamin D: A longitudinal study of Danish adults. *J Epidemiol Community Health*. Epub ahead of print 1998. DOI: 10.1136/jech.52.3.161.

[44] *World Food and Agriculture – Statistical Yearbook 2022*. FAO. Epub ahead of print 12 December 2022. DOI: 10.4060/cc2211en.

[45] BOLSA DE COMERCIO DE ROSARIO.

[46] Amending the Bread and Flour Regulations 1998 and the Bread and Flour Regulations (Northern Ireland) 1998.

[47] Ministerio de Salud de la Nación. Indicadores Básicos. Argentina 2022.

[48] Ahmed A, Anjum FM, Randhawa MA, et al. Effect of multiple fortification on the bioavailability of minerals in wheat meal bread. *J Food Sci Technol* 2012; 49: 737–744.

[49] Abioye AI, Okuneye TA, Odesanya AMO, et al. Calcium Intake and Iron Status in Human Studies: A Systematic Review and Dose-Response Meta-Analysis of Randomized Trials and Crossover Studies. *J Nutr* 2021; 151: 1084–1101.

https://doi.org/10.1017/S1368980024001228 Published online by Cambridge University Press

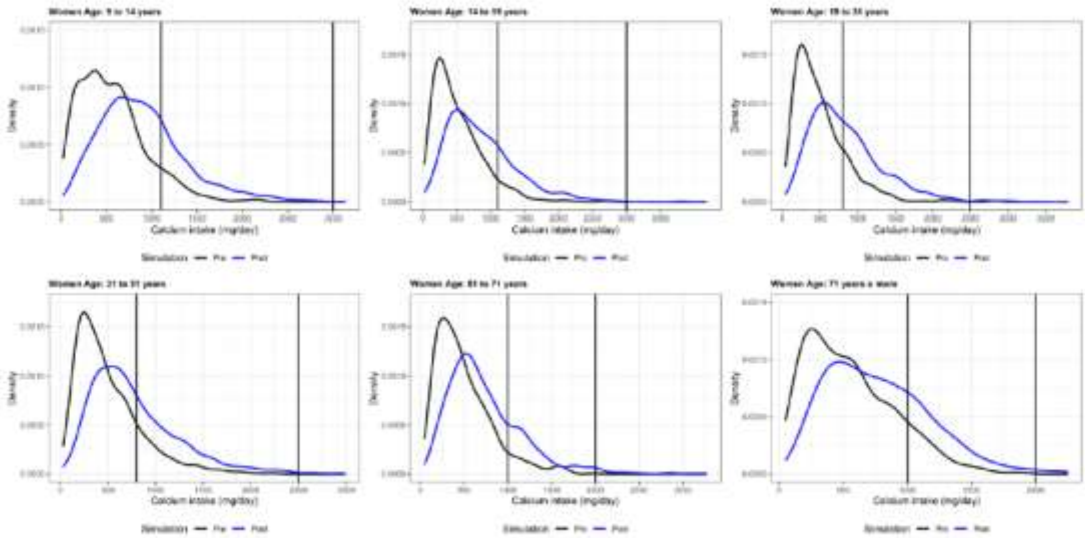

Figure 1: Distribution of calcium intake in women after simulating a fortification with 400 mg of calcium per 100 g of wheat flour

https://doi.org/10.1017/S1368980024001228 Published online by Cambridge University Press

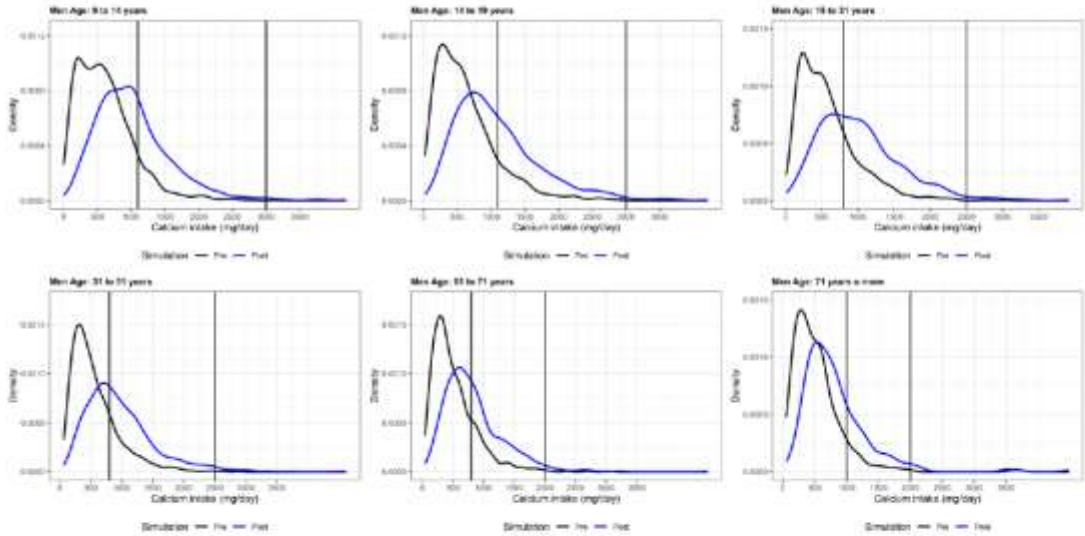

Figure 2: Distribution of calcium intake in men after simulating a fortification with 400 mg of calcium per 100 g of wheat flour

https://doi.org/10.1017/S1368980024001228 Published online by Cambridge University Press

Table 1: *Dietary reference values, white wheat flour and calcium intake, percentage of the population below the estimated average requirement (EAR) and percentage of the population over the recommended upper intake level (UL) for calcium intake before and after the simulation of wheat flour fortification with 200, 400 and 500 mg of calcium per 100 g of wheat flour using dietary intake from the ENNyS2 carried out in Argentina (2018-2019)*

	N (repeated recall)	EAR	UL	White Flour Intake			Calcium intake before simulations				Calcium intake after simulations														
											Fortified with 200 mg in 100 g of flour					Fortified with 400 mg in 100 g of flour					Fortified with 500 mg in 100 g of flour				
Population group				%	Mean (g)	S.D.	Mean (mg)	SD	<EAR * (%)	>UL ** (%)	Mean (mg)	SD	<EAR (%)	>UL (%)	% ***Reduction	Mean (mg)	SD	<EAR (%)	>UL (%)	% ***Reduction	Mean (mg)	SD	<EAR (%)	>UL (%)	% *Reduction
Children																									
1 <= Age < 4	4055 (924)	400	2500	95.6	42.2	36.3	722	379	20.3	0.1	808	383	12.4	0.1	-7.9	894	394	7.5	0.2	-12.8	937	402	5.8	0.2	-14.5
4 <= Age	2622	64	25	98.	77.1	52.	652	288	53.2	0.0	806	294	31.0	0.0	-22.2	961	316	14.6	0.0	-38.6	103	329	9.6	0.0	-43.6

https://doi.org/10.1017/S1368980024001228 Published online by Cambridge University Press

< 9	(575)	0	00	9		5															8				
Boys and adult Males																									
9 <= Age < 14	1283 (300)	1100	3000	99.0	103.1	69.8	606	285	94.4	0.0	812	316	82.8	0.0	-11.6	1019	358	63.1	0.0	-31.3	1124	384	52.1	0,0	-42.3
14 <= Age < 19	1039 (241)	1100	3000	98.9	114.1	80.1	618	307	92.5	0.0	851	329	79.9	0.0	-12.6	1084	375	56.8	0.0	-35.7	1200	402	44.7	0.0	-47.8
19 <= Age < 31	884 (195)	800	2500	97.7	110.0	74.3	578	286	80.6	0.0	802	331	55.5	0.0	-25.1	1027	388	30.5	0.2	-50.1	1139	421	21.9	0.5	-58.7
31 <= Age < 51	1069 (234)	800	2500	97.2	101.8	77.2	560	197	88.4	0.0	763	210	61.6	0.0	-26.8	965	258	27.8	0.0	-60.6	1066	287	17.5	0.0	-70.9
51 <= Age < 71	781 (169)	800	2000	96.3	79.6	56.3	511	245	88.1	0.0	672	258	73.8	0.0	-14.3	833	281	50.7	0.2	-37.4	913	296	39.1	0.3	-49.0
71 <= Age	243 (52)	1000	2000	97.5	67.9	50.8	545	305	92.2	0.3	686	326	85,7	0.5	-6.5	825	353	74.7	0.9	-17.5	895	372	67.9	1.3	-24.3

https://doi.org/10.1017/S1368980024001228 Published online by Cambridge University Press

Girls and not pregnant adult females																									
9 <= Age < 14	1153 (279)	1100	3000	99.1	83.9	57.5	558	243	97.3	0.0	729	256	91.6	0.0	-5.7	900	286	77.6	0.0	-19.7	984	304	68.2	0.0	-29.1
14 <= Age < 19	1071 (234)	1100	3000	97.1	87.3	64.8	524	229	98.0	0.0	701	261	79.9	0.0	-18.1	877	312	78.4	0.0	-19.6	966	342	69.2	0.0	-28.8
19 <= Age < 31	1189 (255)	800	2500	97.3	85.1	61.0	502	210	91.0	0.0	675	244	55.5	0.0	-35.5	848	274	47.8	0.2	-43.2	935	298	35.9	0.0	-55.1
31 <= Age < 51	1561 (366)	800	2500	95.9	68.7	54.7	502	231	89.4	0.0	644	249	61.6	0.0	-27.8	785	277	57.6	0.0	-31.8	856	292	47.4	0.0	-42.0
51 <= Age < 71	993 (221)	1000	2000	96.8	59.4	46.4	500	230	96.5	0.0	622	250	73.8	0.0	-22.7	743	277	83.7	0.1	-12.8	804	294	77.8	0.2	-18.7
71 <= Age	365 (94)	1000	2000	97.8	55.4	40.7	557	265	93.3	0.0	666	274	85.7	0.5	-7.6	776	292	79.1	0.0	-14.2	831	305	73.6	0.2	-19.7

https://doi.org/10.1017/S1368980024001228 Published online by Cambridge University Press

Table 2: *White wheat flour and calcium intake by country region, National Nutrition and Health Survey (ENNyS 2) carried out in Argentina (2018-2019)*

	GBA			Centro			NEA			NOA			Cuyo			Patagonia		
Population group	At least some flour Intake, n/N (%)	Flour Intake, Mean (SD)	Calcium Intake, Mean (SD)	At least some flour Intake, n/N (%)	Flour Intake, Mean (SD)	Calcium Intake, Mean (SD)	At least some flour Intake, n/N (%)	Flour Intake, Mean (SD)	Calcium Intake, Mean (SD)	At least some flour Intake, n/N (%)	Flour Intake, Mean (SD)	Calcium Intake, Mean (SD)	At least some flour Intake, n/N (%)	Flour Intake, Mean (SD)	Calcium Intake, Mean (SD)	At least some flour Intake, n/N (%)	Flour Intake, Mean (SD)	Calcium Intake, Mean (SD)
1 <= Age	586/61	47	686	678/69	47	755	646/69	46	774	706/75	37	728	639/67	36	700	584/61	40 (31)	641
4 <= Age	386/39	73	670	475/47	84	691	386/39	90	734	474/48	72	576	426/42	69	594	437/44	77 (58)	641
Male: 9	177/17	98	654	208/21	116	735	207/21	121	641	236/23	102	494	222/22	92	549	217/22	91 (63)	632
Male: 14	138/14	116	743	167/17	118	765	188/19	135	578	194/19	109	527	205/20	108	589	133/13	95 (63)	592
Male: 19	105/10	113	601	123/12	104	728	173/17	127	628	182/18	103	525	167/17	110	492	110/11	100 (72)	531

https://doi.org/10.1017/S1368980024001228 Published online by Cambridge University Press

	GBA			Centro			NEA			NOA			Cuyo			Patagonia		
Population group	At least some flour Intake, n/N (%)	Flour Intake, Mean (SD)	Calcium Intake, Mean (SD)	At least some flour Intake, n/N (%)	Flour Intake, Mean (SD)	Calcium Intake, Mean (SD)	At least some flour Intake, n/N (%)	Flour Intake, Mean (SD)	Calcium Intake, Mean (SD)	At least some flour Intake, n/N (%)	Flour Intake, Mean (SD)	Calcium Intake, Mean (SD)	At least some flour Intake, n/N (%)	Flour Intake, Mean (SD)	Calcium Intake, Mean (SD)	At least some flour Intake, n/N (%)	Flour Intake, Mean (SD)	Calcium Intake, Mean (SD)
Male: 31	139/15	86	626	180/18	109	630	153/15	126	562	188/19	103	491	206/21	92	495	163/17	96 (67)	597
Male: 5	187/91	75	653	133/14	79	607	116/12	92	524	123/12	87	428	170/17	76	439	120/12	69 (48)	514
Male: 7	129/29	66	483	54/54	63	652	41/45	80	545	29/29	90	410	41/42	58	486	42/44	58 (54)	562
Female: 9	149/15	79	571	221/22	89	659	172/17	103	596	206/21	77	472	205/20	76	494	186/18	80 (55)	573
Female:	125/12	91	605	172/18	91	582	184/19	95	520	199/20	91	450	183/19	80	464	166/17	75 (58)	520
Female:	128/13	85	493	175/17	88	603	207/21	96	535	241/24	89	445	226/23	77	430	169/17	75 (53)	507

https://doi.org/10.1017/S1368980024001228 Published online by Cambridge University Press

	GBA			Centro			NEA			NOA			Cuyo			Patagonia		
Population group	At least some flour Intake, n/N (%)	Flour Intake, Mean (SD)	Calcium Intake, Mean (SD)	At least some flour Intake, n/N (%)	Flour Intake, Mean (SD)	Calcium Intake, Mean (SD)	At least some flour Intake, n/N (%)	Flour Intake, Mean (SD)	Calcium Intake, Mean (SD)	At least some flour Intake, n/N (%)	Flour Intake, Mean (SD)	Calcium Intake, Mean (SD)	At least some flour Intake, n/N (%)	Flour Intake, Mean (SD)	Calcium Intake, Mean (SD)	At least some flour Intake, n/N (%)	Flour Intake, Mean (SD)	Calcium Intake, Mean (SD)
Female:	186/19	67	563	238/25	73	578	243/25	74	521	270/28	73	428	274/28	64	435	276/29	62 (48)	513
Female:	121/12	55	588	186/19	58	505	152/16	65	536	184/18	61	421	156/16	58	439	157/16	59 (40)	519
Female:	37/38	47	580	82/83	57	596	67/69	62	630	53/56	63	441	64/64	55	507	53/55	43 (32)	523

GBA: Greater Buenos Aires; NEA: Argentine Northeast region; NOA: Argentine Northwest region

https://doi.org/10.1017/S1368980024001228 Published online by Cambridge University Press