The European lactase persistence genotype determines the lactase persistence state and correlates with gastrointestinal symptoms in the Hispanic and Amerindian Chilean population: a case-control and population-based study

Eugenia Morales, Lorena Azocar, Ximena Maul, Claudio Perez, Jose Chianale, Juan Francisco Miquel

ABSTRACT

Background: The lactase persistent (LP) or lactase non-persistent (LNP) state in European adults is genetically determined by a single nucleotide polymorphism (SNP) located 13.9 kb upstream of the lactase (LCT) gene, known as LCT C>T-13910 (rs4988235). The LNP condition leads to an inability to digest the milk sugar lactose leading to gastrointestinal symptoms and can affect nutrient and calcium intake in certain populations.

Objectives: The authors studied a group of 51 Chilean patients to assess whether this SNP influences the LP/LNP state in this population, and determined the prevalence of LCT C>T-13910 genotypes in a representative sample of 216 Hispanics and 43 Amerindians with correlation to digestive symptoms.

Design: Case-control study done in Chilean patients with clinical suspicion of LNP that were assessed using clinical survey, hydrogen breath test (HBT) and SNP genotyping. The population sample of Hispanics and Amerindians was assessed by clinical survey, hydrogen breath test and lactose tolerance in a group of patients with clinical suspicion of lactase non-persistence in our population.

Results: Of the 51 patients with clinical suspicion of LNP, 29 were HBT-positive. The CC genotype (LNP) was present in 89.7% of the patients with positive HBT and in only 4.7% of those with negative HBT. The prevalence of the CC genotype was 56.9% in the Hispanic population and 88.3% in Amerindians, and was associated with a higher self-reported clinical intolerance to ingestion of dairy products.

Conclusion: The LP/LNP state is determined by the LCT C>T-13910 Variant in Chileans. This variant predicts digestive symptoms associated with the ingestion of lactose and is a good tool for the diagnosis of primary adult hypolactasia. The LCT T-13910 allele is rare in the Amerindian population and is suggestive of European ancestry in this contemporary population.

ARTICLE SUMMARY

Article focus

The aims of the present study were three questions; (1) to determine if the European variant C/T-13910 determined the lactose-persistent and lactose non-persistent state in the adult Chilean Hispanic and Amerindian population; (2) to determine if there is any correlation between the C/T-13910 genotyping and the hydrogen breath test for diagnosis of lactase non-persistence in our population; (3) to determine for the first time in a Latin American population the prevalence of the lactose non-persistence genotype (CC) and its correlation with digestive symptoms and ingestion of dairy products.

Key messages

We demonstrate for the first time that the European lactase persistence −13910T variant determines lactase persistence in the Chilean Hispanic and Amerindian population.

We demonstrate a strong correlation between the C-13910>T genotype with the hydrogen breath test and lactose tolerance in a group of patients with clinical suspicion of lactose intolerance.

In a representative sample of the Hispanic Chilean population (Mestizos) and in Amerindians, we observed a high prevalence of the lactase non-persistence genotype (CC) with a clear gradient between ethnic groups (56% and 88%, respectively). Interestingly, the C-13910>T genotype was significantly associated with digestive symptoms and self-reporting intolerance to ingestion of dairy products. This could explain the observed low consumption of dairy products (30 l milk/person/year) in our population.
European lactase genotype determines lactase phenotype in Chilean population

Article summary

Strengths and limitations of this study
- This is the first study in Latin America to assess whether the European LP–13910T variant determines lactase persistence in the Chilean Hispanic and Amerindian general population.
- Our results may be of clinical and epidemiological relevance, not only for the Chilean population, but also for other Hispanic and Amerindian populations of the Americas of a similar genetic background. The fact that the lactase non-persistence state is an inherited frequent condition in Mestizo and Amerindians should be considered when developing public programmes that encourage consumption of dairy products, and should be a stimulus for the food industry to develop new and high-quality lactose-free dairy products in these regions.
- We randomly selected a representative sample of the Hispanic Chilean population (n = 216) and Amerindians (n = 43), and performed the genotyping of LCT C>T_{13910}. We observed a high prevalence of the lactose non-persistence genotype (CC) with a clear gradient between both ethnic groups (56% and 88%, respectively) that correlates with digestive symptoms and self-reporting intolerance to ingestion of dairy products.
- Non-randomised recruitment of the 51 patients with suspicion of lactose intolerance could induce selection bias.
- A small number of patients with suspicion of lactose intolerance (n = 51).
- Semi-quantitative food-frequency questionnaire with a 24 h dietary recall obtained in a subgroup of the Hispanics and performed years before the genetic analysis.

INTRODUCTION

Lactose, the main sugar in milk, must be hydrolysed by lactase-phlorizin hydrolase into glucose and galactose for absorption. Intestinal activity of the lactase enzyme (LCT) (MIM 603202) decreases in all mammals after weaning, resulting in poor lactose absorption. In humans, this condition is termed ‘lactase non-persistence’ (LNP), ‘adult type hypolactasia’ (MIM 223100) and is estimated to occur in approximately 65% of the contemporary world population. LNP can generate intolerance to the ingestion of dairy products with the development of abdominal and systemic symptoms that lead to medical consultations and evaluations. In contrast, lactase-persistent (LP) individuals remain tolerant of lactose and maintain high levels of LCT expression throughout adult life. The prevalence of the LP phenotype, which is an autosomal dominant condition (MIM 223100), is reported to vary between 0 and 95% in different populations, but is unknown in contemporary Latin American populations.

The recent discovery of single nucleotide polymorphisms (SNPs) that determine the LP state in humans, both in Europe and among some pastoral populations in Africa, has generated growing interest in the study of this condition. The appearance of these SNPs seems to have occurred on more than one occasion in human evolution between 1500 and 12 000 years ago in northern Europe and among some nomadic populations of Asia and Africa. The SNP known as LCT C>T_{13910} (rs4988235) is located 13.9 kb upstream of the LCT gene in the 13th intron of an adjacent gene (MCM6). The T allele of this SNP correlates with the LP state in European populations, and individuals with this allele have higher levels of LCT transcripts in enterocytes compared with individuals who carry the C allele. In vitro studies show that cells transfected with the LCT T_{13910} variant show increased activity of the LCT promoter. Another SNP known as LCT G>A_{22018} shows some association with the LP/LNP phenotype, and while it does not appear to be the causal variant, it is present in a block of linkage disequilibrium with little evidence of recombinination in this region of the genome.

In clinical practice, the LNP state is relevant because it can generate malabsorption and intolerance of lactose, with the development of clinical symptoms such as abdominal pain and distension, diarrhoea, bloating, nausea and vomiting. A significant percentage of patients do not relate these symptoms to ingestion of dairy products, and the recurring nature of the symptoms can lead to misdiagnosis of chronic diarrhoea, irritable bowel syndrome, celiac illness or other clinical conditions. The diagnosis of LNP is often based on clinical suspicion and the favourable response to a lactose-restricted diet.

The most widely used diagnostic test of poor lactose absorption is the hydrogen breath test (HBT). Nevertheless, this test has practical limits, and its sensitivity and specificity vary between 69 and 100% and between 89 and 100%, respectively, compared with measurement of LCT activity in intestinal biopsies. Additionally, there is a false-negative rate of 11–30% and a false-positive rate of up to 57% using this test. Using SNP genotyping in patients with suspected LNP may therefore aid in proper diagnosis. The only epidemiological study of adult hypolactasia in a Chilean population was performed more than three decades ago and suggested that the prevalence of LNP was 56% and 75% for the paediatric and adult populations, respectively. Our objectives were to determine the influence of the LCT C>T_{13910} SNP on the LP/LNP state in the Chilean population and to determine the population prevalence of the SNP genotypes in a representative Hispanic and Amerindian population with comparison of the genotypes to clinical symptoms related to ingestion of dairy products.

SUBJECTS AND METHODS

Patients with clinical suspicion of LNP

In 2006, 51 patients were enrolled in a prospective study after being referred to the Gastroenterological Department of the Clinical Hospital at the Pontificia Universidad Catolica de Chile because of symptoms suggestive of LNP. A pre-coded survey was obtained from all patients to obtain demographic, anthropometric, familial and clinical data, including any symptoms experienced during the diagnostic HBT such as abdominal pain, diarrhoea, bloating, nausea and vomiting. A 5 ml...
ethylenediaminetetraacetic acid blood sample was obtained to extract DNA. Serum levels of immunoglobulin A and tissue antitransglutaminase antibodies (hu (TG ELISA, IMMCO Diagnostics, Buffalo, NY) were quantified in all the patients to rule out the existence of celiac disease. This study was approved by the Ethics Committee of the Faculty of Medicine, Pontificia Universidad Católica de Chile, and all patients signed a written informed consent form prior to the study.

**HBT for diagnosis of LNP**

Patients were instructed to maintain a low-fibre diet without lactose for 48 h prior to the day of the examination. After 12 h of fasting, a baseline concentration of H$_2$ in exhaled breath was determined using a Quintron microLyzer (QuinTron Instrument Company, Milwaukee, Wisconsin). Subjects then ingested 25 g of lactose, and the H$_2$ concentration in breath was quantified every 20 min for a maximum of 4 h. Individuals were considered LNP with an increase in H$_2$ concentration 20 ppm above the base value.$^{17}$

**Population study**

A representative sample of 216 unrelated Hispanics and 43 unrelated Amerindians were randomly selected from an initial sample of 1581 Hispanics and 120 Amerindians (Mapuches, the Chilean native population) which were collected between 1993 and 2000 as described previously.$^{28}$ By using an Amerindian Admixture Index based on ABO blood-group distribution, we have previously demonstrated in these cohorts a 40% and 80% Amerindian ancestry in the Hispanic and Mapuche population, respectively. Furthermore, 88% of Hispanics and 100% of Mapuches shared ancestral Amerindian mtDNA polymorphism.$^{28}$ These results were in accordance with the biparental founder origin of the mixed Chilean population, which could be similar to other Hispanic populations from America.$^{30-32}$

The sample size was selected by estimating an expected prevalence of the LCT-13910CC genotype to be at least 50% in the Hispanic population and 80% in the Amerindians, with an error of 5% and a level of confidence of 80%. All study subjects provided a DNA sample and a medical survey that provided anthropometric and clinical data including information about diarrhoea, abdominal pain or bloating in response to ingestion of dairy products.$^{28}$

Furthermore, a subgroup of the Hispanic subjects provided a semiquantitative food-frequency questionnaire with a 24 h dietary recall. From these data, specific energy and nutrient ingestion from dairy products was estimated using the Datadiet programme.$^{28}$

For all subjects, the occurrences of digestive symptoms in response to consumption of lactose were correlated to SNP genotyping results.

**Genotyping of LCT C$^*$T$^{*}<_{13910}$ and LCT G$^*$A$^{*}<_{22018}$ SNPs**

SNP genotyping was performed using PCR-restriction fragment length polymorphism (RFLP) methods$^{34}$ (GenBank reference sequence NM_005915:4). Briefly, genomic DNA was extracted from 300 μl of blood according to the manufacturer’s instructions (Wizard SV Genomic DNA Purification System; Promega, Madison, Wisconsin), and the regions surrounding the SNPs were amplified through PCR using primers (F) 5′-GGA TGC ACT GCT GTG ATG AG-3′ and (R) 5′-CCC ACT GAC GTA TCC TCG TG-3′ for the LCT C$^*$T$^{*}<_{13910}$ and (F) 5′-AAC AGG CAC GTG GAG GAG TT-3′ and (R) 5′-CCC ACC TCA GCC TCT TGA GT-3′ for LCT G$^*$A$^{*}<_{22018}$. In both cases, the amplified products were of 448 bp. The PCR reactions and RFLP assays for the analysis of both genetic variants were carried out as described previously.$^{34}$ Briefly, the amplified product for the LCT C$^*$T$^{*}<_{13910}$ SNP was digested with BsmFI, generating two fragments of 351 and 97 bp in the presence of the CC genotype, and three fragments of 253, 98 and 97 bp in the presence of the TT genotype (figure 1). For the LCT G$^*$A$^{*}<_{22018}$ SNP, the PCR product was digested with HhaI, generating two fragments of 284 and 184 bp in the presence of the GG genotype and one undigested fragment of 448 bp in the presence of the A/A genotype. The amplified and digested PCR products were separated by electrophoresis on 2% agar gels in 1X TAE buffer stained with ethidium bromide. Genotyping confirmation was carried out on 35 samples by direct sequencing of the 448 bp amplified fragments (models

![Figure 1](http://bmjopen.bmj.com/)

**Figure 1** Restriction fragment length polymorphism (RFLP) and sequence analysis of a 448 bp region of MCM6 intron 13 containing the lactase (LCT) C$^*$T$^{*}<_{13910}$ single nucleotide polymorphism. Upper panel: RFLP analysis of the 448 bp amplicon digested with BsmFI. Left lane, 50 bp DNA ladder. Right lane, undigested PCR amplicon. Centre lanes, digested products from representative individuals having the three different SNP genotypes. The ancestral LCT-13910CC genotype results in two bands of 350 bp and 110 bp; the LCT-13910CT genotype results in three bands of 350 bp, 240 bp and 110 bp; the LCT-13910TT genotype results in two bands of 240 bp and 110 bp. Lower panel: representative sequence tracings showing confirmation of RFLP data. A direct sequence analysis was performed on 35 of the 51 samples.
European lactase genotype determines lactase phenotype in Chilean population

ABI-310 and ABI-3100 automated DNA sequencers, Applied Biosystems, Foster City, California) (figure 1). There was complete concordance between the PCR-RFLP analysis and the sequencing in all cases.

Statistical analysis
Means and standard deviations were used to describe numeric variables. The variables of categorical types were given as a number and a percentage. Comparisons of continuous variables were performed using the Student t test for independent samples. Comparisons of categorical variables were carried out using the $\chi^2$ test. Using the HBT breath test as diagnostic for LNP, an analysis of the sensitivity and specificity of the genetic test as an alternative diagnostic test was carried out. Differences were considered significant when $p<0.05$.

RESULTS

HBT and SNP genotyping
Fifty-one patients with clinical suspicion of LNP (44 women and 7 men, age 14–79 years) were included in the study. Twenty-nine patients (56.8%) had a positive HBT, and 22 were negative (43.2%) (table 1). There were no significant differences in the distribution by sex and age between the two groups. There was a positive correlation between the HBT results and digestive symptoms reported during the test: 82% of the patients with positive HBT had symptoms associated with the lactose load, such as bloating, abdominal pain and diarrhoea (79%, 58% and 20%, respectively). In contrast, only 27% of the patients with negative HBT presented symptoms after ingesting lactose ($p<0.001$). Additionally, 76% of patients with positive HBT indicated a personal and/or family history of functional digestive disorders, compared with 36% of those with negative HBT ($p<0.001$).

The LCTC $\text{T}_{-13910}$ SNP genotyping results for the 51 patients are shown in table 1. Of the 29 patients with positive HBT, 26 (89.7%) had the LCT-13910CC genotype (the LNP genotype), and three (10.3%) had the LCT-13910CT genotype and were therefore phenotypically LNP but genotypically LP. However, two of these three patients experienced bloating and diarrhea during the HBT, which suggests malabsorption of lactose. Of the 22 patients who had a negative HBT, 19 were LCT-13910CT, two were LCT-13910TT, and a single 16-year-old patient had the LNP LCT-13910CC genotype (table 1). However, this patient experienced abdominal pain during the HBT. Subsequent evaluation of this patient with a lactulose HBT (10 g load) revealed that this patient was not a non-producer of hydrogen. A single patient with LNP genotype and positive HBT had high levels of anti-tTG (27 EU/ml), which suggests the possibility of coexistence of LNP and celiac disease. All the patients showed normal levels of serum IgA (data not shown).

There was a complete genotypic correlation between the LCTC $\text{T}_{-13910}$ and the LCTG $\text{A}_{-22018}$ SNPs, such that any subject homozygous or heterozygous for one SNP was at the same time homozygous or heterozygous for the other SNP (data not shown). Furthermore, there was a good correlation between the LCTC $\text{T}_{-13910}$ SNP findings and the HBT test results (table 2). Genotyping results were confirmed by sequencing for 35 of the 51 samples (figure 2). Interestingly, one of the three discordant patients with LNP phenotype but LP genotype was also heterozygous at a second location not previously described in the literature, LCTG $\text{A}_{-13937}$.

Population study
We collected DNA samples and medical surveys from 216 unrelated Hispanic individuals and 43 unrelated Amerindians. The survey information is summarised in table 3. The two groups were similar in age, with a higher representation of females among the Amerindians. The Amerindian cohort reported a higher frequency of intolerance to ingesting dairy products and recurring diarrhoea, while both groups reported recurring abdominal bloating with equal frequency.

The genotype and allele frequencies for the LCTC $\text{T}_{-13910}$ SNP are shown in table 3. As was found in the study group of 51 Chilean patients with suspected lactase intolerance, there was complete concordance between the genotypes of the LCTC $\text{T}_{-13910}$ and LCTG $\text{A}_{-22018}$ SNPs in each individual (data not shown). The cohort of Amerindian individuals was in Hardy–Weinberg (HW) equilibrium (figure 2), but we observed a slightly higher-than-expected frequency of the T$\text{−13910}$ allele in the Hispanic population (deviation from HW equilibrium, $p<0.05$). Interestingly, this

| Table 1 Clinical and genetic characteristics of 51 Chilean patients having undergone a hydrogen breath test for suspected lactose non-persistence |
|-------------------------------------------------|-----------------|-----------------|-----------|
| | Hydrogen breath test-positive (n=29) | Hydrogen breath test-negative (n=22) | p Value |
|-------------------------------------------------|-----------------|-----------------|
| Female gender (%) | 82.7 | 86.3 | NS |
| Age (years) | 36±19 | 32±12 | NS |
| $N^o$ reporting gastrointestinal symptoms after lactose load | 24 (82%) | 6 (27%) | <0.001 |
| $N^o$ reporting family history of irritable bowel syndrome | 22 (76%) | 8 (36%) | <0.001 |
| Lactase-13910 CC genotype | 26 (89.6%) | 1 (4.5%) | <0.001 |
| Lactase-13910 CT/TT genotype | 3 (10.3%) | 21 (95.5%) | <0.001 |

deviation from HW equilibrium has also been observed in other mixed ethnicity groups. The prevalence of the ancestral LCT-13910CC genotype (the LNP genotype) was 56.9%, significantly lower than the prevalence of this genotype among the Amerindian individuals (88.3%). In turn, 41.7% of the Hispanics were LCT-13910CT genotype, compared with only 11.7% of the Amerindians. The LCT-13910TT genotype was found in only three Hispanic subjects. Allele frequencies for the LCTC>T-13910 SNP were significantly different between the two groups, with the T-13910 allele being very infrequent in Amerindians.

For the 216 Hispanic individuals studied, we were able to gather clinical and genetic data (table 3). Individuals with the LNP LCT-13910CC genotype were three times more likely to report intolerance to the ingestion of dairy products and recurring diarrhoea than those with LP genotypes (LCT-13910CT or LCT-13910TT). For 112 of these individuals, we collected complete nutritional information. The consumption of dairy products was in general very low, equivalent to an average of 30 l of fresh milk per year per person. However, the group of individuals with an LP genotype had a 38% higher consumption of dairy products than the group of individuals with the LNP genotype (38.4±67 vs 27.7±40 l milk/year, respectively), although this difference was not statistically significant.

**DISCUSSION**

The normal physiological decrease in lactase (LCT) production in the mammalian intestine following weaning is known as LNP and results in the inability to digest the milk sugar, lactose, which can cause gastrointestinal symptoms after ingestion of dairy products. The condition of lactase persistence (LP), found only in humans, allows the individual to continue to ingest and absorb lactose into adulthood. In European populations and some Afro-Arab pastoral groups, the LP condition has been shown to be due to SNPs found 13.9 kb upstream of the LCT gene and actually located within the 13th intron of the MCM6 gene. One of these SNPs, LCTC>T-13910 (rs4988235), appeared approximately 10 000 years ago in the human history and spread progressively from Northern Europe to the rest of the world owing to population migration and mixing, thereby increasing the state of LP in different populations. The original populations of the Americas and Asia were likely LNP. There is no evidence of the existence of American variants that might have generated the LP state in the pre-Columbian era. The T-13910 allele, which leads to the LP state, was likely introduced to the Americas by the migration of European carriers of this variant approximately 500 years ago and spread rapidly in the descending admixed Hispanic (Mestizo) populations of contemporary America, as is shown in this study as well as others.

Our study of a representative population of Chile consisting of Hispanic and Amerindian individuals showed the prevalence of the LNP state (LCT-13910CC genotype) to be 57% and 88%, respectively. It is interesting to note that this observed genotypic frequency is very similar to the Amerindian admixture index estimated by us in these same populations based on the distribution of ABO blood groups. This suggests that the analysis of the LCTC>T-13910 SNP in Latin American populations can be a good indicator of the degree of Amerindian or Caucasian inheritance.
In all Chilean patients genotyped in this study, the LCTG>A-22018 SNP genotype correlated completely with the genotype found for the LCTC>T-13910 SNP, a finding reported in many studies. This phenomenon can be explained by the fact that both SNPs are located within a highly conserved block of linkage disequilibrium of at least 500 kb and likely co-segregate.

According to HW equilibrium, in the group of 216 unrelated Hispanic individuals we observed a higher-than-expected frequency of the T-13910 allele. While this could be explained by selection bias or by a higher frequency of LP in the Spanish population that founded the Chilean colony, it could also be reflective of positive selection for LP allele carriers, as has been suggested for decades. Any evolutionary advantage conferred by the T-13910 allele may or may not be related to the consumption of dairy products. Indeed, it was reported that this allele confers protection not only against bone fractures but also against colon cancer.

The validity of using LCTC>T-13910 SNP genotyping for diagnosis of the LNP or LP state was evaluated in the group of 51 Chilean patients with suspected LNP. The HBT showed a high positive and negative predictive value, sensitivity and specificity compared with genetic testing (table 2). These results are similar to those recently reported by other groups and confirm the utility of the analysis of this SNP as a clinical test for the diagnosis of LP/LNP in the adult Chilean population. Only three patients (10.3%) with malabsorption of lactose shown by HBT were genetically LP (LCT-13910CT genotype). It was not possible to recall these three patients to carry out complementary studies to rule out other causes of lactose malabsorption—for example, intestinal parasitic infections such as Giardiasis, seronegative celiac disease or other conditions, as has been shown in other recent studies.

Interestingly, one of these patients was also heterozygous at an additional SNP not previously described, LCTG>A-13937. We do not know if this new variant can explain the phenotype—genotype discordance.

A recent study showed a high prevalence of celiac illness among patients with an initial diagnosis of LNP, suggesting that lactose intolerance can be the first manifestation of celiac illness; the authors recommend considering the existence of celiac illness in all patients with LNP before recommending a lactose-free diet for life. In our study of 51 patients with clinical suspicion of lactose intolerance, only one with LNP confirmed by HBP and SNP genotyping had positive anti-CTG (2% of the total) suggesting the coexistence of both conditions.

One 16-year-old patient had negative HBT yet had the LNP genotype. It is possible that this patient has not yet manifested the LNP phenotype and still maintains sufficient levels of intestinal lactase to digest a 25 g load. The age at which the LNP state is initiated varies among different populations and ethnic groups, starting as early as 1–8 years in black and Asian populations, and much later (20 years) in northern European populations. The age of initiation of the LNP state in Chilean individuals remains unknown.

Among the 51 Chilean patients with positive HBT and the LCT-13910CC genotype, significantly more report having relatives with functional digestive disorders than their HBT-negative counterparts, suggesting that the condition of LNP could be in part responsible for digestive symptoms. In our complete clinical, nutritional and genetic study of 112 Hispanic individuals, those with the LCT-13910CC genotype were significantly more likely to report lactose intolerance, despite very low (30 l milk/person/year) consumption of dairy products. This level is well below the WHO recommended level of 240 l of milk/person/year. Reasons for the low level of consumption are likely due to multiple causes including cost, preference and societal habits which are likely influenced by the existence of a high prevalence of LNP and lactose intolerant state within this population. It has been reported that the allele frequencies of the LCTC>T-13910 SNP within a population correlate with the tendency of that population to consume dairy products and ingest calcium. Both this study and one other show that the effective consumption of dairy products and calcium in Chile remains below international recommendations.
In summary, the LNP state continues to be predominant in the Chilean population. Epidemiologically, this may cause the development of digestive symptoms affecting quality of life and leading to medical consultations as well as a lower tendency to ingest dairy products and calcium within the adult population of the contemporary Americas. The fact that the LNP state is an inherent condition should be considered when developing public programmes that encourage consumption of dairy products, and should be a stimulus for the food industry to develop new lactose-free dairy products.

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Competing interests None.

Patient consent Obtained.

Ethics approval Ethics approval was provided by the Ethics Committee of the Pontificia Universidad Católica de Chile.

Contributors Study concept and design (JFM); acquisition of data (JFM, EM, LA, XM and CP); analysis and interpretation of data (JFM, EM, JC); drafting of the manuscript (JFM, EM, XM, CP, LA); critical revision of the manuscript for important intellectual content (JC); statistical analysis (JFM, EM, XM, CP); obtained funding (JFM, JC); final revision and edition (JFM, CP, XM, EM, LA, JC).

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