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ORIGINAL ARTICLE

Risk factors for congenital diaphragmatic hernia in the Bogota birth defects surveillance and follow-up program, Colombia

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Abstract
Purpose The mortality rate for congenital diaphragmatic hernia (CDH) remains high and prevention efforts are limited by the lack of known risk factors. The aim of this study was to determine prevalence, risk factors, and neonatal results associated with CDH on a surveillance system hospital-based in Bogotá, Colombia.
Methods The data used in this study were obtained from The Bogota Birth Defects Surveillance and Follow-up Program (BBDSFP), between January 2001 and December 2013. With 386,419 births, there were 81 cases of CDH. A case–control methodology was conducted with 48 of the total cases of CDH and 192 controls for association analysis.
Results The prevalence of CDH was 2.1 per 10,000 births. In the case–control analysis, risk factors found were maternal age ≥35 years (OR, 33.53; 95 % CI, 7.02–160.11), infants with CDH were more likely to be born before 37 weeks of gestation (OR, 5.57; 95 % CI, 2.05–15.14), to weigh less than 2500 g at birth (OR, 9.05; 95 % CI, 3.51–23.32), and be small for gestational age (OR, 5.72; 95 % CI, 2.18–14.99) with a high rate of death before hospital discharge in the CDH population (CDH: 38 % vs BBDSFP: <1 %; $p < 0.001$).
Conclusions The prevalence of CDH calculated was similar to the one reported in the literature. CDH is strongly associated with a high rate of death before hospital discharge and the risk factors found were maternal age ≥35 years, preterm birth, be small for gestational age, and have low weight at birth. These neonatal characteristics in developing countries would help to identify early CDH. Prevention efforts have been limited by the lack of known risk factors and established epidemiological profiles, especially in developing countries.

Keywords Congenital diaphragmatic hernia · Risk factors · Case–control · Surveillance

Abbreviations

CDH	Congenital diaphragmatic hernia
BBDSFP	The Bogota Birth Defects Surveillance and Follow-up Program
BMI	Maternal Body Mass Index
CNS	Central nervous system
ECLAMC	Latin American Collaborative Study of Congenital Malformations
ICBDSR	International Clearinghouse for Birth Defects Surveillance and Research
ECMO	Extracorporeal membrane oxygenation

Background

Congenital diaphragmatic hernia (CDH) is a congenital anomaly characterised by a discontinuity of the diaphragm, which allows the abdominal viscera to herniate into the

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chest. CDH is a rare anomaly with a prevalence ranging from 2.2 to 3.8 per 10,000 live births, which causes substantial morbidity and mortality in neonates affected by this condition [1, 2]. The pathogenesis of CDH is still poorly understood, although genetic and early environmental factors during pregnancy have been attributed as the main causes [3]. The developmental defects that result in CDH occur during embryogenesis and foetal development from the third to the sixteenth week of gestation. This implies that exposure to risk factors for CDH must take place at very early stages during pregnancy [3].

The survival rate reported in various studies is 61 % at birth, and up to 32 % at 1 year of age [4]. The overall mortality rate for CDH remains high despite advances in neonatal care, such as prenatal therapies like open foetal diaphragmatic repair, and postnatal therapies like high frequency ventilation, inhaled nitric oxide, extracorporeal membrane oxygenation, and delayed surgical repair [5]. The main resulting clinical problem that patients affected by CDH undergo is severe respiratory failure induced by pulmonary hypoplasia and persistent pulmonary hypertension [4–6]. Predictors of mortality for CDH are lung-to-head ratio (LHR) determined by ultrasonography [7], foetal lung volume (FLV) determined by magnetic resonance imaging, associated major anomalies and hepatic herniation [7–12].

Congenital diaphragmatic hernia could be part of a syndrome, an isolated anomaly or associated with other abnormalities. Isolated cases comprise 50–70 % of cases with pulmonary hypoplasia, intestinal malrotation and cardiac dextroposition and are considered hemodynamic or mechanical consequences [13]. The rest of the cases are complex or syndromic. The most common chromosomopathies are Trisomies 18, 13, and 21; tetrasomy 12 p (isochromosome 12p), partial trisomy 5, monosomy X, partial trisomy 20 have also been reported in the literature [13, 14]. The most common associated anomalies are cardiovascular or central nervous system (CNS) [7–15].

Ultrasonography is the method currently employed to carry out prenatal diagnosis of CDH [11], and typical findings include the presence of a stomach bubble in the thoracic cavity, and/or cardiac displacement by abdominal viscera [14]. It is known that prenatal care providers may play an important role with regard to this condition's diagnosis and prognosis, because the key to survival lies in prompt diagnosis [11, 16–18].

Since few epidemiological studies have demonstrated a clear association between CDH and risk factors, the aim of this study was to determine prevalence, potential maternal and gestational risk factors, vitality, prenatal diagnosis, and major anomalies associated with CDH.

Methods

The population for this study was obtained from The Bogota Birth Defects Surveillance and Follow-up Program (BBDSFP) between January 2001 and December 2013. The BBDSFP is a birth defects surveillance program that operates in Bogota, Colombia. The program is directed by the local health authorities (Secretaría de Salud de Bogotá), and Institute of Human Genetics of Pontificia Universidad Javeriana in Bogota. Since 2001, the program has been part of the Estudio Colaborativo Latinoamericano de Malformaciones Congénitas (ECLAMC), and the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) [19, 20].

The BBDSFP keeps track of all hospital births that take place in Bogota, and registers basic information about the mother, the pregnancy, and the neonate. Physicians trained by the BBCSFP carried out data collection for case–control analysis on a daily basis by performing a systematic physical examination making use of a standardised guideline for the detection of congenital anomalies for all newborns from 11 institutions in Bogota. Physicians of the program collected the registry data used for the case–control analysis by means of interviews to the mothers. On the other hand, data of the exposures were self-reported by the mothers. This information was entered on a form designed by the ECLAMC containing 167 variables regarding prenatal, neonatal, and maternal aspects [19]. In the case group, all live-born infants diagnosed with CDH were included, as well as all stillborns with a weight greater than 500 g diagnosed with CDH. The control group included healthy infants born in the same month and hospital as each of the cases. No sex matching was performed. All participants signed an informed consent before filling out the form. The case–control ratio was 1:4.

This study used the International Statistical Classification of Diseases and Related Health Problems (ICD-10), which assigns code Q79.0 for CDH. A patient with multiple anomalies was defined as one with a major anomaly in two different body systems. The variables analysed were: prevalence, annual trends, maternal age, parity, sex, weight at birth, gestational age at birth, stillbirths, deaths before hospital discharge, and associated anomalies excluding those not considered to be major defects. The case control–control analysis also included the following variables: maternal body mass index (BMI), early pregnancy, maternal years of education, family income, family history of congenital anomalies, parental consanguinity, number of prenatal visits, prenatal diagnosis, types of delivery, and exposure to smoking, alcohol, and drug use during pregnancy. The maternal exposure data were reported by themselves and the exposure period was limited to 1 month

before conception through each month until the end of pregnancy.

All data were registered in Microsoft Excel® 2010. Data analysis was performed with SPSS 17.0 (SPSS Corp., Chicago, IL, USA) and Epi Info 7.1.0.6 (Epi Info ™ Centers for Disease Control and Prevention, Atlanta, GA, USA). Pearson's Chi-squared or Fisher's exact tests were performed to compare variables related to the mother, the newborn, and the pregnancy according to the situation. This study used a confidence level of 95 % (95 % CI).

Results

During the 2001–2013 period, 386,419 births were registered in the BBDSFP, of which 81 were CDH cases. The total prevalence of CDH was 2.1 per 10,000 births [CI 95 % (2.09–2.10)]. Figure 1 shows the variation in annual trends during the last 6 years, with a prevalence of 2.3 and 3.0 per 10,000 live births in 2008 and 2013, respectively. Table 1 shows the demographic characteristics of the population. Compared with the general population, newborns with CDH were at an increased risk of having mothers 35 years of age or older ($p < 0.001$). Average weight-at-birth in the CDH population was 2540 g (±629), compared with 2953 g (±522) in the general population ($p < 0.001$). The average gestational age at birth in the CDH population was 36.7 weeks (±3.3), compared with 37.5 weeks (±5.5) in the general population ($p < 0.05$). Cases of CDH were more often male with a male to female ratio of 2.6:1, compared with 1.04:1 in the general population ($p < 0.001$). The rate of stillbirth ($p < 0.05$) and death before hospital discharge was higher in the CDH group, compared with the general population ($p < 0.001$). The major congenital anomalies were present in 22 % of CDH cases, and were mainly cardiovascular, urogenital, neurological, and musculoskeletal. Chromosomal abnormalities were present in 4 % of the CDH population, and included cases of Pallister-Killian syndrome, and Edwards syndrome (Fig. 2).

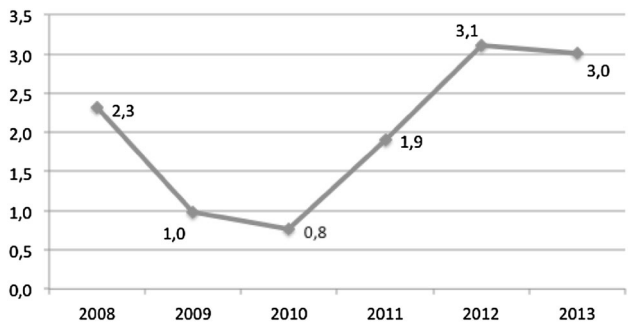

Fig. 1 Annual trends in prevalence per 10,000 births in BBDSFP in the last 6 years. According to the year, the confidence interval 95 % was in 2008 (2.30–2.32), 2009 (0.97–0.99), 2010 (0.75–0.77), 2011 (1.90–1.91), 2012 (3.10–3.13), 2013 (2.98–3.02). Prevalence was determined on all births in the database for this reason the intervals are narrow

Table 1 Demographic characteristics of the BBDSFP population

	BBDSFP (*n*: 386419)	CDH (*n*: 81)	*p*
Maternal age (years)			
≤20 (%)	78103 (23)	20 (25)	>0.05
>20–34 (%)	219366 (64)	38 (47)	
≥35 (%)	42618 (13)	23 (28)	<0.001*
Parity			
≤2 (%)	231110 (74)	57 (76)	
>2 (%)	79228 (26)	18 (24)	
Primipara (%)	136289 (44)	34 (45)	>0.05
Sex			
Female (%)	168117 (49)	22 (27)	
Male (%)	176127 (51)	59 (73)	<0.001*
Weight (grams)			
<2500 g (%)	50767 (15)	30 (39)	<0.001*
≥2500 g (%)	292224 (85)	46 (61)	
Gestational age at birth (weeks)			
<37 (%)	39116 (12)	21 (26)	<0.05*
37–42 (%)	297437 (88)	60 (74)	
Still birth (%)	1494 (<1)	3 (4)	<0.05*
Deaths before hospital discharge (%)	1337 (<1)	31 (38)	<0.001*

Maternal age: the two *p* values refer to comparison of <20 and ≥35 with 20–34

* Statistically significant

Case–control

There were 48 cases of CDH with 192 controls for this analysis. Demographic characteristics of the case group and the control group can be found in Table 2. CDH cases had 21 % of mothers 35 years of age or older compared to 2 % of the controls ($p < 0.001$). Ultrasonography was performed on 79 % of the patients. Of the patients with an ultrasound performed, 63 % were diagnosed with CDH, 18 % were diagnosed with other major associated anomalies and 18 % were reported as normal. Postnatal diagnosis after the first day of birth was performed for 15 % of the cases. Average weight at birth for CDH cases was 2519 g (±641), compared with 2987 (±513) for controls ($p < 0.001$). From the case group, 39 % weighed less than 2500 g at birth. Average gestation age at birth for CDH cases was 36.4 weeks (±3.4),

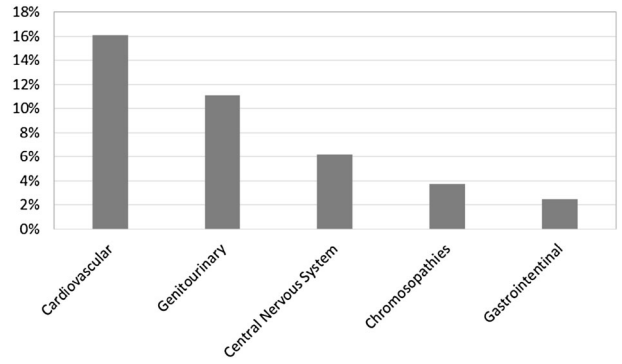

Fig. 2 Percentages of CDH cases with associated anomalies by systems

compared with 38.1 weeks (±2.1) for controls ($p < 0.001$). Also 31 % of cases were preterm births. Being small for gestational age comprised 35 % of the cases compared with 16 % of controls ($p < 0.05$).

In univariate analysis, mothers 35 years of age or older were at increased risk of having a CDH infant (OR, 12.37; 95 % CI, 3.69–41.5), infants with CDH were more likely to be born before 37 weeks of gestation (OR, 3.26; 95 % CI, 1.54–6.9), to weigh less than 2500 g at birth (OR, 4.88; 95 % CI, 2.33–10.23), and be small for gestational age (OR, 2.74; 95 % CI, 1.33–5.64) (see Table 3). No association was found between CDH and exposure to cigarette smoke, alcohol, or other psychoactive substances. Nor was an association found between CDH and other demographic variables such as maternal BMI, early pregnancy, maternal years of education, family income, family history of congenital anomalies, and parental consanguinity.

Logistic regression was performed with the significant odds ratios. Mothers 35 years of age or older were at increased risk of having a CDH infant (OR, 33.53; 95 % CI, 7.02–160.11), infants with CDH were more likely to be born before 37 weeks of gestation (OR, 5.57; 95 % CI, 2.05–15.14), to weigh less than 2500 g at birth (OR, 9.05; 95 % CI, 3.51–23.32), and be small for gestational age (OR, 5.72; 95 % CI, 2.18–14.99) (see Table 4).

Discussion

This study examined prevalence, risk factors, and neonatal results associated with CDH for the BBDSFP population, in addition to a case–control population, and found some similarities with the demographic characteristics of mothers and newborns with CDH described in the literature. A clear association was demonstrated between CDH and increased risk for adverse neonatal results.

Table 2 Demographic characteristics of controls compared to cases of CDH

	Cases (*n*: 48)	Control (*n*: 192)	*p*
Maternal age (years)			
≥20 (%)	14 (29)	50 (26)	>0.05
<20–34 (%)	24 (50)	138 (72)	
>35 (%)	10 (21)	4 (2)	<0.001*
Parity			
Primipara (%)	23 (48)	96 (50)	>0.05
Maternal body mass index			
<18(%)	2 (10)	10 (7)	>0.05
18–25 (%)	14 (67)	104 (77)	
>25 (%)	5 (24)	21 (16)	>0.05
Maternal education (years)			
≥12 (%)	23 (61)	127 (67)	>0.05
>12 (%)	15 (39)	62 (33)	
Family income			
Low (%)	11 (92)	55 (71)	>0.05
Mild-high (%)	1 (8)	23 (29)	
Antecedent of family malformations (%)	3 (6)	12 (6)	>0.05
Consanguinity parental (%)	3 (6)	3 (2)	>0.05
Number of prenatal visits			
<4 (%)	14 (37)	29 (15)	
≥4 (%)	22 (58)	159 (83)	
None (%)	2 (5)	4 (2)	>0.05
Delivery			
Cesarean (%)	33 (79)	83 (44)	<0.001*
Vaginal (%)	9 (21)	104 (56)	
Any maternal alcohol consumption	4 (11)	18 (10)	>0.05
Maternal smoking	4 (11)	20 (11)	>0.05
Another psychoactive drugs	2 (5)	8 (4)	>0.05
Sex			
Female (%)	20 (42)	79 (41)	>0.05
Male (%)	28 (58)	113 (59)	>0.05
Weight (g)			
<2500 g (%)	18 (39)	22 (12)	<0.001*
≥2500 g (%)	28 (61)	167 (88)	
Gestational age (weeks)			
<37 (%)	15 (31)	23 (12)	<0.001*
≥37 (%)	33 (69)	165 (88)	

Table 2 continued

	Cases (*n*: 48)	Control (*n*: 192)	*p*
Size for gestational age[a]			
SGE (%)	16 (35)	30 (16)	<0.05*
AGE (%)	30 (65)	154 (83)	
Deaths before hospital discharge	12 (27)	1 (2)	<0.001*

Maternal age: the two *p* values refer to comparison of <20 and ≥35 with 20–34

* Statistically significant

[a] Normal weight for gestational age was considered between the 10th and 90th percentiles of the weight for gestational age chart; small for gestational age was considered to be below the 10th percentile; and large for gestational age was considered to be above the 90th percentile

The total prevalence of CDH was 2.1 per 10,000 live births, and annual trends showed little variation during the last 6 years, see Fig. 1. No differences in annual trends were found for CDH in the Texas Birth Defects Registry in 2011, or the New York State Congenital Malformation Registry in 2013 [21, 22]. In 2011, EUROCAT did report a decrease in annual trends for CDH between the 1999–2008 period in some European countries [23].

Among the demographic characteristics associated with an increased risk for CDH reported in the literature, there were non-modifiable risk factors such as Caucasian ethnicity, and male foetus, as well as modifiable risk factors such as advanced maternal age, cigarette smoking, and alcohol intake during pregnancy [16]. A significant percentage of the patients with CDH were male with statistically significantly different from the controls and the mothers 35 years of age or older were at increased risk of having a CDH infant (OR, 33.53; 95 % CI, 7.02–160.11). The case–control analysis did not find any association between CDH and cigarette smoking or alcohol intake during pregnancy. Neither did the case control analysis find associations between CDH and maternal BMI early pregnancy, maternal years of education, family income, family history of congenital anomalies, and parental consanguinity.

Stillbirths accounted for 9–10 % of cases of CDH as reported in the literature [16, 24]. In this study, the rate of stillbirths was higher in the CDH population compared to the BBDSFP population (CDH: 4 % vs BBDSFP: <1 %; $p < 0.005$), although the stillbirth rate from this study was lower than the one reported in the literature. This was possibly due to the low rate of CDH prenatal diagnosis in pregnancies resulting in stillbirth. Our program has reported a low prenatal detection rate for CDH [25]. Mortality has decreased noticeably in tertiary centres, as shown by rates of 8–30 % reported in the literature. This was possibly due to the postponement of surgical treatment and emphasis on preoperative intensive care to avoid pulmonary injury [16, 26]. This study found a higher rate of death before hospital discharge in the CDH population,

Table 3 Univariate analysis-unadjusted odds ratios and 95 % CI of all demographic and exposure variables for CDH cases compared to controls

	CDH (*n*: 48) UOR (95% CI)
Maternal age (years)	
>20–34	Reference
≤20	1,17 (0.58–2,36)
>35	12.37 (3.69–41.5)
Parity	
Multipara	Reference
Primipara	0.92 (0.49–1.7)
Body mass index	
18–25	Reference
<18	1.31 (0.27–6.4)
Maternal education (years)	
≥12	Reference
<12	1.54 (0.74–3.20)
Family income	
Medium and high	Reference
Low	1.30 (0.67–2.51)
Type of delivery	
Vaginal	Reference
Cesarean	4.59 (2.08–10.14)
Any maternal alcohol consumption	
No	Reference
Yes	1.14 (0.36–3.58)
Maternal smoking	
No	Reference
Yes	1.02 (0.33-3.17)
Another psychoactive drugs	
No	Reference
Yes	1.33 (0.27–6.52)
Sex	
Male	Reference
Female	0.98 (0.52–1.86)
Weight at birth (g)	
≥2500	Reference
<2500	4.88 (2.33–10.23)
Gestational age (weeks)	
Aterm 37–42	Reference
Preterm 32-36	3.45 (1.62–7.34)
Size for gestational age	
Adequate	Reference
Small	2.74 (1.33–5.64)

Table 4 Logistic regression analysis

	CDH (*n*: 48) AOR (95% CI)
Maternal age (years)	
>20–34	Reference
>35	33.53 (7.02–160.11)
Weight at birth (g)	
≥2500	Reference
<2500	9.05 (3.51–23.32)
Gestational age (weeks)	
Aterm 37–42	Reference
Preterm 32–36	5.57 (2.05–15.14)
Size for gestational age	
Adequate	Reference
Small	5.72 (2.18–14.99)

compared to the BBDSFP population (CDH: 38 % vs BBDSFP: <1 %; $p < 0.001$). This high rate is possibly due to a lack of specialised centres for the treatment of CDH, which results in a limited number of CDH patients being treated in multiple centres with limited outcomes. This rate could increase if follow-up was performed for a longer period than it is currently.

The rate of preterm births for CDH patients reported in the literature was 12–30 % [24, 27]. This came close to the preterm birth rate found in this study (CDH: 26 % vs BBDSFP: 11 %; $p < 0.005$), and the rate found in the case–control analysis (cases: 31 % vs controls: 12 %; $p < 0.001$). In 2006, Levison et al. reported a preterm birth rate of 30 % for CDH patients, as well as a decrease of 50 % in the survival rate of preterm infants compared to term infants with the same condition (35 vs 64 %, respectively; unadjusted OR 3.45; 95 % CI, 1.83–6.50) [24]. Among CDH patients who died before hospital discharge, 38 % were preterm.

This study found a higher rate of weight at birth less than 2500 g in patients with CDH, compared with the BBDSFP population (CDH: 39 % vs BBDSFP: 15 %; $p < 0.001$), as did the case–control analysis (cases: 39 % vs controls: 12 %; $p < 0.001$) and it was a risk factor (OR, 9.05; 95 % CI, 3.51–23.32) for our population. In case–control methodology, infants with CDH being small for gestational age were statistically significant different compared to the controls (cases: 35 % vs controls: 16 %; $p < 0.05$) and it was a risk factor (OR, 5.72; 95 % CI, 2.18–14.99) for our population. The rate of small gestational age was greater than the one reported by other studies conducted in other developing countries such as the one by Lee et al., reporting a rate of 11.1 % [28].

In 2010, The Canadian Pediatric Surgery Network demonstrated that Caesarean delivery did not improve outcomes in CDH cases, compared with vaginal delivery [29]. In 2012, Kotecha et al. also found that the delivery route for 548 infants with CDH did not affect survival, although vaginal delivery was associated with higher use of extracorporeal membrane oxygenation (ECMO), suggesting that obstetric decisions should guide mode of delivery [6]. In the case–control analysis of this study, the rate of vaginal delivery was higher in the case group, compared to the control group (cases: 79 % vs controls: 44 %; $p < 0.001$); this rate was considerably greater in comparison with the one reported in other studies performed in other developing countries, like the one by Bhat et al., reporting a rate of 31.25 % [30].

Prenatal diagnosis rate for CDH was 63 % in this study, which was close to the one reported in the literature, from 54 to 73 % [11, 31, 32]. Various studies have demonstrated that prenatal diagnosis as well as multidisciplinary perinatal care allows for improvement in the mortality and morbidity of CDH patients [11, 16].

The rate of infants with CDH affected by major associated anomalies reported in other studies was 37–47 % [10, 33, 34]. In this study, the rate of major associated anomalies was 22 %, which was low compared with the rate reported in the literature. This was possibly due to subdiagnosis, which was partly caused by lack of follow-up after hospital discharge, the presence of major anomalies non-detectable by systematic physical examination, and prenatal diagnosis errors. As reported in the literature, around one-third of CDH cases presented associated cardiovascular anomalies, and a smaller proportion presented skeletal, neural, genitourinary, gastrointestinal, or other defects [35]. Similar to the associated congenital anomalies found in this study (Fig. 2), although the rate of associated cardiovascular anomalies was lower than the one reported in the literature, which was 33 % [35]. Two cases of Pallister-Killian syndrome were found in this study.

Conclusion

CDH was strongly associated with a higher risk of adverse neonatal outcomes, such as death before hospital discharge. Furthermore, patients with CDH had risk factors as being preterm birth, being small for gestational age, and having low weight at birth. Detection of these neonatal characteristics may lead to thinking about CDH as an early diagnosis, thus improving the prognosis of these patients especially in developing countries where knowledge of this pathology is limited, and where health systems do not destine enough resources for the treatment of this entity. Data obtained in this study show the importance of improving prenatal diagnosis, creating reference centers for the treatment of this condition, improving access to health services, and

improving performance of reference and counter-reference in our countries. This would reduce mortality and morbidity among CDH patients in our population. Despite advances in the medical and surgical treatment of CDH, mortality rates remain high. Consequently, further studies and efforts are necessary to determine a clear aetiology, as well as potentially modifiable risk factors, to identify mechanisms for primary prevention of this condition.

Compliance with ethical standards

None of the authors have any proprietary interests or conflicts of interest related to this submission. All the authors state that this manuscript, figures or tables have not been published anywhere previously and that it is not simultaneously being considered for any other publication.

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Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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