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Amniotic band syndrome and limb body wall complex in Europe 1980–2019

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Abstract

Amniotic band syndrome (ABS) and limb body wall complex (LBWC) have an overlapping phenotype of multiple congenital anomalies and their etiology is unknown. We aimed to determine the prevalence of ABS and LBWC in Europe from 1980 to 2019 and to describe the spectrum of congenital anomalies. In addition, we investigated maternal age and multiple birth as possible risk factors for the occurrence of ABS and LBWC. We used data from the European surveillance of congenital anomalies (EUROCAT) network including data from 30 registries over 1980–2019. We included all pregnancy outcomes, including live births, stillbirths, and terminations of pregnancy for fetal anomalies. ABS and LBWC cases were extracted from the central EUROCAT database using coding information responses from the registries. In total, 866 ABS cases and 451 LBWC cases were included in this study. The mean prevalence was 0.53/10,000 births for ABS and 0.34/10,000 births for LBWC during the 40 years. Prevalence of both ABS and LBWC was lower in the 1980s and higher in the United Kingdom. Limb anomalies and neural tube defects were commonly seen

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in ABS, whereas in LBWC abdominal and thoracic wall defects and limb anomalies were most prevalent. Twinning was confirmed as a risk factor for both ABS and LBWC. This study includes the largest cohort of ABS and LBWC cases ever reported over a large time period using standardized EUROCAT data. Prevalence, clinical characteristics, and the phenotypic spectrum are described, and twinning is confirmed as a risk factor.

KEYWORDS
ADAM sequence, birth defects, body stalk anomaly, constriction bands, Streeter anomaly

1 | BACKGROUND

Amniotic band syndrome (ABS), also called congenital constriction bands, ADAM-sequence or Streeter anomaly, is characterized by bands in the amniotic fluid that are thought to cause constriction of various parts of the developing fetus. However, bands are not always identified. The clinical spectrum ranges from mild (constriction rings around a digit) to more severe limb defects (e.g., amputations, pes equinovarus, pseudosyndactyly) and multiple congenital anomalies (e.g. atypical neural tube defects (NTDs), atypical oro-facial clefts, ectopia cordis, abdominal wall defects, congenital heart defects (CHDs), anophthalmos, tracheo-esophageal fistula, kidney agenesis, and anal atresia) (Chen, 2012).

Limb body wall complex (LBWC), or body stalk anomaly, has an overlapping phenotype with ABS. According to Van Allen et al. (1987), two of the following three anomalies should be present in order to diagnose LBWC: (1) exencephaly/encephalocele with facial clefts, (2) thoraco- and/or abdominoschisis and (3) limb defects. However, there is no consensus about the diagnostic criteria for LBWC. Martinez-Frias defines LBWC as an abdominal wall defect in combination with a large spectrum of other major malformations (Bugge, 2012; Martinez-Frias, 1997). Furthermore, a short umbilical cord, kyphoscoliosis, persistent extra-embryonic coelomic cavity, and other congenital anomalies (e.g., bowel atresia, renal agenesis, anorectal malformations) can be present (Bugge, 2012). LBWC is a lethal anomaly and affected pregnancies are currently often terminated (Singh et al., 2017). In some LBWC patients, constriction bands are present, and it is currently uncertain whether LBWC and ABS are part of the same phenotypic spectrum, or whether they are two overlapping disorders (Hunter et al., 2011; Lowry et al., 2017; Martinez-Frias, 1997; Rittler et al., 2019).

The etiology of ABS and LBWC is unknown. Several theories have been proposed, starting with the Streeter intrinsic theory which states that anomalies and constriction bands are the result of defective germinal disc development (early embryonic defect) (Streeter, 1930). Later, the Torpin extrinsic theory gained more attention, which implies that the anomalies are caused by amniotic membrane rupture leading to constriction bands which entangle the embryo (Torpin, 1965). This theory can explain the occurrence of atypical oro-facial clefts, pseudosyndactyly, amputations, and body wall defects, but it does not explain the internal organ anomalies. Van Allen and colleagues proposed that the wide range of anomalies affecting different organ systems are due to a vascular disruption event in week 4 to week 6 of gestation (Van Allen et al., 1987). Several other theories have been proposed, among which are the occurrence of both intrinsic and extrinsic factors, a disturbance of the embryonic folding process related to a malfunctioning of the body wall ectodermal placode (Hartwig et al., 1989), a primary defect of the ectoderm of the embryonic disc (Hunter et al., 2011), vitelline vascular steal (Stevenson, 2021), and nicotinamide adenine dinucleotide (NAD+) deficiency (Mark, 2022). It is also possible that the etiology is heterogeneous, with several or all pathogenetic mechanisms being responsible in a subset of patients (Martinez-Frias, 1997). In addition, a genetic cause could possibly be present. Several candidate genes were postulated, among which are the human homologue of the mouse "disorganization gene" for ABS (Donnai & Winter, 1989) and the *IQCK* gene (Kruszka et al., 2015) and genes involved in heterotaxy or caudal development for LBWC (Gajzer et al., 2015). ABS and LBWC almost always occur sporadically, but familial cases have been described (Lowry et al., 2017).

Prevalence estimates of ABS and LBWC are scarce and imprecise, as there are currently no agreed diagnostic criteria for these disorders, which may explain the variable level of case ascertainment. Also, inclusion criteria differ between studies (e.g., if prenatal cases/TOPFA were included). The ABS prevalence was reported to be 0.19/10,000 live births in Canada, 0.89/10,000 births in South America, 1.12/10,000 births in Finland and 2.03/10,000 births in Western Australia (Bower et al., 1993; Froster & Baird, 1993; Orioli et al., 2003; Syvänen et al., 2021). A higher ABS prevalence was found in previable fetuses before 20 weeks of gestation (Kalousek & Bamforth, 1988). The reported prevalence of LBWC also varies widely, with estimates ranging from 0.04 to 3.3/10,000 births (Bugge, 2012; Luehr et al., 2002; Martinez-Frias, 1997; Mastroiacovo et al., 1992).

Many risk factors have been implicated in the development of ABS/LBWC, but no risk factor was consistently found. Examples of proposed risk factors are young maternal age, primiparity, unplanned pregnancy, black race, hemorrhage, and febrile episode during the first trimester of pregnancy, maternal pre-gestational diabetes, maternal smoking or alcohol use, medication use (aspirin, misoprostol, beta-blockers, progestogens, bronchodilators), living at high altitude, obstetric procedures (amniocentesis and chorionic villus sampling), and twinning (Adrien et al., 2020; Lowry et al., 2017; Luehr et al., 2002; Orioli et al., 2003; Syvänen et al., 2021; Tinker et al., 2020; Werler et al., 2009).

In this study, we used data from the European surveillance of congenital anomalies (EUROCAT) network to determine the prevalence of ABS and LBWC in Europe from 1980 to 2019. In addition, we described the spectrum of congenital anomalies that are present in ABS and LBWC patients and presented information on pregnancy characteristics. Finally, we investigated maternal age and multiple births as possible risk factors for the occurrence of ABS and LBWC.

2 | METHODS

2.1 | EUROCAT network

EUROCAT is a European network of population-based congenital anomaly registries which was founded in 1979 (Tucker et al., 2018). All registries submit their standardized data once or twice a year to the Joint Research Centre (JRC)-EUROCAT Central Registry using a secure portal (EUROCAT Central Registry, University of Ulster, 2013; Kinsner-Ovaskainen et al., 2018). Cases with congenital anomalies are identified from various sources, for example, hospital discharge records, birth certificates, and autopsy results (https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-members/registries_en). Live births (LB), stillbirths (SB), fetal deaths (FD) with a gestational age of 20 weeks or more, and terminations of pregnancy for fetal anomaly (TOPFA) at any gestational age are submitted to the JRC-EUROCAT central database. Congenital anomalies are coded with the International Statistical Classification of Diseases and Related Health Problems with British Paediatric Association extension (ICD-BPA codes). The ICD9-BPA was used in the early years, but since 2005 all registries use the ICD10-BPA.

2.2 | Cohort

All 32 full member EUROCAT registries were invited to participate in this study and were asked to complete a questionnaire in order to obtain detailed information about the coding and text description of ABS and LBWC cases in their registry over time. Thirty registries from 15 countries agreed to participate and returned the questionnaire. Three registries include cases diagnosed up to 1 week of age, one registry up to 1 month of age and 26 registries up to at least 1 year of age. A detailed description of the participating registries can be found on the EUROCAT website (https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-members/registries_en). Based on the questionnaire coding information responses, data were extracted from the JRC-EUROCAT central database on December 17, 2019, for birth years 1980–2017 and a second data extraction was completed on January 18, 2022, for birth years 2018 and 2019:

1. ABS extraction: ICD9-BPA code 7628 or 880013 or 755504 or 755605 or ICD10-BPA code Q798 or Q719 or Q729 or Q738 or Q8687 or Online Mendelian Inheritance in Man (OMIM) code 217100 or ORPHA code 295000 or a text description of ABS or one if its synonyms in the different languages.
2. LBWC extraction: ICD9-BPA code 75679 or 7626 or 890042 or ICD10-BPA code starting with Q795 or Q8971 or ORPHA code 2369 or a text description of LBWC or one of its synonyms in different languages.

More information on the codes can be found in the Supporting Information.

Data were extracted for 4749 unique potential ABS/LBWC cases born between 1980 and 2017 and 448 unique potential ABS/LBWC cases born between 2018 and 2019. The data were cleaned manually and registries were asked to check the diagnosis in the medical records when this was unclear. Only cases with a registered diagnosis of ABS or LBWC were included in the study. Cases with LBWC and amniotic bands were classified as LBWC. After data cleaning, a total of 866 ABS cases and 451 LBWC cases remained (Table 1). Specific ICD9-BPA and ICD10-BPA codes were available for ABS; therefore all birth years were included in prevalence calculations. There is no specific ICD9-BPA or ICD10-BPA code for LBWC; therefore only the birth years with available text description were included in prevalence calculations. Some registries used a local specific ICD10-BPA code for LBWC. In addition to diagnosis, information was obtained on year of birth/pregnancy end, pregnancy outcome, gestational age, birthweight, sex, time of diagnosis (prenatal vs. postnatal), maternal age, multiple birth, 1 week survival, genetic testing, autopsy information, and associated congenital anomalies. For the analysis of the spectrum of anomalies, cases with a genetic/teratogenic disorder and a diagnosis of ABS/LBWC were excluded. Only cases with at least one major congenital anomaly and a diagnosis of ABS/LBWC were included.

2.3 | Statistical analyses

Descriptive data are presented as numbers and percentages for categorical data and means for continuous data. Prevalence and the 95% confidence intervals (CI) were calculated based on the Poisson distribution. Due to small numbers and wide CIs, no trend analysis was performed for prevalence over time.

2.4 | Ethics approval

For this study, pseudonymized data from EUROCAT registries was used, which all have their own ethics approval. Therefore, no specific ethics approval for this study was required.

3 | RESULTS

In total, 866 ABS cases and 451 LBWC cases were included in this study. The prevalence for years 1980–2019 was 0.53/10,000 births for ABS and 0.34/10,000 births for LBWC (Table 1). ABS was least prevalent between 1980 and 1989, while LBWC was least prevalent between 1980 and 1999. The first ABS cases were registered in 1980, but few registries had data before 1990 (only 35 ABS cases

TABLE 1 Prevalence of amniotic band syndrome and limb body wall complex in 30 EUROCAT registries, 1980–2019[a]

	ABS		LBWC	
Surveillance period	*N* cases	Prevalence per 10,000 births (95% CI)	*N* cases	Prevalence per 10,000 births (95% CI)
1980–1989	35	0.35 (0.24, 0.49)	2	0.11 (0.01, 0.39)
1990–1999	160	0.62 (0.53, 0.73)	21	0.14 (0.09, 0.21)
2000–2009	333	0.55 (0.50, 0.62)	175[b]	0.35 (0.30, 0.41)
2010–2019	338	0.51 (0.45, 0.56)	253[b]	0.38 (0.34, 0.43)
Total	866	0.53 (0.50, 0.57)	451[b]	0.34 (0.31, 0.37)

Abbreviations: ABS, amniotic band syndrome; CI, confidence interval; LBWC, limb body wall complex; *N*, number.
[a]Only few registries covered the entire period (1980–2019), most covered part of the period. See Table S2 for time coverage of all registries.
[b]Nineteen cases from two registries were not included in the calculation of LBWC prevalence between 2000 and 2019 because of incomplete identification of LBWC cases due to incomplete text description in those years (1 case from Emilia Romagna and 18 cases from South West England).

were registered in 1980–1989). After 1990, the prevalence was stable around 0.54/10,000 births (the 95% CIs of the three 10-year periods all overlap). The first LBWC case was registered in 1988 and only 23 cases were registered between 1980 and 1999. From 2000 onwards, the LBWC prevalence was stable around 0.37/10,000 births (with overlapping 95% CIs for the two 10-year periods).

Between 2000 and 2019, the prevalence of both ABS and LBWC was higher in the UK registries compared to the non-UK registries, with more than half of the LBWC cases recorded in the UK registries (Table S1). The lowest ABS prevalence was found in Tuscany and Valencian Region (0.08 and 0.10/10,000 births, respectively) while no LBWC cases were registered in Mainz, Wielkopolska, Zagreb, and Malta (Table S2). The highest ABS prevalence was found in Isle de Reunion, Vaud, Auvergne, and Wales (1.46, 1.28, 1.23, 1.22/10,000 births, respectively) and the highest LBWC prevalence was found in Northern England and Wessex (1.04 and 0.93/10,000 births, respectively).

Of the 866 ABS cases, 456 were live born (52.7%), 118 were stillborn (13.6%), and 292 cases resulted in a TOPFA (33.7%, Table 2). The prenatal detection rate increased over time, from 18% in 1980–1989 to 60% in 2000–2019. Of the 451 LBWC cases, the great majority were TOPFAs ($n = 387$, 85.8%), with only 37 live births (8.2%) and 27 stillbirths (6.0%). The prenatal detection rate of LBWC was consistently high, with over 90% being prenatally diagnosed between 1980 and 2019 (98.8% was prenatally detected in 2010–2019). At least one cytogenetic test (e.g., probe test, karyotype, array) was done in 21% of ABS cases and in 30% of LBWC cases.

One hundred and thirty-one ABS cases and 154 LBWC cases had another syndrome or had no major congenital anomaly registered and were dropped from the analysis of the spectrum of anomalies, leaving 735 ABS cases and 297 LBWC cases. In Table 3, the type and frequency of anomalies associated with ABS recorded in EUROCAT registries is shown, as well as what is known from the literature (Evans et al., 1994; Koskimies et al., 2015; Martinez-Frias et al., 2000; Orioli et al., 2003). Limb anomalies were most commonly seen (78%), of which limb reduction defects (LRD 64%), syndactyly (23%), and talipes equinovarus (15%) were most frequent. Nervous system anomalies were also common (25%), with NTDs representing the majority (19%, mostly anencephaly and encephalocele). Oro-facial clefts were seen in 10% of cases and an abdominal or thoracic wall defect was apparent in 12%. Eye anomalies, CHDs, respiratory anomalies, gastro-intestinal anomalies, congenital anomalies of kidney and urinary tract (CAKUT), and genital anomalies were seen in 5% or less.

The associated anomalies in LBWC cases are shown in Table 4 (our study vs. published studies; Bamforth, 1992; Bugge, 2012; Mastroiacovo et al., 1992; Moerman et al., 1992; Smrcek et al., 2003). The majority of LBWC cases had an abdominal or thoracic wall defect (66%) and half of them had limb anomalies (LRD in 31% and talipes equinovarus in 11%). Twenty-seven percent had gastro-intestinal anomalies (20% ano-rectal atresia or stenosis) and 26% had CAKUT (12% uni- or bilateral renal agenesis). Nervous system anomalies (20%, mainly anencephaly and spina bifida), genital anomalies (14%), and CHDs (13%) also occurred frequently. Eye anomalies, respiratory anomalies, and oro-facial clefts were less common (6% or less).

Clinical characteristics of ABS and LBWC case are summarized in Table 5. The male-to-female ratio was 1.1 for both ABS and LBWC. Of live born ABS cases, 38% were born preterm, whereas 89% of LBWC live births were preterm. Birthweight in ABS live births was higher than in LBWC live births. One week survival of ABS live born children was 94%, but for LBWC this was only 5%. Almost 6% of ABS cases was part of a twin, triplet or quadruplet, and all pairs/multiples were discordant. Eleven percent of LBWC cases was part of a twin or triplet, with five concordant twin pairs (if the concordant twins are counted once, the twinning percentage was 9.7%). Mean maternal age was 27.4 in ABS and 28.5 years in LBWC cases.

4 | COMMENT

4.1 | Prevalence

In this study, we found an ABS total prevalence of 0.53/10,000 births, which falls within the previously reported ABS prevalence (0.19–2.03/10,000 births; Bower et al., 1993; Froster & Baird, 1993; Orioli et al., 2003; Syvänen et al., 2021). The LBWC total prevalence of 0.34/10,000 births found in this study was also consistent with the

TABLE 2 Outcome of pregnancies and prenatal detection rate of amniotic band syndrome and limb body wall complex in 30 EUROCAT registries, 1980–2019

	ABS						LBWC					
Period	N cases	LB	SB	TOPFA	N prenatal detected/*n* available data	Prenatal detection rate % (95% CI)	N cases	LB	SB	TOPFA	N prenatal detected/*n* available data	Prenatal detection rate % (95% CI)
1980–1989	35	23	10	2	5 of 28	17.9% (3.7%, 32.0%)	2	0	0	2	2 of 2	100.0%
1990–1999	160	101	17	42	58 of 151	38.4% (30.7%, 46.2%)	21	5	3	13	17 of 19	89.5% (75.7%, 100%)
2000–2009	333	163	46	124	186 of 308	60.4% (54.9%, 65.9%)	175	11	15	149	168 of 172	97.7% (95.4%, 99.9%)
2010–2019	338	169	45	124	195 of 326	59.8% (54.5%, 65.1%)	253	21	9	223	248 of 251	98.8% (97.5%, 100%)
Total period	866	456	118	292	444 of 813	54.6% (51.2%, 58.0%)	451	37	27	387	435 of 444	98.0% (96.7%, 99.3%)

Note: No fetal deaths were reported.

Abbreviations: ABS, amniotic band syndrome; CI, confidence interval; LB, live births; LBWC, limb body wall complex; *N*, number; SB, stillbirths; TOPFA, terminations of pregnancy because of fetal anomaly.

literature (0.04–3.3/10,000 births; Bugge, 2012; Luehr et al., 2002; Martinez-Frias, 1997; Mastroiacovo et al., 1992). The lower ABS and LBWC prevalence in the 1980s is at least partly due to underdiagnosis, underreporting, and misclassification. In this study, we found a higher prevalence of both ABS and LBWC in the six UK registries compared to the non-UK registries, which was also found in a previous EUROCAT study on vascular disruption defects (Morris et al., 2022). The United Kingdom had more than three times the prevalence of LBWC compared to non-UK registries (0.64 vs. 0.20/10,000 births). The increased prevalence in the United Kingdom could be a registration artifact (e.g., better ascertainment or coding of ABS/LBWC in the United Kingdom or under ascertainment or coding in non-UK registries) or clinicians in the United Kingdom might more readily recognize and diagnose ABS and LBWC. Another possibility is that there is a truly higher ABS/LBWC prevalence in the United Kingdom, which could be caused by an increased prevalence of risk factors for ABS and LBWC or a decreased prevalence of protective factors (if there are any) in the United Kingdom compared to non-UK countries participating in this study.

The increased pan-European prevalence of both ABS and LBWC in more recent years might be due to better recognition of these entities. Due to the introduction of prenatal screening throughout Europe, more cases have been diagnosed prenatally in recent years. Also, perinatal autopsy is currently often performed and was not so common in the 1980s. This might be the reason why only two LBWC cases were registered prior to 1990. Due to delay in registration of cases, it is possible that the true prevalence over the years 2016–2019 is higher than found in this study.

4.2 | Clinical spectrum

The anomalies present in the ABS cases presented in this study are overall in line with those reported in the literature (Evans et al., 1994; Koskimies et al., 2015; Martinez-Frias et al., 2000; Orioli et al., 2003). In our study, the percentage of cases with LRD and syndactyly was lower than previously reported (63.7% vs. 69.2%–100% and 22.7% vs. 45.5%, respectively). Limb anomalies and NTDs were most prevalent in ABS, whereas in LBWC abdominal and thoracic wall defects and limb anomalies were most common. The frequency of anomalies in LBWC cases was lower than was previously reported in the literature (e.g., fewer NTDs, an/microphthalmos, CHDs, diaphragmatic defects, and genital anomalies). This was to be expected as the previous studies were small case series (not population-based) in which cases were reported in more detail and could have been more severe or unusual cases. It is important to note that the frequency of anomalies reported in EUROCAT is likely to be an underestimate of the true frequency, as not all anomalies are always notified to the registries. In addition, it is possible that not all anomalies have been identified, for example, in SB or TOPFA. For ABS cases in this study, post-mortem results were available for 65% of SB and for 56% of TOPFA cases and for LBWC cases these percentages were 41% and 45%, respectively.

TABLE 3 Type and frequency of major anomalies in non-syndromic amniotic band syndrome cases (analysis was restricted to all cases with at least one major anomaly registered and cases with another syndromic diagnosis[a] were excluded)

ABS cases	This study EUROCAT Europe 1980–2019 ($N = 735$)	Orioli et al. (2003) ECLAMC South America 1967–1997 ($n = 284$)	Martinez-Frias et al. (2000) ECEMC Spain 1976–1998 ($N = 78$)	Koskimies et al. (2015) Finland 1993–2005 ($N = 71$)	Evans et al. (1994) Hungary 1975–1984 ($N = 43$)
Inclusion criteria	Clinical diagnosis of ABS, non-syndromic: 389 LB, 95 SB, 251 TOPFA	Amniotic bands or suggestive LRD, non-syndromic: 255 LB, 29 SB	Amniotic bands with and without body wall defects: LB + SB	ABS with LRD: 65 LB, 6 SB	LRD due to ABS: 30 LB, 13 SB
Congenital anomaly	***N* (%)**	***N* (%)**	***N* (%)**	***N* (%)**	***N* (%)**
Nervous system anomalies	182 (24.8)				
Neural tube defects	140 (19.0)	42 (14.8)			16 (37.2)
Anencephaly and similar	96 (13.1)	21 (7.4)			
Encephalocele	41 (5.6)	15 (5.3)	1 (1.3)		
Spina bifida	3 (0.4)		0		
Hydrocephaly	20 (2.7)	3 (1.1)		≥1	1 (2.3)
Microcephaly	5 (0.7)	2 (0.7)			
Arhinencephaly/holoprosencephaly	9 (1.2)				
Eye anomalies	24 (3.3)				
An/microphthalmos	18 (2.4)	10 (3.5)		≥1	
Congenital heart defects	39 (5.3)	2 (0.7)		6 (8.5)	1 (2.3)
VSD	12 (1.6)			≥1	
ASD	12 (1.6)			≥1	
Respiratory anomalies	10 (1.4)	5 (1.8)			
Oro-facial clefts (OFC)	72 (9.8)	33 (11.6)		5 (7.0)	
Atypical OFC		15 (5.3)			
CL/P	64 (8.7)	18 (6.3)	5 (6.4)		18 (41.9)[b]
CP	8 (1.1)				
Gastro-intestinal anomalies	24 (3.3)				
Ano-rectal atresia or stenosis	4 (0.5)	4 (1.4)	0		1 (2.3)
Diaphragmatic defect/hernia	4 (0.5)	2 (0.7)			1 (2.3)
Abdominal/thoracic wall defects	90 (12.2)	15 (5.3)	7 (9.0)	≥1	20 (46.5)
CAKUT	15 (2.0)	4 (1.4)			
Renal agenesis (uni- or bilateral)	6 (0.8)		0	≥1	1 (2.3)
Genital anomalies	14 (1.9)				
Hypospadias	6 (0.8)			≥1	
Indeterminate sex	1 (0.1)	5 (1.8)	0		
Limb anomalies	576 (78.4)				
Constriction rings		190 (66.9)			
LRD	468 (63.7)	240 (84.5)	54 (69.2)		43 (100)
Talipes equinovarus	110 (15.0)	62 (21.8)		8 (11.3)	
Polydactyly	8 (1.1)	5 (1.8)	1 (1.3)		1 (2.3)
Syndactyly	167 (22.7)	129 (45.4)			

Abbreviations: ABS, amniotic band syndrome; ASD, atrial septal defects; CAKUT, congenital anomalies of kidney and urinary tract; CL/P, cleft lip with or without cleft palate; CP, cleft palate; LB, live births; LRD, limb reduction defects; *N*, number; SB, stillbirths; TOPFA, terminations of pregnancy because of fetal anomaly; VSD, ventricular septal defects.

[a]Excluded cases with the following syndromes: trisomy 18 ($n = 5$), trisomy 21 ($n = 3$), trisomy 13 ($n = 3$), other genetic disorders, including chromosomal aberrations ($n = 8$), other disorders ($n = 6$, including congenital cytomegalovirus infection, twin–twin-transfusion syndrome, pentalogy of Cantrell, caudal regression).

[b]Including palpebral fissure cleft.

TABLE 4 Type and frequency of major anomalies in non-syndromic limb body wall complex cases (analysis was restricted to all cases with at least one major anomaly registered and cases with another syndromic diagnosis were excluded)

LBWC cases	This study EUROCAT Europe 1980–2017 ($N = 297$)	Bamforth (1992) review literature ($N = 54$)	Mastroiacovo et al. (1992) ICBDSR (Australia, Denmark, France, Italy, Mexico, South America, Sweden) 1965–1989 ($N = 40$)	Bugge (2012) Denmark 1970–1989 ($N = 16$)	Moerman et al. (1992) Belgium birth years not stated ($N = 12$)	Smrcek et al. (2003) Germany 1994–2001 ($N = 11$)
Inclusion criteria	Clinical diagnosis of LBWC, non-syndromic, 24 LB, 17 SB, 256 TOPFA	Studies that published ABS/LBWC cases, LB + SB + TOPFA	Amelia or body wall defect with short umbilical cord, LB + SB	Large body wall defect + absent/very short umbilical cord, 7 LB, 9 SB	Amniotic bands with MCA from fetal/pediatric autopsy files, 2 LB, 10 TOPFA	Prenatal discovered LBWC, 1 LB, 10 TOPFA
Congenital anomaly	***N* (%)**	***N* (%)**	***N* (%)**	***N* (%)**	***N* (%)**	***N* (%)**
Nervous system anomalies	59 (19.9)					
Neural tube defects	49 (16.5)	23 (42.6)				
Anencephaly and similar	24 (8.1)		1 (2.5)		4 (33.3)	
Encephalocele	7 (2.4)		0		3 (25)	3 (27.3)
Spina bifida	18 (6.1)	3 (5.6)	4 (10)	3 (18.8)		
Hydrocephaly	4 (1.3)				1 (8.3)	
Microcephaly	0					
Arhinencephaly/holoprosencephaly	1 (0.3)					
Eye anomalies	4 (1.3)	9 (16.7)				
An/microphthalmos	4 (1.3)		10 (25)	1 (6.3)	2 (16.7)	
Congenital heart defects	40 (13.5)	14 (25.9)	-	-	3 (25)	
VSD	3 (1.0)	1 (1.9)			1 (8.3)	
ASD	0	1 (1.9)			1 (8.3)	
Respiratory anomalies	7 (2.4)	18 (33.3)		-		
Oro-facial clefts (OFC)	17 (5.7)	28 (51.9)	1 (2.5)			
Atypical OFC			0		3 (25)	
CL/P	12 (4.0)	25 (46.3)	1 (2.5)		4 (33.3)	
CP	5 (1.7)	3 (5.6)	0	1 (6.3)	2 (16.7)	
Gastro-intestinal anomalies	80 (26.9)					
Ano-rectal atresia or stenosis	58 (19.5)	4 (7.4)	6 (15)	9 (56.3)		
Absent gallbladder	0	6 (11.1)				
Diaphragmatic defect/hernia	5 (1.7)		0	3 (18.8)	5 (41.7)	
Abdominal/thoracic wall defects	196 (66.0)		>22 (>55)	16 (100)	10 (83.3)	11 (100)
CAKUT	76 (25.6)	20 (37.0)			1 (8.3)	
Renal agenesis (uni- or bilateral)	36 (12.1)	11 (20.4)		10 (62.5)		
Genital anomalies	42 (14.1)	14 (25.9)				
Hypospadias	1 (0.3)			1 (6.3)		

(Continues)

TABLE 4 (Continued)

LBWC cases	This study EUROCAT Europe 1980–2017 (*N* = 297)	Bamforth (1992) review literature (*N* = 54)	Mastroiacovo et al. (1992) ICBDSR (Australia, Denmark, France, Italy, Mexico, South America, Sweden) 1965–1989 (*N* = 40)	Bugge (2012) Denmark 1970–1989 (*N* = 16)	Moerman et al. (1992) Belgium birth years not stated (*N* = 12)	Smrcek et al. (2003) Germany 1994–2001 (*N* = 11)
Indeterminate sex	14 (4.7)		12 (30)	6 (37.5)		
Limb anomalies	146 (49.2)					
LRD	92 (31.0)		34 (85)	9 (56.3)	9 (75)	1 (9.1)
Talipes equinovarus	32 (10.8)		1 (2.5)	7 (43.8)	8 (66.7)	2 (18.2)
Polydactyly	5 (1.7)			1 (6.3)		
Syndactyly	10 (3.4)		2 (5)	2 (12.5)	4 (33.3)	

Note: Excluded cases with the following syndromes: trisomy 18 (*n* = 4), other genetic disorders, including chromosomal aberrations (*n* = 3), other disorders (*n* = 2, pentalogy of Cantrell and twin reversed arterial perfusion, TRAP).
Abbreviations: ASD, atrial septal defects; CAKUT, congenital anomalies of kidney and urinary tract; CL/P, cleft lip with or without cleft palate; CP, cleft palate; LB, live births; LBWC, limb body wall complex; LRD, limb reduction defects; MCA, multiple congenital anomalies; *N*, number; SB, stillbirths; TOPFA, terminations of pregnancy because of fetal anomaly; VSD, ventricular septal defects.

Availability of post-mortem result varied between registries. The ABS and LBWC cases in this study were included when they had a clinical diagnosis of ABS or LBWC (which can vary among countries/registries), whereas in previous studies other inclusion criteria were used; for example, in some studies with ABS cases, an LRD needed to be present and in other studies with LBWC cases a body wall defect, short umbilical cord or amelia needed to be present. The different inclusion criteria will have influenced the reported clinical spectrum in reported studies.

4.3 | Risk factors

In this study, twinning was found in 5.9% of ABS cases and 10.7% of LBWC cases. In the UK registries, the twinning percentages were slightly different; 6.6% in ABS cases and 8% in LBWC cases. The twinning percentages in ABS and LBWC found in this study are much higher than the average twinning rate in Europe, which has increased from 0.91% in 1980–1985 to 1.44% in 2010–2015 (Monden et al., 2021). Previous studies have also found increased twinning rates in LBWC (Bugge, 2012; Martinez-Frias et al., 2000; Mastroiacovo et al., 1992; Nagase et al., 2021; Smrcek et al., 2003) with twinning percentages between 11% and 18%. A recent literature review by Adam et al. showed that there is a great excess of monozygotic versus dizygotic twins in LBWC with a 70% discordance rate. Similar rates were seen in other recurrent constellations of embryonic malformations (RCEM), such as pentalogy of Cantrell, OEIS complex (Omphalocele, Exstrophy, Imperforate anus, and Spinal defects), VACTERL association (Vertebral defects, Anal atresia, Cardiac defects, Tracheo-Esophageal fistula, Renal anomalies, and Limb anomalies), OAVS (Oculo-Auriculo-Vertebral Spectrum), and MURCS (MÜllerian duct aplasia, Renal dysplasia, Cervical Somite anomalies also called Mayer-Rokitansky-Küster-Hauser syndrome type 2) (Adam et al., 2020). Adam et al. state that RCEM are part of a spectrum and have a similar pathogenesis. LBWC and pentalogy of Cantrell are expected to arise very early during gestation and can be seen together. In our dataset, there were three ABS/LBWC cases who were also diagnosed with pentalogy of Cantrell. There were no cases with other RCEM in our dataset. Martinez-Frias et al. reported a twinning rate of 7.4% in ABS cases without a body wall defect and in 14.3% of ABS cases with a body wall defect (Martinez-Frias et al., 2000), whereas other studies did not report increased twinning rates in ABS (Lowry et al., 2017; Orioli et al., 2003). Possible underlying mechanisms by which twinning could increase the risk of ABS/LBWC are hypoxia during early embryogenesis (Adam et al., 2020; Van Allen et al., 1987) or the twinning process itself could damage the ectoderm of the embryonic disc (Hunter et al., 2011).

Some studies have postulated that a younger maternal age or primiparity could be a risk factor for ABS and LBWC (Martinez-Frias et al., 2000; Mastroiacovo et al., 1992; Orioli et al., 2003), but this was not consistently found (Bugge, 2012; Koskimies et al., 2015). Mean maternal age for ABS and LBWC cases in this study was 27.4 and 28.5 years, respectively. This falls within the previously reported mean maternal age for ABS and LBWC (ABS between 25.7 and 27.9 years; Guzman-Huerta et al., 2013; Iqbal et al., 2015; and LBWC between 23 and 31 years; Bugge, 2012; Gazolla et al., 2014; Luehr et al., 2002; Martinez-Frias et al., 2000; Nagase et al., 2021). In the UK registries, mean maternal age for ABS and LBWC was 26.3 and 28.4 years, respectively. For 55% of ABS cases (330 of 601) and for 54% of LBWC cases (143 of 264), this was the first birth to the mother.

TABLE 5 Characteristics of patients with amniotic band syndrome and limb body wall complex in 30 EUROCAT registries, 1980–2019

	ABS	LBWC
Sex	*N* cases (%[a])	*N* cases (%[a])
Male	431 (52.9%)	160 (49.7%)
Female	380 (46.7%)	148 (46.0%)
Indeterminate sex	3 (0.4%)	14 (4.3%)
Unknown	52	129
Gestational age in LB	*N* cases (%[a])	*N* cases (%[a])
<37 weeks	168 (37.8%)	33 (89.2%)
37–41 weeks	271 (60.9%)	4 (10.8%)
≥42 weeks	6 (1.3%)	0
Birthweight in LB	Mean	Mean
<37 weeks	1847 ($n = 158$)	1423 ($n = 31$)
37–41 weeks	3175 ($n = 263$)	2905 ($n = 3$)
≥42 weeks	3604 ($n = 5$)	- ($n = 0$)
1 week survival in LB	381 of 406 (94%)	2 of 37 (5%)
Multiple birth	*N* cases (%[a])	*N* cases (%[a])
Singleton	810	399
Multiple	51 (5.9%)	48 (9.7–10.7%[b])
Missing	5	4
Maternal age[c]	Mean (95% CI)	Mean (95% CI)
	27.4 (27.0, 27.5)	28.5 (27.9, 28.6)

Note: Trisomy 13, 18, 21 cases and other syndromic cases are included here.
Abbreviations: ABS, amniotic band syndrome; LB, live births; LBWC, limb body wall complex; *N*, number.
[a]Percentages of non-missing values.
[b]LBWC, when counting the five concordant twins once, the twinning percentage is 9.7% (in ABS all twins were discordant).
[c]Maternal age was missing for 21 ABS cases and 4 LBWC cases.

4.4 | Strengths and limitations

This study presents data on the largest cohort of ABS and LBWC cases ever reported over a 40-year study period (1980–2019), all pregnancy outcomes (including TOPFA) and reports the complete spectrum of congenital anomalies in a population-based cohort from different European countries. Standardized data from EUROCAT registries were used, which enabled comparison between different countries. Our data extraction was as broad as possible (only 25% of extracted cases had ABS/LBWC) and therefore we expect that we will have included the great majority of cases with a registered diagnosis of ABS/LBWC in this study. Information on multiple births and maternal age was present for almost all cases, which enabled us to give a precise estimate of twinning rates and average maternal age in ABS and LBWC.

However, this study also has limitations. The prevalence estimates are dependent on the case ascertainment, which will have changed per registry and also within registries over time. It is possible that ABS/LBWC was not always recognized in 1980–1990 and also case ascertainment in this period might have been lower due to the lack of electronic medical records. The reported prevalence in this study is likely therefore to be an underestimation of the true prevalence. Also, the lack of clear diagnostic criteria for ABS and LBWC is problematic. In this study, we have only included cases that were registered as having ABS/LBWC, which means that ABS/LBWC was diagnosed by a doctor in the clinic. We have not applied the ABS/LBWC diagnosis ourselves based on registry data entries, as we did not personally examine the patients and because we may lack data that are present in the clinic (family history and genetic test results). However, when we found a case with many features of ABS or LBWC, the registry was asked to check the medical records, including the autopsy report, to see whether the diagnosis ABS/LBWC had been made in the clinic (and if it was, the case was included in the study). Only limited genetic data were available: the result of a cytogenetic test was known in 21% of ABS cases and 30% of LBWC cases. In addition, the lack of a specific ICD9 and ICD10-BPA code made it more difficult to study LBWC prevalence, because it was impossible to identify LBWC cases without text description. Furthermore, for the study of the spectrum of anomalies it must be noted that all percentages are likely to be an underestimate of the true frequency of associated anomalies, as the range of anomalies are not always registered. We were not able to study other risk factors (e.g., assisted conception, medication use, maternal illness before and during pregnancy), because too much data were missing.

5 | CONCLUSIONS

This study includes the largest cohort of ABS and LBWC cases ever reported over 1980–2019 using standardized EUROCAT data. The European ABS prevalence was estimated at 0.53/10,000 births and the LBWC prevalence at 0.34/10,000 births with heterogeneity between registries and higher prevalence in the United Kingdom. Both ABS and LBWC were less frequently reported in the 1980s. Prenatal detection of ABS increased with the wider implementation of prenatal screening programs, whereas prenatal detection of LBWC was consistently high. The clinical spectrum of ABS and LBWC was explored in detail and we confirmed that twinning is a risk factor for both ABS and LBWC.

AUTHOR CONTRIBUTIONS

Jorieke E. H. Bergman conceived the project idea and drafted the study protocol together with Ingeborg Barišić, Erica H. Gerkes, Annie Perraud, Maria A. Loane, Diana Wellesley, and Hermien E. K. de Walle. Jorieke E. H. Bergman wrote the manuscript. All registry leaders have filled out the questionnaire and have checked the diagnosis of their cases in the medical records when this was unclear. All authors have read and approved the final version of this manuscript.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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