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Prevalence and Infant Mortality of Major Congenital Malformations Stratified by Birthweight

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Keywords
Birth defect · Congenital anomaly · Very-low-birthweight infant · Epidemiology · Survival

Abstract
Background: Low birthweight and major congenital malformations (MCMs) are key causes of infant mortality. ***Objectives:*** The aim of this study was to explore the prevalence of MCMs in infants with low and very low birthweight and analyze the impact of MCMs and birthweight on infant mortality. ***Methods:*** We determined prevalence and infant mortality of 28 life-threatening MCMs in very-low-birthweight (<1,500 g, VLBW), low-birthweight (1,500–2,499 g, LBW), or normal-birthweight (≥2,500 g, NBW) infants in a cohort of 2,727,002 infants born in Germany in 2006–2017, using de-identified administrative data of the largest statutory public health insurance system in Germany. ***Results:*** The rates of VLBW, LBW, and NBW infants studied were 1.3% (34,401), 4.0% (109,558), and 94.7% (2,583,043). MCMs affected 0.5% (13,563) infants, of whom >75% (10,316) had severe congenital heart disease. The prevalence (per 10,000) of any/cardiac MCM was increased in VLBW (286/176) and LBW (244/143), as compared to NBW infants (38/32). Infant mortality rates were significantly higher in infants with an MCM, as opposed to infants without an MCM, in each birthweight group (VLBW 28.5% vs. 11.5%, LBW 16.7% vs. 0.9%, and NBW 8.6% vs. 0.1%). For most MCMs, observed survival rates in VLBW and LBW infants were lower than expected, as calculated from survival rates of VLBW or LBW infants without an MCM, and NBW infants with an MCM. ***Conclusions:*** Infants with an MCM are more often born with LBW or VLBW, as opposed to infants without an MCM. Many MCMs carry significant excess mortality when occurring in VLBW or LBW infants.

Introduction

Low (LBW) or very low birthweight (VLBW) and major congenital malformations (MCMs) that require surgery during infancy are the leading causes of infant mortality, with low birthweight ranking first among neonatal deaths and MCMs among postneonatal deaths [1]. These conditions however are rarely analyzed together. While MCMs are assumed to be more common in VLBW (<1,500 g) or LBW (1,500–2,449 g) than in normal-birthweight (NBW, ≥2,500 g) infants, there are little compre-

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hensive data to calculate the birth prevalence of various MCMs in VLBW or LBW infants, as opposed to NBW newborns.

In studies assessing mortality, VLBW infants with an MCM are often excluded, while reports about treatment results of infants with an MCM usually do not provide separate data on LBW or VLBW infants. The extent to which MCMs and VLBW combined to increase infant mortality therefore warrants further investigation. Surgery may be more challenging in very small preterm infants, as compared to normal-weight infants. Furthermore, these infants may be too unstable to perform surgery, requiring its delay. Moreover, the presence of an MCM in an extremely preterm infant may also prompt an individual decision for comfort care rather than surgical intervention. In this study, we set out to use population-based administrative data to describe the prevalence of MCMs in VLBW, LBW, and NBW infants and to assess the individual and combined impact of VLBW/LBW and MCM on survival to 1 year of age.

Methods

The investigation was based on de-identified legally mandated routine data sent from hospital administrations in Germany to the largest statutory health insurance system (Allgemeine Ortskrankenkasse [AOK]), covering up to one-third of all residents as described previously [2]. Here, we present an analysis of infants born alive between January 1, 2006, and December 31, 2017, and insured by one of the 11 regional AOK health care funds. We considered MCM diagnoses (ICD-10) and vital status of the infants during their first year of life.

We investigated 28 life-threatening MCMs that require early surgery grouped into neural tube defects (spina bifida/meningomyelocele or encephalocele), congenital heart defects, gastrointestinal malformations, and abdominal defects (esophageal atresia with or without trachea-esophageal fistula, congenital diaphragmatic hernia, duodenal or small-bowel atresia, anal or rectal atresia, omphalocele, and gastroschisis), malformations of the urethra and urinary bladder (epispadias/exstrophy of the urinary bladder, congenital posterior urethral valves/prune belly syndrome), and biliary atresia. Congenital heart defects were further grouped according to their dominant effect on cardiovascular physiology as described by the Vermont Oxford Network (VON) [3] and the International Network for Evaluation of Outcomes in Neonates (iNeo) [4]: category A, defects primarily compromising the systemic output (critical aortic stenosis, congenital mitral valve stenosis or insufficiency, coarctation of the aorta, hypoplastic left-heart syndrome, and interrupted aortic arch); category B, defects presenting primarily with cyanosis (tetralogy of Fallot, transposition of the great arteries, pulmonary valve atresia, pulmonary artery atresia, Ebstein anomaly, tricuspid atresia, total anomalous pulmonary venous return, and hypoplastic right-heart syndrome); and category C, defects resulting in congestive heart failure with pulmonary over-circulation (complete atrioventricular canal, double-outlet right ventricle, truncus arteriosus, and other single-ventricle physiologies). An isolated patent ductus arteriosus was not considered a severe cardiac MCM and was excluded from this analysis. Birthweight was categorized as VLBW (<1,500 g), LBW (1,500–2,449 g), or NBW (≥2,500 g).

Statistical Analysis

All statistical analyses were considered hypothesis generating, without choosing formally a level of significance. Survival rates were modeled as a function of exposure to LBW, VLBW, or MCM, by coefficients calculated from survival rates in exposed to a condition (LBW, VLBW, or MCM) and the survival rate of unexposed infants (NBW infants without an MCM). The coefficients were used to calculate expected survival rates and mortality attributable to LBW, VLBW, and MCM. Statistical analyses were carried out using Stata (Version 16; StataCorp, College Station, TX, USA).

Results

Prevalence

The database included 2,727,002 infants born between January 1, 2006, and December 31, 2017, which corresponds to 32.3% of all live-born infants in Germany registered by the Federal Office of Statistics during the same years (8,431,015). VLBW, LBW, and NBW infants represented 1.3% (34,401), 4.0% (109,558), and 94.7% (2,583,043) of the total study population, respectively.

Neural tube defects were reported in 921 infants (0.034%), severe cardiac MCM in 10,316 infants (0.378%), gastrointestinal and abdominal malformations (gastrointestinal atresias, diaphragmatic hernias, and abdominal defects) in 5,286 infants (0.194%), biliary atresia in 165 infants (0.006%), and severe lower urinary tract malformations (posterior urethral valves and bladder exstrophies) in 557 infants (0.020%) (Table 1). Multiple MCMs occurred in 2,513 infants (0.092%).

The rate of each type of MCM investigated was significantly higher in VLBW and LBW than in NBW infants. Rates in VLBW and LBW infants were >10-fold higher than those in NBW infants for esophageal atresia, duodenal/small-bowel atresia, and gastroschisis, while for most other MCMs, rates were on an average 3–8-fold higher in VLBW and LBW infants than in NBW infants (Table 1). Almost 27% of all infants with an MCM were LBW or VLBW infants.

Survival and Mortality

In the total population of VLBW infants, the 1-year survival rate was 88.0% (30,269/34,401), as compared to 98.7% (108,128/109,558) in LBW infants, and 99.9%

Table 1. Infants with MCMs by birthweight, numbers, and prevalence (per 10,000 live births, with 95% CIs)

Birthweight	Infants, *n*				Prevalence			
	<1,500 g	1,500, 2,499 g	≥2,500 g	all	<1,500 g	1,500–2,499 g	≥2,500 g	all
All infants	34,401	109,558	2,583,043	2,727,002				
Infants without an MCM	33,417	106,889	2,573,133	2,713,439				
ICD-10								
Any MCM	984	2,669	9,910	13,563	286.04 (268.94, 304.19)	243.62 (234.65, 252.91)	38.37 (37.62, 39.13)	49.74 (48.91, 50.58)
Neural tube defects	41	130	750	921	11.92 (8.79, 16.16)	11.87 (10.00, 14.09)	2.90 (2.70, 3.12)	3.38 (3.17, 3.60)
Encephalocele								
Q01	10	16	119	145	2.91 (1.58, 5.35)	1.46 (0.90, 2.37)	0.46 (0.39, 0.55)	0.53 (0.45, 0.63)
Spina bifida/meningomyelocele								
Q05	31	114	631	776	9.01 (6.35, 12.79)	10.41 (8.66, 12.50)	2.44 (2.26, 2.64)	2.85 (2.65, 3.05)
Severe cardiac malformations	607	1,564	8,145	10,316	176.45 (163.07, 190.91)	142.76 (135.90, 149.95)	31.53 (30.86, 32.22)	37.83 (37.11, 38.57)
Category A (compromised systemic output)	270	559	3,304	4,133	78.49 (69.70, 88.38)	51.02 (46.97, 55.42)	12.79 (12.36, 13.23)	15.16 (14.70, 15.63)
Aortic valve stenosis								
Q23.0	32	71	500	603	9.30 (6.59, 13.13)	6.48 (5.14, 8.17)	1.94 (1.77, 2.11)	2.21 (2.04, 2.40)
Congenital mitral stenosis								
Q23.2	13	42	235	290	3.78 (2.21, 6.47)	3.83 (2.84, 5.18)	0.91 (0.80, 1.03)	1.06 (0.95, 1.19)
Congenital mitral insufficiency								
Q23.3	102	95	489	686	29.65 (24.43, 35.98)	8.67 (7.10, 10.60)	1.89 (1.73, 2.07)	2.52 (2.33, 2.71)
Hypoplastic left-heart syndrome								
Q23.4	33	95	660	788	9.59 (6.83, 13.47)	8.67 (7.10, 10.60)	2.56 (2.37, 2.76)	2.89 (2.70, 3.10)
Coarctation, interrupted aortic arch								
Q25.1	86	242	1,358	1,686	25.00 (20.25, 30.86)	22.09 (19.48, 25.05)	5.26 (4.99, 5.54)	6.18 (5.90, 6.49)
Aortic atresia/hypoplasia								
Q25.2	4	14	62	80	1.16 (0.45, 2.99)	1.28 (0.76, 2.15)	0.24 (0.19, 0.31)	0.29 (0.24, 0.37)
Category B (sustained cyanosis)	173	528	2,876	3,647	50.29 (43.35, 58.34)	48.19 (44.26, 52.47)	11.13 (10.74, 11.55)	13.37 (12.95, 13.81)
Transposition of the great arteries								
Q20.3	30	94	1,006	1,130	8.72 (6.11, 12.45)	8.58 (7.01, 10.50)	3.89 (3.66, 4.14)	4.14 (3.91, 4.39)
Tetralogy of Fallot								
Q21.3	62	187	753	1,002	18.02 (14.06, 23.10)	17.07 (14.79, 19.69)	2.92 (2.71, 3.13)	3.67 (3.45, 3.91)

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Table 1 (continued)

Birthweight	Infants, *n*				Prevalence			
	<1,500 g	1,500, 2,499 g	≥2,500 g	all	<1,500 g	1,500–2,499 g	≥2,500 g	all
Pulmonary valve atresia								
Q22.0	24	71	229	394	6.98 (4.69, 10.38)	6.48 (5.14, 8.17)	0.89 (0.78, 1.01)	1.44 (1.31, 1.60)
Tricuspid atresia								
Q22.4	11	31	177	219	3.20 (1.79, 5.73)	2.83 (1.99, 4.02)	0.69 (0.59, 0.79)	0.80 (0.70, 0.92)
Ebstein anomaly								
Q22.5	6	21	108	135	1.74 (0.80, 3.81)	1.92 (1.25, 2.93)	0.42 (0.35, 0.51)	0.50 (0.42, 0.59)
Hypoplastic right-heart syndrome								
Q22.6	13	30	142	185	3.78 (2.21, 6.47)	2.74 (1.92, 3.91)	0.55 (0.47, 0.65)	0.68 (0.59, 0.78)
Pulmonary artery atresia								
Q25.5	18	57	260	335	5.23 (3.31, 8.27)	5.20 (4.02, 6.74)	1.01 (0.89, 1.14)	1.23 (1.10, 1.37)
Total anomalous pulmonary venous return								
Q26.2	9	37	201	247	2.62 (1.38, 4.97)	3.38 (2.45, 4.65)	0.78 (0.68, 0.89)	0.91 (0.80, 1.03)
Category C (congestive heart failure/pulmonary over-circulation)	164	477	1,965	2,606	47.67 (40.93, 55.53)	43.54 (39.81, 47.62)	7.61 (7.28, 7.95)	9.56 (9.18, 9.92)
Truncus arteriosus								
Q20.0	16	31	136	183	4.65 (2.86, 7.55)	2.83 (1.99, 4.02)	0.53 (0.45, 0.62)	0.67 (0.58, 0.78)
Double-outlet right ventricle								
Q20.1	26	119	465	610	7.56 (5.16, 11.07)	10.86 (9.08, 13.00)	1.80 (1.64, 1.97)	2.24 (2.07, 2.42)
Other single ventricle (double-inlet ventricle)								
Q20.4	10	23	188	221	2.91 (1.58, 5.35)	2.10 (1.40, 3.15)	0.73 (0.63, 0.84)	0.81 (0.71, 0.93)
Atrioventricular septal defect								
Q21.2	112	304	1,176	1,592	32.56 (27.07, 39.16)	27.75 (24.80, 31.04)	4.55 (4.30, 4.82)	5.84 (5.56, 6.13)
Multiple cardiac MCMs	67	275	1,526	1,868	19.48 (15.34, 24.72)	25.10 (22.31, 28.24)	5.91 (5.62, 6.21)	6.85 (6.55, 7.17)
Gastrointestinal and abdominal malformations	499	1,622	3,165	5,286	145.05 (132.95, 158.24)	148.05 (141.07, 155.37)	12.25 (11.83, 12.69)	19.38 (18.87, 19.91)
Esophageal atresia (±tracheoesophageal fistula)								
Q39.0, Q39.1	96	252	350	698	27.91 (22.86, 34.06)	23.00 (20.33, 26.02)	1.35 (1.22, 1.51)	2.56 (2.38, 2.76)
Duodenal/small-bowel atresia								
Q41	190	363	564	1,117	55.23 (47.93, 63.63)	33.13 (29.90, 36.71)	2.18 (2.01, 2.37)	4.10 (3.86, 4.34)

Table 1 (continued)

Birthweight	Infants, *n*				Prevalence			
	<1,500 g	1,500, 2,499 g	≥2,500 g	all	<1,500 g	1,500–2,499 g	≥2,500 g	all
Anal/rectal atresia								
Q42	95	277	1,088	1,460	27.62 (22.60, 33.74)	25.28 (22.48, 28.44)	4.21 (3.97, 4.47)	5.35 (5.09, 5.64)
Diaphragmatic hernia								
Q79.0	35	135	541	711	10.17 (7.32, 14.15)	12.32 (10.41, 14.58)	2.09 (1.93, 2.28)	2.61 (2.42, 2.81)
Omphalocele								
Q79.2	38	134	381	553	11.05 (8.05, 15.16)	12.23 (10.33, 14.48)	1.48 (1.33, 1.63)	2.03 (1.87, 2.20)
Gastroschisis								
Q79.3	45	461	241	747	13.08 (9.78, 17.50)	42.08 (38.42, 46.09)	0.93 (0.82, 1.06)	2.74 (2.55, 2.94)
Biliary atresia								
Q44.2	15	16	134	165	4.36 (2.64, 7.19)	1.46 (0.90, 2.37)	0.52 (0.44, 0.61)	0.61 (0.52, 0.71)
Urethral and urinary bladder malformations	26	75	456	557	7.56 (5.16, 11.07)	6.85 (5.46, 8.58)	1.77 (1.61, 1.94)	2.04 (1.88, 2.22)
Bladder exstrophy/epispadia								
Q64.0 and Q64.1	10	20	93	123	2.91 (1.58, 5.35)	1.83 (1.18, 2.82)	0.36 (0.29, 0.44)	0.45 (0.38, 0.54)
Posterior urethral valve/prune belly syndrome								
Q64.2 and Q79.4	16	55	363	434	4.65 (2.86, 7.55)	5.02 (3.86, 6.53)	1.41 (1.27, 1.56)	1.59 (1.45, 1.75)
Multiple MCMs	153	540	1,820	2513	44.48 (37.98, 52.08)	49.29 (45.31, 53.61)	7.05 (6.73, 7.38)	9.22 (8.86, 9.58)

MCM, major congenital malformation; CI, confidence interval.

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Table 2. Infant mortality of MCMs in VLBW (<1,500 g) infants, LBW (1,500–2,499 g) infants, and NBW (≥2,500 g) infants

Birthweight	<1,500 g					1,500–2,499 g					≥2,500 g			All		
	died	total	mortality			died	total	mortality			died	total	mortality	died	total	mortality
All infants	4,132	34,401	0.1201			1,430	109,558	0.0131			2,938	2,583,043	0.0011	8,500	2,727,002	0.0031
No MCM	3,852	33,417	0.1153			985	106,889	0.0092			2,084	2,573,133	0.0008	6,921	2,713,439	0.0026
ICD-10				O/E survival rate	95% CI				O/E survival rate	95% CI						
Any MCM	280	984	0.285	0.88	0.86, 0.91	445	2,669	0.167	0.92	0.91, 0.93	854	9,910	0.086	1,579	13,563	0.116
Neural tube defects	24	41	0.585	0.48	0.33, 0.64	20	130	0.153	0.87	0.81, 0.92	14	750	0.019	58	921	0.063
Encephalocele																
Q01	6	10	0.600	0.49	0.22, 0.81	5	16	0.313	0.76	0.53, 0.91	10	119	0.084	21	145	0.145
Spina bifida/meningomyelocele																
Q05	18	31	0.581	0.48	0.30, 0.67	15	114	0.132	0.88	0.81, 0.93	4	631	0.006	37	776	0.048
Severe cardiac malformations	220	607	0.362	0.86	0.81, 0.89	434	1,564	0.277	0.87	0.85, 0.88	1,275	8,145	0.157	1,929	10,316	0.187
Category A (compromised systemic output)	90	270	0.333	0.91	0.85, 0.97	158	559	0.283	0.88	0.85, 0.91	582	3,304	0.176	830	4,133	0.201
Aortic valve stenosis																
Q23.0	8	32	0.250	0.97	0.78, 1.09	19	71	0.268	0.85	0.75, 0.92	65	500	0.130	92	603	0.153
Congenital mitral stenosis																
Q23.2	8	13	0.615	0.64	0.32, 0.98	19	42	0.452	0.81	0.65, 0.94	74	235	0.315	101	290	0.348
Congenital mitral insufficiency																
Q23.3	17	102	0.167	1.04	0.97, 1.08	8	95	0.084	1.02	0.97, 1.04	45	489	0.092	70	686	0.102
Hypoplastic left-heart syndrome																
Q23.4	26	33	0.788	0.38	0.21, 0.64	64	95	0.674	0.52	0.41, 0.65	246	660	0.373	336	788	0.426
Coarctation, interrupted aortic arch																
Q25.1	29	86	0.337	0.83	0.72, 0.93	41	242	0.169	0.93	0.89, 0.96	138	1,358	0.102	208	1,686	0.123
Aortic atresia/hypoplasia																
Q25.2	2	4	0.500	0.73	0.26, 1.11	7	14	0.500	0.65	0.41, 0.86	14	62	0.226	23	80	0.288
Category B (sustained cyanosis)	73	173	0.422	0.75	0.67, 0.83	140	528	0.265	0.85	0.82, 0.88	369	2,876	0.128	582	3,647	0.160
Transposition of the great arteries																
Q20.3	16	30	0.533	0.58	0.38, 0.78	20	94	0.213	0.87	0.79, 0.93	90	1,006	0.089	126	1,130	0.112
Tetralogy of Fallot																
Q21.3	21	62	0.339	0.79	0.66, 0.90	32	187	0.171	0.89	0.84, 0.92	44	753	0.058	97	1,002	0.097
Pulmonary valve atresia																
Q22.0	11	24	0.458	0.81	0.57, 1.01	24	71	0.338	0.88	0.79, 0.95	56	229	0.245	91	394	0.231
Tricuspid atresia																
Q22.4	3	11	0.273	0.95	0.61, 1, 12	7	31	0.226	0.90	0.75, 0.99	24	177	0.136	34	219	0.155
Ebstein anomaly																
Q22.5	3	6	0.500	0.72	0.30, 1.07	12	21	0.571	0.55	0.35, 0.75	23	108	0.213	38	135	0.281
Hypoplastic right-heart syndrome																
Q22.6	6	13	0.462	0.74	0.44, 0.99	11	30	0.367	0.78	0.62, 0.90	26	142	0.183	43	185	0.232
Pulmonary artery atresia																
Q25.5	9	18	0.500	0.69	0.43, 0.93	18	57	0.316	0.85	0.73, 0.93	48	260	0.185	75	335	0.224
Total anomalous pulmonary venous return																
Q26.2	4	9	0.444	0.88	0.47, 1.19	16	37	0.432	0.81	0.64, 0.93	58	201	0.289	78	247	0.316

Table 2 (continued)

Birthweight	<1,500 g					1,500–2,499 g					≥2,500 g			All		
	died	total	mortality			died	total	mortality			died	total	mortality	died	total	mortality
Category C (congestive heart failure/ pulmonary over-circulation)	57	164	0.348	0.88	0.80, 0.95	136	477	0.285	0.86	0.83, 0.89	324	1,965	0.165	517	2,606	0.198
Truncus arteriosus Q20.0	8	16	0.500	0.70	0.43, 0.94	11	31	0.355	0.80	0.64, 0.92	26	136	0.191	45	183	0.246
Double-outlet right ventricle Q20.1	21	26	0.808	0.27	0.13, 0.51	41	119	0.345	0.82	0.74, 0.88	89	465	0.191	151	610	0.248
Other single ventricle (double-inlet ventricle) Q20.4	5	10	0.500	0.73	0.38, 1.04	9	23	0.391	0.80	0.58, 0.95	43	188	0.229	57	221	0.258
Atrioventricular septal defect Q21.2	23	112	0.205	1.05	0.96, 1.10	75	304	0.247	0.88	0.80, 0.89	166	1,176	0.141	264	1,592	0.166
Multiple cardiac MCMs	39	67	0.582	0.61	0.46, 0.76	95	275	0.345	0.85	0.80, 0.89	336	1,526	0.220	470	1,868	0.252
Gastrointestinal and abdominal malformations	135	499	0.271	0.89	0.85, 0.92	206	1,622	0.127	0.95	0.94, 0.95	218	3,165	0.069	559	5,286	0.106
Esophageal atresia (±tracheoesophageal fistula) Q39.0 and Q39.1	28	96	0.292	0.86	0.78, 0.94	41	252	0.163	0.91	0.89, 0.94	26	350	0.074	95	698	0.136
Duodenal/small-bowel atresia Q41	31	190	0.163	0.99	0.94, 1.02	24	363	0.066	0.98	0.97, 0.99	23	564	0.041	78	1,117	0.070
Anal/rectal atresia Q42	22	95	0.232	0.90	0.80, 0.97	42	277	0.152	0.89	0.85, 0.92	36	1,088	0.033	100	1,460	0.068
Diaphragmatic hernia Q79.0	25	35	0.714	0.40	0.24, 0.61	59	135	0.437	0.70	0.63, 0.78	105	541	0.194	189	711	0.266
Omphalocele Q79.2	19	38	0.500	0.60	0.43, 0.76	29	134	0.216	0.84	0.78, 0.89	22	381	0.058	70	553	0.127
Gastroschisis Q79.3	10	45	0.222	0.90	0.76, 1.00	11	461	0.024	1.01	1.01, 1.02	6	241	0.025	27	747	0.036
Biliary atresia Q44.2	1	15	0.067	1.14	0.92, 1.16	3	16	0.188	0.89	0.66, 0.98	10	134	0.075	14	165	0.085
Urethral and urinary bladder malformations	8	26	0.308	0.80	0.59, 0.95	11	75	0.147	0.88	0.80, 0.94	11	456	0.024	30	557	0.054
Bladder exstrophy/epispadia Q64.0 and Q64.1	4	10	0.400	0.69	0.38, 0.94	2	20	0.100	0.93	0.76, 0.99	2	93	0.022	8	123	0.065
Posterior urethral valve/prune belly syndrome Q64.2 and Q79.4	4	16	0.250	0.87	0.60, 1.02	9	55	0.164	0.87	0.76, 0.93	9	363	0.025	22	434	0.051
Multiple MCMs	76	153	0.497	0.72	0.63, 0.81	152	540	0.281	0.92	0.89, 0.95	389	1,820	0.214	617	2513	0.246

Expected survival rates were calculated by multiplying survival rates of VLBW or LBW infants without malformations, respectively, with survival rates of NBW infants with malformations and used to calculate O/E ratios (with 95% CIs). VLBW, very low birthweight; LBW, low birthweight; NBW, normal birthweight; O/E, observed-to-expected ratio; ICD, International Classification of Diseases; CI, confidence interval.

(2,580,105/2,583,043) in NBW infants. NBW infants without an MCM had a survival rate of 99.92% (2,571,049/2,573,133). In NBW infants, noncardiac MCMs were associated with survival rates exceeding 90%, except for diaphragmatic hernia (80.6%) (Table 2). Most cardiac MCMs showed survival rates between 70% and 90% in NBW infants. The lowest survival rates were observed in infants with hypoplastic left-heart syndrome (62.7%), congenital mitral stenosis (68.5%), and total anomalous venous return (71.1%). Infants with multiple cardiac MCMs and infants with multiple cardiac and noncardiac MCMs had lower survival rates than infants with any MCM (Table 2).

MCM survival was lower in LBW and VLBW infants than in NBW infants. Observed survival rates in VLBW or LBW infants were significantly lower than expected survival rates for most MCMs (Table 2). Extremely low ratios (<0.5) of observed-to-expected survival rates were seen in VLBW infants with neural tube defects, hypoplastic left-heart syndrome, double-outlet right ventricle, and diaphragmatic hernia, indicating that in these MCMs, the survival disadvantage conferred by MCMs and VLBW combined clearly exceeded that of either condition alone.

Finally, we estimated the contribution of MCM, LBW, and VLBW to infant mortality by calculating survival coefficients for each exposure (background, LBW, VLBW, and MCM). In total, 26.0% of infant deaths appeared unrelated to LBW/VLBW or MCM (background), while 57.2% were related to LBW and VLBW, and 13.6% were related to an MCM. There were 3.2% excess deaths in infants exposed simultaneously to an MCM and LBW or VLBW.

Discussion

This population-based head-to-head comparison of the prevalence of a life-threatening MCM by birthweight category demonstrates an increased prevalence of an MCM in VLBW and LBW, as compared to NBW infants, for many of the MCMs studied. The difference was most pronounced for various congenital heart diseases and for virtually all gastrointestinal malformations.

The study exploits the mandatory data exchange between hospitals and insurance companies (for reimbursement) and collection of data independent from hospital admissions. This allows for the calculation of mortality until 1 year of age. In contrast, most cohort studies report death prior to discharge which underestimates mortality of infants with an MCM who are transferred for specialized care to other hospitals and subject to >1 surgical intervention. Moreover, infants with some MCMs such as hypoplastic left-heart syndrome may die at home or other institutions between staged surgeries. In contrast, the use of administrative data allows for follow-up of patients through varying hospitals and outpatient centers.

A major drawback of the study results from reliance on the limited data set specified by law, which does not include gestational age or socioeconomic status. No additional data could be retrieved from charts of the infants as we used only completely de-identified data. This precluded any manual review, for example, to verify diagnoses nor recategorize cardiac MCMs. Sometimes cardiac MCMs might not fit perfectly into the given categories. For example, there is often an overlap in cases diagnosed as tetralogy of Fallot (category B) and double-outlet right ventricle with mild pulmonary stenosis (category C). These cases may present clinically with either systemic cyanosis or pulmonary over-circulation depending on the degree of pulmonary stenosis. Isolated ventricular septal defects are not considered life-threatening congenital heart defects [3, 4] but may create considerable pulmonary over-circulation (category C) when the left-to-right shunt is large.

As the statutory health insurance companies cover all residents in Germany (including welfare recipients) with an annual income below 57,600 EUR (2017) but only a fraction of those who earn more, the data do not fully represent the general population. Furthermore, the analysis is based on live births, excluding spontaneous fetal losses, terminations of pregnancy, and stillbirths. The data of this study therefore underestimate the overall prevalence of an MCM for which termination of pregnancy is common after a prenatal diagnosis, such as neural tube defects or hypoplastic left-heart syndrome [5]. In Germany, prenatal ultrasound screening is covered by the statutory health insurance, and maternally indicated termination of pregnancy for severe fetal anomalies is legal.

In the study presented here, no distinction was made between an isolated MCM and those occurring within the context of chromosomal anomalies or genetically defined syndromes. Only frank genetic anomalies, such as numeric chromosomal aberrations, have ICD-10 codes, and exclusion of these cases had no major impact on the results. Infants with multiple anomalies however had on average higher mortality rates than those with an MCM affecting only 1 organ.

Prematurity, intrauterine growth restriction, and obstetrical conditions contribute to the increased rate of MCMs in VLBW and LBW infants as opposed to NBW

Table 3. General prevalence of major congenital malformations in German, European, and American cohorts (per 10,000 live births, with 95% CIs)

	AOK 2006–2017	EUROCAT (German registries) 2005–2017	EUROCAT (all full registries) 2005–2017	US, NBDPN (European descent) 2010–2014	US, NBDPN (all ethnicities) 2010–2014
N	2,727,002	225,420	9,417,881	~2,345,000	5,186,504
ICD10					
Encephalocele					
Q01	0.53 (0.45, 0.63)	0.47 (0.24, 0.81)	0.34 (0.30, 0.37)	0.77 (0.67, 0.89)	1.03 (0.90, 1.12)
Spina bifida/meningomyelocele					
Q05	2.85 (2.65, 3.05)	2.33 (1.78, 3.00)	1.72 (1.63, 1.80)	3.74 (3.50, 3.99)	3.86 (3.69, 4.03)
Aortic valve stenosis					
Q23.0	2.21 (2.04, 2.40)				
Congenital mitral stenosis or insufficiency					
Q23.2 and Q23.3	3.58 (3.36, 3.81)	4.85 (4.04, 5.78)	1.16 (1.09, 1.23)		
Hypoplastic left-heart syndrome					
Q23.4	2.89 (2.70, 3.10)	1.75 (1.27, 2.34)	1.38 (1.31, 1.46)	2.73 (2.52, 2.95)	2.61 (2.47, 2.75)
Aortic atresia/hypoplasia					
Q25.2	0.29 (0.24, 0.37)	2.29 (1.74, 2.95)	1.25 (1.18, 1.32)		
Coarctation, interrupted aortic arch					
Q25.1	6.18 (5.90, 6.49)	5.55 (4.48, 6.87)	3.92 (3.77, 4.08)	6.79 (6.37, 7.23)	6.17 (5.89, 6.45)
Transposition of the great arteries					
Q20.3	4.14 (3.91, 4.39)	3.26 (2.60, 4.04)	3.02 (2.91, 3.13)	3.82 (3.57, 4.08)	3.80 (3.63, 3.98)
Tetralogy of Fallot					
Q21.3	3.67 (3.45, 3.91)	3.65 (2.95, 4.47)	2.86 (2.75, 2.97)	4.61 (4.34, 4.89)	4.60 (4.42, 4.79)
Pulmonary valve atresia					
Q22.0	1.44 (1.31, 1.60)	0.82 (0.50, 1.25)	0.81 (0.76, 0.87)	1.25 (1.11, 1.40)	1.43 (1.33, 1.54)
Tricuspid atresia					
Q22.4	0.80 (0.70, 0.92)	0.62 (0.35, 1.01)	0.43 (0.39, 0.47)	0.97 (0.84, 1.12)	1.01 (0.92, 1.10)
Ebstein anomaly					
Q22.5	0.50 (0.42, 0.59)	0.54 (0.30, 0.91)	0.38 (0.34, 0.42)	0.82 (0.71, 0.94)	0.79 (0.70, 0.87)
Hypoplastic right-heart syndrome					
Q22.6	0.68 (0.59, 0.78)	0.43 (0.21, 0.76)	0.33 (0.29, 0.37)		
Pulmonary artery atresia					
Q25.5	1.23 (1.10, 1.37)				
Total anomalous pulmonary venous return					
Q26.2	0.91 (0.80, 1.03)	0.78 (0.47, 1.20)	0.63 (0.58, 0.68)	0.95 (0.83, 1.08)	1.39 (1.29, 1.50)
Truncus arteriosus					
Q20.0	0.67 (0.58, 0.78)	0.74 (0.44, 1.15)	0.45 (0.41, 0.50)	0.60 (0.51, 0.71)	0.67 (0.60, 0.74)
Double-outlet right ventricle					
Q20.1	2.24 (2.07, 2.42)	0.97 (0.63, 1.43)	1.05 (0.99, 1.12)	1.56 (1.41, 1.74)	1.69 (1.58, 1.81)
Other single ventricle (double-inlet ventricle)					
Q20.4	0.81 (0.71, 0.93)	0.23 (0.08, 0.51)	0.41 (0.37, 0.46)	0.61 (0.52, 0.73)	0.79 (0.72, 0.88)
Atrioventricular septal defect					
Q21.2	5.84 (5.56, 6.13)	3.26 (2.60, 4.04)	3.15 (3.04, 3.27)	5.62 (5.32, 5.93)	5.37 (5.17, 5.58)
Esophageal atresia (±tracheoesophageal fistula)					
Q39.0 and Q39.1	2.56 (2.38, 2.76)	2.25 (1.71, 2.91)	2.28 (2.18, 2.38)	2.77 (2.56, 2.99)	2.37 (2.24, 2.51)
Duodenal/small-bowel atresia					
Q41	4.10 (3.86, 4.34)	2.49 (1.70, 3.55)	2.11 (1.99, 2.25)	3.40 (3.30, 3.60)	3.30 (3.10, 3.40)

Table 3 (continued)

	AOK 2006–2017	EUROCAT (German registries) 2005–2017	EUROCAT (all full registries) 2005–2017	US, NBDPN (European descent) 2010–2014	US, NBDPN (all ethnicities) 2010–2014
Anal/rectal atresia Q42	5.35 (5.09, 5.64)	3.69 (2.98, 4.51)	2.54 (2.43, 2.64)	4.39 (4.12, 4.68)	4.57 (4.38, 4.77)
Diaphragmatic hernia Q79.0	2.61 (2.42, 2.81)	1.75 (1.27, 2.34)	2.10 (2.01, 2.19)	2.83 (2.62, 3.06)	2.87 (2.72, 3.02)
Omphalocele Q79.2	2.03 (1.87, 2.20)	1.16 (0.79, 1.66)	1.21 (1.15, 1.29)	2.47 (2.27, 2.68)	2.45 (2.32, 2.59)
Gastroschisis Q79.3	2.74 (2.55, 2.94)	3.22 (2.57, 3.99)	2.32 (2.22, 2.42)	5.20 (4.91, 5.50)	5.39 (5.19, 5.59)
Biliary atresia Q44.2	0.61 (0.52, 0.71)	0.43 (0.21, 0.76)	0.33 (0.30, 0.37)	0.70 (0.60, 0.70)	0.50 (0.50–0.60)
Bladder exstrophy/epispadia Q64.0, Q64.1	0.45 (0.38, 0.54)	0.58 (0.33, 0.96)	0.50 (0.45, 0.54)		
Posterior urethral valve/prune belly Q64.2, Q79.4	1.59 (1.45, 1.75)	0.66 (0.38, 1.06)	0.90 (0.84, 0.96)		

AOK, Allgemeine Ortskrankenkasse; EUROCAT, European Surveillance of Congenital Anomalies; US-NBDPN, United States National Birth Defects Prevention Network; ICD, International Classification of Diseases; CI, confidence interval.

infants. Birth defects have been reported to be twice as common in preterm infants (gestational age <37 weeks) compared to term infants [6–9] and 4–7-fold as common in very preterm infants (gestational age <32 weeks) [8, 10, 11]. Gestational age however has been found to account for <50% of the effect of cardiac MCMs on birthweight [12]. More infants with an MCM, as compared to those without an MCM, are born small for gestational age [13–18]. In a cohort of infants born alive with a birthweight below 400 g, the rate of the MCM was close to 7% (15/220) [19]. Some MCMs lead to polyhydramnios, such as gastroschisis, esophageal, or duodenal atresia, and thereby cause premature rupture of the membranes, uterine contractions, and preterm delivery [20]. In addition, an antenatal diagnosis of gastroschisis often prompts a decision for an elective cesarean section several weeks before the estimated date of birth to reduce in utero harm from amniotic fluid to the exposed bowel. Therefore, it is not surprising that LBW infants with gastroschisis in our study outnumbered those with NBW even in absolute numbers.

Depending on the type of MCM, VLBW and NBW infants with MCMs had lower rates of survival as expected, suggesting a synergistic rather than additive effect on mortality. The contribution of some MCMs to LBW/VLBW may actually underestimate this synergism. Excess mortality in very preterm infants, as opposed to term infants, has been reported before in US, French, and English cohorts of infants with severe cardiac MCMs [6, 13, 14] and may be related to technical challenges during early surgical repair or complications by deferring surgery. Moreover, if surgery provides palliation without true repair, for example, in infants with hypoplastic left-heart syndrome or spina bifida, palliative care may be preferred when such MCMs occur in VLBW infants.

The prevalence of most MCMs from our study was higher than the estimate provided by the European Surveillance of Congenital Anomalies (EUROCAT) [21] 2005–2017 and 2 local registries in the Eastern and Western part of Germany (Sachsen, Anhalt, and Mainz) combined, with the exception of congenital mitral stenosis or insufficiency, aortic atresia/hypoplasia, gastroschisis, and bladder exstrophy/epispadias (Table 3). Thus, the approach appears to have good sensitivity for the MCM studied. Our prevalence data were similar to those reported by the National Birth Defects Prevention Network (NBDPN) in the USA [22] with the exception of gastroschisis, which was more common in the USA than in Germany. This may be explained by the strongly increased rates of gastroschisis in women below 20 years of age [23]

Table 4. Prevalence (p/10,000) of major congenital malformations in VLBW infants

	AOK (2006–2017)		NICHD (1,998–2007)		Pediatrix (1,997–2012)		VON (2006–2007)		NRN-J (2003–2016)		iNeo (2007–2015)	
	n	p/10,000 (95% CI)	*N*	p/10,000 (95% CI)	*n*	p/10,000 (95% CI)	*n*	p/10,000 (95% CI)	*N*	p/10,000 (95% CI)	*N*	p/10,000 (95% CI)
	34,401		37,262		105,539		99,786		57,730		78,956	
ICD-10												
Neural tube defects	41	11.92 (8.79, 16.16)							46	7.97 (5.67, 10.27)		
Encephalocele												
Q01	10	2.91 (1.58, 5.35)							2	0.35 (0.00, 0.83)		
Spina bifida/meningomyelocele												
Q05	31	9.01 (6.35, 12.79)	22	5.90 (3.44, 8.37)					44	7.62 (5.37, 9.87)		
Severe cardiac malformations	607	176.45 (163.07, 190.91)	365	97.96 (87.96, 107.95)	299	28.33 (25.12, 31.54)						
Category A (compromised systemic output)												
Aortic valve stenosis												
Q23.0	32	9.30 (6.59, 13.13)			30	2.84 (1.83, 3.86)	23	2.30 (1.36, 3.25)	2	0.35 (0.00, 0.83)	55	6.97 (5.12, 8.81)
Congenital mitral stenosis												
Q23.2	13	3.78 (2.21, 6.47)									3	0.38 (0.00, 0.81)
Congenital mitral insufficiency												
Q23.3	102	29.65 (24.43, 35.98)									7	0.89 (0.23, 1.54)
Hypoplastic left-heart syndrome												
Q23.4	33	9.59 (6.83, 13.47)	19	5.10 (2.81, 7.39)	20	1.90 (1.06, 2.73)	54	5.41 (3.97, 6.85)	29	5.02 (3.20, 6.85)	11	1.39 (0.57, 2.22)
Coarctation, interrupted aortic arch												
Q25.1	86	25.00 (20.25, 30.86)	30	8.05 (5.17, 10.93)	72	6.82 (5.25, 8.40)	155	15.53 (13.09, 17.98)	62	10.74 (8.07, 13.41)	37	4.69 (3.18, 6.20)
Aortic atresia/hypoplasia												
Q25.2	4	1.16 (0.45, 2.99)							3	0.52 (0.00, 1.11)	7	0.89 (0.23, 1.54)
Category B (sustained cyanosis)												
Transposition of the great arteries												
Q20.3	30	8.72 (6.11, 12.45)	19	5.10 (2.81, 7.39)	18	1.71 (0.92, 2.49)	62	6.21 (4.67, 7.76)	28	4.85 (3.05, 6.65)	55	6.97 (5.12, 8.81)
Tetralogy of Fallot												
Q21.3	62	18.02 (14.06, 23.10)	38	10.20 (6.96, 13.44)	53	5.02 (3.67, 6.37)	166	16.64 (14.11, 19.16)	87	15.07 (11.91, 18.23)	118	14.95 (12.25, 17.64)
Pulmonary valve atresia												
Q22.0	24	6.98 (4.69, 10.38)	9	2.42 (0.84, 3.99)			57	5.71 (4.23, 7.19)	60	10.39 (7.76, 13.02)	22	2.79 (1.62, 3.95)

Neonatology 2022;119:41–59
DOI: 10.1159/000520113

Table 4 (continued)

	AOK (2006–2017)		NICHD (1,998–2007)		Pediatrix (1,997–2012)		VON (2006–2007)		NRN-J (2003–2016)		iNeo (2007–2015)	
	n	p/10,000 (95% CI)	*N*	p/10,000 (95% CI)	*n*	p/10,000 (95% CI)	*n*	p/10,000 (95% CI)	*N*	p/10,000 (95% CI)	*N*	p/10,000 (95% CI)
Tricuspid atresia												
Q22.4	11	3.20 (1.79, 5.73)	1	0.27 (0.00, 0.79)	10	0.95 (0.36, 1.53)	25	2.51 (1.52, 3.49)	11	1.91 (0.78, 3.03)	1	0.13 (0.00, 0.37)
Ebstein anomaly												
Q22.5	6	1.74 (0.80, 3.81)			5	0.47 (0.06, 0.89)			4	0.69 (0.01, 1.37)	5	0.63 (0.08, 1.19)
Hypoplastic right-heart syndrome												
Q22.6	13	3.78 (2.21, 6.47)	19	5.10 (2.81, 7.39)			54	5.41 (3.97, 6.85)			2	0.25 (0.00, 0.60)
Pulmonary artery atresia												
Q25.5	18	5.23 (3.31, 8.27)			16	1.52 (0.77, 2.26)	73	7.32 (5.64, 8.99)			7	0.89 (0.23, 1.54)
Total anomalous pulmonary venous return												
Q26.2	9	2.62 (1.38, 4.97)	5	1.34 (0.17, 2.52)	7	0.66 (0.17, 1.15)	21	2.10 (1.20, 3.00)	24	4.16 (2.49, 5.82)	1	0.13 (0.00, 0.37)
Category C (congestive heart failure/pulmonary over-circulation)												
Truncus arteriosus												
Q20.0	16	4.65 (2.86, 7.55)	6	1.61 (0.32, 2.90)	9	0.85 (0.30, 1.41)	24	2.41 (1.44, 3.37)	14	2.43 (1.15, 3.70)	32	4.05 (2.65, 5.46)
Double-outlet right ventricle												
Q20.1	26	7.56 (5.16, 11.07)	10	2.68 (1.02, 4.35)			68	6.81 (5.20, 8.43)	93	16.11 (12.84, 19.38)	17	2.15 (1.13, 3.18)
Other single ventricle (double-inlet ventricle)												
Q20.4	10	2.91 (1.58, 5.35)	1	0.27 (0.00, 0.79)	6	0.57 (0.11, 1.02)	86	8.62 (6.80, 10.44)	10	1.73 (0.66, 2.81)	5	0.63 (0.08, 1.19)
Atrioventricular septal defect												
Q21.2	112	32.56 (27.07, 39.16)	8	2.15 (0.66, 3.63)	58	5.50 (4.08, 6.91)	81	8.12 (6.35, 9.88)	32	5.54 (3.62, 7.46)	58	7.35 (5.46, 9.24)
Multiple cardiac MCMs	67	19.48 (15.34, 24.72)	87	23.35 (18.45, 28.25)								
Gastrointestinal and abdominal malformations	499	145.05 (132.95, 158.24)	186	49.92 (42.76, 57.07)					528	91.46 (83.69, 99.23)		
Esophageal atresia (±tracheoesophageal fistula)												
Q39.0 and Q39.1	96	27.91 (22.86, 34.06)	48	12.88 (9.24, 16.52)					163	28.23 (23.91, 32.56)		
Duodenal/small-bowel atresia												
Q41	190	55.23 (47.93, 63.63)	39	10.47 (7.18, 13.75)					136	23.56 (19.60, 27.51)		
Anal/rectal atresia												
Q42	95	27.62 (22.60, 33.74)	11	2.95 (1.21, 4.70)					101	17.50 (14.09, 20.90)		

Table 4 (continued)

	AOK (2006–2017)		NICHD (1,998–2007)		Pediatrix (1,997–2012)		VON (2006–2007)		NRN-J (2003–2016)		iNeo (2007–2015)	
	n	p/10,000 (95% CI)	*N*	p/10,000 (95% CI)	*n*	p/10,000 (95% CI)	*n*	p/10,000 (95% CI)	*N*	p/10,000 (95% CI)	*N*	p/10,000 (95% CI)
Diaphragmatic hernia												
Q79.0	35	10.17 (7.32, 14.15)	22	5.90 (3.44, 8.37)					51	8.83 (6.41, 11.26)		
Omphalocele												
Q79.2	38	11.05 (8.05, 15.16)	22	5.90 (3.44, 8.37)					39	6.76 (4.64, 8.88)		
Gastroschisis												
Q79.3	45	13.08 (9.78, 17.50)	44	11.81 (8.32, 15.30)					38	6.58 (4.49, 8.67)		
Biliary atresia												
Q44.2	15	4.36 (2.64, 7.19)							4	0.69 (0.01, 1.37)		
Urethral and urinary bladder malformations	26	7.56 (5.16, 11.07)										
Bladder exstrophy/epispadia												
Q64.0 and Q64.1	10	2.91 (1.58, 5.35)	3	0.81 (0.00, 1.72)					1	0.17 (0.00, 0.51)		
Posterior urethral valve/prune belly syndrome												
Q64.2 and Q79.4	16	4.65 (2.86, 7.55)							1	0.17 (0.00, 0.51)		

Comparison of 6 contemporaneous cohorts. AOK, Allgemeine Ortskrankenkasse, denominator: all infants <1,500 g birthweight; NICHD, National Institute of Child Health and Human Development, denominator: infants weighing 401–1,500 g at birth [14]; Pediatrix, denominator: infants <1,500 g birthweight and<32 weeks gestational age; VON, Vermont Oxford Network, denominator: infants <1,500 g birthweight or <30 weeks gestational age [26]; NRN-J, Neonatal Research Network Japan, denominator: preterm infants ≤1,500 g birthweight [27]; iNeo, International Network for Evaluation of Outcomes in Neonates, denominator: birthweight <1,500 g and gestational age 24–31 weeks [4]; VLBW, very low birthweight; ICD, International Classification of Diseases.

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Table 5. Mortality (95% CI) of major congenital malformations in VLBW infants

	AOK			NICHD			Pediatrix			VON			NRN-J			iNeo		
	died	total	mortality	died	total	mortality	died	total	mortality	died	total	mortality	died	total	mortality	died	total	mortality
All infants	4,132	34,401	0.120 (0.117, 0.124)	7,361	37,262	0.074 (0.071, 0.076)		105,539		13,066	99,786	0.131 (0.129, 0.133)	2,069	57,730	0.036 (0.034, 0.037)	6,928	78,956	0.088 (0.086, 0.090)
Neural tube defects	24	41	0.585 (0.434, 0.722)										7	46	0.152 (0.048, 0.256)			
Encephalocele Q01	6	10	0.600 (0.313, 0.832)										0	2	0.000 (0.000, 0.000)			
Spina bifida/meningomyelocele Q05	18	31	0.581 (0.408, 0.736)	9	22	0.409 (0.204, 0.615)							7	44	0.159 (0.051, 0.267)			
Severe cardiac malformations	220	607	0.362 (0.325, 0.401)	129	365	0.353 (0.304, 0.402)	163	299	0.545 (0.489, 0.602)									
Category A (compromised systemic output)	90	270	0.323 (0.270, 0.380)													16	77	0.208 (0.117, 0.298)
Aortic valve stenosis Q23.0	8	32	0.250 (0.133, 0.421)				6	30	0.200 (0.057, 0.343)	6	23	0.250 (0.073, 0.427)	0	2	0.000 (0.000, 0.000)	18	55	0.327 (0.203, 0.451)
Congenital mitral stenosis Q23.2	8	13	0.615 (0.355, 0.823)													1	3	0.333 (0.000, 0.867)
Congenital mitral insufficiency Q23.3	17	102	0.167 (0.107, 0.251)													1	7	0.143 (0.000, 0.402)
Hypoplastic left-heart syndrome Q23.4	26	33	0.788 (0.622, 0.893)	16	19	0.842 (0.678, 1.000)	17	20	0.850 (0.694, 1.000)	46	54	0.852 (0.757, 0.947)	20	29	0.690 (0.521, 0.858)	6	11	0.545 (0.251, 0.840)
Coarctation, interrupted aortic arch Q25.1	29	86	0.337 (0.246, 0.442)	8	30	0.267 (0.108, 0.425)	39	72	0.542 (0.427, 0.657)	47	155	0.303 (0.231, 0.375)	22	62	0.355 (0.236, 0.474)	6	37	0.162 (0.043, 0.281)
Aortic atresia/hypoplasia Q25.2	2	4	0.500 (0.150, 0.850)										0	3	0.000 (0.000, 0.000)	3	7	0.429 (0.062, 0.795)

Table 5 (continued)

	AOK			NICHD			Pediatrix			VON			NRN-J			iNeo		
	died	total	mortality	died	total	mortality	died	total	mortality	died	total	mortality	died	total	mortality	died	total	mortality
Category B (sustained cyanosis)	73	173	0.422 (0.351, 0.496)													66	429	0.154 (0.120, 0.188)
Transposition of the great arteries Q20.3	16	30	0.533 (0.361, 0.698)	7	19	0.368 (0.152, 0.585)	13	18	0.722 (0.515, 0.929)	27	62	0.433 (0.310, 0.556)	9	28	0.321 (0.148, 0.494)	18	55	0.327 (0.203, 0.451)
Tetralogy of Fallot Q21.3	21	62	0.339 (0.233, 0.463)	16	38	0.421 (0.264, 0.578)	26	53	0.491 (0.365, 0.625)	54	166	0.323 (0.252, 0.394)	14	87	0.161 (0.084, 0.238)	12	118	0.102 (0.047, 0.156)
Pulmonary valve atresia Q22.0	11	24	0.458 (0.279, 0.649)	4	9	0.444 (0.120, 0.769)				29	57	0.507 (0.377, 0.637)	28	60	0.467 (0.340, 0.593)	2	22	0.091 (0.000, 0.211
Tricuspid atresia Q22.4	3	11	0.273 (0.097, 0.566)	1	1	1.000 (1.000, 1.000)	7	10	0.700 (0.416, 0.984)	17	25	0.667 (0.482, 0.852)	4	11	0.364 (0.079, 0.648)	1	1	1.000 (1.000, 1.000)
Ebstein anomaly Q22.5	3	6	0.500 (0.188, 0.812)				3	5	0.600 (0.171, 1.000)				2	4	0.500 (0.010, 0.990)	3	5	0.600 (0.171, 1.000)
Hypoplastic right-heart syndrome Q22.6	6	13	0.462 (0.232, 0.709)													0	2	0.000 (0.000, 0.000)
Pulmonary artery atresia Q25.5	9	18	0.500 (0.290, 0.710)				12	16	0.750 (0.538, 0.962)	37	73	0.507 (0.392, 0.622)				1	7	0.143 (0.000, 0.402)
Total anomalous pulmonary venous return Q26.2	4	9	0.444 (0.189, 0.733)	2	5	0.400 (0.000, 0.829)	5	7	0.714 (0.380, 1.000)	15	21	0.714 (0.521, 0.907)	8	24	0.333 (0.145, 0.522)	1	1	1.000 (1.000, 1.000)
Category C (congestive heart failure/pulmonary over-circulation)	57	164	0.348 (0.279, 0.423)													31	103	0.301 (0.212, 0.390)
Truncus arteriosus Q20.0	8	16	0.500 (0.280, 0.720)	3	6	0.500 (0.100, 0.900)	9	9	1.000 (1.000, 1.000)	16	24	0.667 (0.478, 0.856)	6	14	0.429 (0.169, 0.688)	9	32	0.281 (0.125, 0.437)

Neonatology 2022;119:41–59
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Table 5 (continued)

	AOK			NICHD			Pediatrix			VON			NRN-J			iNeo		
	died	total	mortality	died	total	mortality	died	total	mortality	died	total	mortality	died	total	mortality	died	total	mortality
Double-outlet right ventricle																		
Q20.1	21	26	0.808 (0.621, 0.915)	5	10	0.500 (0.190, 0.810)				35	68	0.522 (0.403, 0.641)	39	93	0.419 (0.319, 0.520)	6	17	0.353 (0.126, 0.580)
Other single ventricle (double-inlet ventricle)																		
Q20.4	5	10	0.500 (0.237, 0.763)	1	1	1.000 (1.000, 1.000)	5	6	0.833 (0.535, 1.000)	21	25	0.840 (0.696, 0.984)	7	10	0.700 (0.416, 0.984)	3	5	0.600 (0.171, 1.000)
Atrioventricular septal defect																		
Q21.2	23	112	0.205 (0.141, 0.289)	1	8	0.125 (0.000, 0.354)	35	58	0.603 (0.478, 0.729)	39	81	0.481 (0.372, 0.590)	10	32	0.313 (0.152, 0.473)	17	58	0.293 (0.176, 0.410)
Multiple cardiac MCMs	39	67	0.582 (0.463, 0.693)	38	87	0.437 (0.333, 0.541)												
Gastrointestinal and abdominal malformations	135	499	0.271 (0.233, 0.311)	66	186	0.355 (0.286, 0.424)							174	528	0.330 (0.289, 0.370)			
Esophageal atresia (±tracheoesophageal fistula)																		
Q39.0 and Q39.1	28	96	0.292 (0.210, 0.389)	12	48	0.250 (0.128, 0.373)							69	163	0.423 (0.347, 0.499)			
Duodenal/small-bowel atresia																		
Q41	31	190	0.163 (0.117, 0.222)	8	39	0.205 (0.078, 0.332)							27	136	0.199 (0.131, 0.266)			
Anal/rectal atresia																		
Q42	22	95	0.232 (0.158, 0.326)	0	11	0.000 (0.000, 0.000)							17	101	0.168 (0.095, 0.241)			
Diaphragmatic hernia																		
Q79.0	25	35	0.714 (0.549, 0.837)	19	22	0.864 (0.720, 1.000)							35	51	0.686 (0.559, 0.814)			
Omphalocele																		
Q79.2	19	38	0.500 (0.348, 0.652)	11	22	0.500 (0.291, 0.709)							17	39	0.436 (0.280, 0.592)			
Gastroschisis																		
Q79.3	10	45	0.222 (0.125, 0.363)	16	44	0.364 (0.221, 0.506)							9	38	0.237 (0.102, 0.372)			

Table 5 (continued)

	AOK			NICHD			Pediatrix			VON			NRN-J			iNeo		
	died	total	mortality	died	total	mortality	died	total	mortality	died	total	mortality	died	total	mortality	died	total	mortality
Biliary atresia Q44.2	1	15	0.067 (0.012, 0.298)										0	4	0.000 (0.000, 0.000)			
Urethral and urinary bladder malformations	8	26	0.308 (0.165, 0.500)															
Bladder exstrophy/epispadia Q64.0 and Q64.1	4	10	0.400 (0.168, 0.687)	1	3	0.333 (0.000, 0.867)							0	1	0.000 (0.000, 0.000)			
Posterior urethral valve/prune belly syndrome Q64.2 and Q79.4	4	16	0.250 (0.102, 0.495)										0	1	0.000 (0.000, 0.000)			

Comparison of 6 contemporaneous cohorts. AOK, Allgemeine Ortskrankenkasse; denominator: all infants <1,500 g birthweight; NICHD, National Institute of Child Health and Human Development; denominator: infants weighing 401-1,500 g at birth [14]; Pediatrix, denominator: infants <1,500 birthweight and gestational age <32 weeks [25]; VON, Vermont Oxford Network; denominator: infants <1,500 g birthweight or <30 weeks gestational age [26]; NRN-J, Neonatal Research Network Japan; denominator: preterm infants ≤1,500 g birthweight [27]; iNeo, International Network for Evaluation of Outcomes in Neonates; denominator: birthweight <1,500 g and gestational age 24–31 weeks [4]; VLBW, very low birthweight; ICD, International Classification of Diseases.

and the almost 4 times increased rates of teenage pregnancies in the USA, as compared to Europe [24].

The prevalence of MCMs in VLBW infants was compared with recent reports of 5 network-based cohort studies: the VON (99,786 VLBW infants 2006–2007, USA) [25], the Pediatrix Medical Group (105,539 VLBW infants 1,997–2012, USA) [26], the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network (NICHD, 35,231 VLBW infants 1,998–2007, USA) [14], the Neonatal Research Network of Japan 2003–2016 (NRN-J, 57,730 VLBW infants 2003, 2016 Japan) [27], and the iNeo (78,956 VLBW infants 2007–2015, Australia, New Zealand, Canada, Finland, Japan, Israel, Italy, Spain, Sweden, and Switzerland) [4]. The prevalence of most reported MCMs for VLBW infants was significantly lower in the network-based cohort studies than in the current population-based study with the exception of the rates of spina bifida and esophageal atresia that were similar to NRN-J, and the rate of gastroschisis that was similar to the reported NICHD rate (Table 4). While the data presented here include all infants below 1,500 g birthweight, the definitions of VLBW as the denominator differed slightly, excluding infants ≤400 g birth (NICHD), <24 weeks (iNeo), >32 weeks (Pediatrix) or >36 weeks gestational age (NRN-J), or including also infants >1,500 g but with a gestational age <30 weeks (VON). Furthermore, the selection criteria for participation in networks are different. Our data are based on a large insurance database representing the population studied (excess for high-income residents), while networks in the USA represent neonatal intensive care units collaborating for research activities (NICHD), economic reasons (Pediatrix), or quality improvement (VON).

We found that the overall 1-year survival rate of VLBW infants of our study cohort born from 2006–2017 (88.0%) was higher than the rates of survival to discharge of the 1,998–2007 NICHD cohort (80.25%) [14], similar to the 1-year survival rate of the VON 2006–2007 cohort (87.3%) [26] but lower than the rates of survival to discharge of the 2007–2015 iNeo (91.0%) [4] or the 2003–2016 NRN-J (92.8%) [27] cohorts. Post-discharge mortality of VLBW infants has been estimated close to 1.5% [28].

In contrast, our 1-year survival rates of VLBW infants with MCMs did not differ significantly from reported network survival to discharge rates except for a lower survival of VLBW infants with spina bifida/meningomyelocele than the NRN-J cohort (Table 5). We assume that decisions to withhold or withdraw intensive care in a VLBW infant with spina bifida are probably more commonly undertaken in Germany or the USA than in Japan,

which may explain the marked difference of mortality. However, universal availability of prenatal diagnostic testing including ultrasound may lead to prenatal selection via abortion, resulting in a higher percentage of live-born babies whose parents request active care.

Conclusions

This population-based cohort analysis provides a robust estimate of prevalence and mortality of a large series of MCMs in live-born NBW, LBW, and VLBW infants. The data collected routinely for nonscientific purposes over prolonged periods of time may be helpful as a source of reference for physicians, parents, and health policy makers. While virtually all MCMs are more common in VLBW and LBW, as compared to NBW infants, many also carry excess mortality when occurring in VLBW/LBW infants. The high burden of disease calls for efforts to channel treatment of VLBW/LBW infants with MCMs to a limited number of specialized hospitals.

Statement of Ethics

This study was approved by the Institutional Review Board (Ethikkommission der Charité, Universitätsmedizin Berlin, EA2/191/20). Requirement for informed consent was waived as the analysis was restricted to de-identified data collected according to federal laws.

Conflict of Interest Statement

The authors have no conflict of interest to disclose.

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Author Contributions

Janine Kröger, Christian Günster, Elke Jeschke, and Jürgen Malzahn collected, verified, and analyzed data; Günther Heller, Dieter Grab, Klaus Vetter, Michael Abou, Dakn, and Helmut Hummler contributed to study design, data interpretation, and literature search; Christoph Bührer analyzed data, framed the analytical conclusions, drafted the initial, and edited the final manuscript; all the authors conceptualized the study, reviewed and revised the manuscript, and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Data Availability Statement

The Ethical Committee restricted analysis and publication to aggregated data, all of which are shown in this manuscript. No further data can be shared without further ethical approval.

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