Supplementary data for the manuscript: Prevalence of congenital hemolytic disorders in Denmark, 2000-2016

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Supplementary table 1 – Grouping of ICD-8 and ICD-10 diagnoses from the Danish National Patient Register and laboratory test results from the Hemolysis Laboratory Database

Group	Disease	DNRP definition ICD 8	DNRP definition ICD 10	Laboratory definition (*)
Alpha Thalassemia				
	Alpha Thalassemia trait	n/a	n/a	Compound Heterozygote α-Thalassemia (α4,2 , α3,7) Heterozygote α-Thalassemia (α3,7 , α) Homozygote α-Thalassemia (α3,7, α3,7) Heterozygote α-Thalassemia (αSEA, α) Heterozygote α-Thalassemia (α4,2, α) Homozygote α-Thalassemia (α4,2, α4,2) Heterozygote α-Thalassemia (αMED, α) Heterozygote α-Thalassemia (α20,5 , α) Heterozygote α-Thalassemia (αFIL , α)
	HbH disease	n/a	n/a	HbH disease
	Alpha Thalassemia NOS	n/a	D560	n/a
Beta Thalassemia				
	Beta Thalassemia minor	n/a	D563	Heterozygote ß-Thalassemia Heterozygotic beta deletion Heterozygote for Delta-Beta-Thalassemia Compound Heterozygote ß-Thalassemia and Heterozygotic HbD
	Beta Thalassemia intermedia	n/a	D561C, D563C	Homozygote ß-Thalassemia Compound Heterozygote HbE / ß-Thalassemia
	Beta Thalassemia major	n/a	D561A, D561B	Homozygote ß-Thalassemia
	Thalassemia NOS	28249	D56, D568, D569	n/a
	HbE trait	n/a	n/a	Heterozygote HbE
	HbEE disease	n/a	D582E	Homozygote HbEE
Sickle cell				
	Sickle cell trait	n/a	D573	Heterozygote HbS
	Sickle cell disease	28250	D57, D570, D571, D572, D572A, D572B, D572C, D572D, D578	Homozygote HbSS Compound Heterozygote HbS / ß-Thalassemia Compound Heterozygote HbS / HbC
Other congenital				
	G6PD	28229	D550	G6PD deficiency
	PKD	28230	D552	PK-deficiency
	Hereditary Spherocytosis	28209	D580, D580A	n/a
	Hereditary Elliptocytosis	28219	D581, D581A	n/a
Poorly defined				
	Congenital hemolysis NOS	28299, 28239	D58, D588, D589	n/a
	Residual	28258 28259	D582, D582A, D582B,	Heterozygote HbC Homozygote HbC Heterozygote HbD

		D582C,	Homozygote HbDD
		D582D,	Heterozygotic other hemoglobin variant
		D588A,	Rare variant of Alpha1 or Alpha2 gene.
		D55, D551,	Rare variant of Beta-gene
		D553,	Only genetic changes
		D558, D559	HbBart's hydrops foetalis
			Unknown variant
			Homozygotic GammaG promotor mutation
			Heterozygotic GammaG promotor mutation
			Heterozygotic Hereditary persistence of fetal hemoglobin
			Heterozygotic high affinity hemoglobin
			Heterozygotic low affinity hemoglobin
Not congenital hemolysis			
Acquired hemolysis	28309, 28390, 28391, 28392, 28393, 28394, 28395, 28399	D59, D590, D591, 591A, D592, D593, D594, D594C, D596A,D598, D599,	n/a
Immune thrombocytopenia	28710, 28711, 28718, 28719	D693	n/a

ICD-8 and ICD-10 codes used to define the extraction and grouping of diseases from the Danish National Patient Register and the laboratory database to form the cohort. The suffixes "A", "B", "C" and "D" is a Danish adaptation in the ICD-10 system. The acquired hemolysis codes and the ITP codes are included to identify patients with acquired hemolysis, which are excluded from this study. The Herlev Laboratory Database include laboratory test of hemoglobinopathies and enzymopathies, hence Hereditary Spherocytosis and Elliptocytosis are based on diagnosis in the Danish National Patient Register. The list of diagnoses therefore include diagnosis made by the laboratory and their association with a corresponding ICD-8/10 diagnosis. The diagnoses made by the laboratory are based on hemoglobin separation based on high-pressure liquid chromatography (HPLC) and subsequent verification of genetic abnormalities in the alpha- and beta-globin genes by polymerase chain reaction. Enzymopathies are diagnosed by enzyme activity assays (G6PD) or genetic sequencing (PKD). Specifications of the test can be provided by the corresponding author or by direct contact to the hemolysis laboratory. G6PD: Glucose-6-phosphate-deficiency, HbH: hemoglobin H, deficiency, HbC: heterozygotic hemoglobin C, HbCC: homozygotic hemoglobin C, HbD: heterozygotic hemoglobin D, HbDD: homozygotic hemoglobin D, HbE: heterozygotic hemoglobin E, HbEE: homozygotic hemoglobin EE, HbS: heterozygotic hemoglobin S, n/a: not applicable, ICD: International classification of diseases, NOS: Not otherwise specified, PKD: Pyruvate kinase

Supplementary table 2 – Comparison of the population of diagnosis and agreement of diagnosis between main model and sensitivity model

Disease	Subgroup	Main model, count	Sensitivity model, count	Agreement	Recall	PPV (%)
Alpha Thalassemia NOS		70	227	70	100.0	30.8
Alpha Thalassemia trait		1477	n/a	0	0.0	.
Beta Thalassemia intermedia		31	14	11	35.5	78.6
Beta Thalassemia minor		2566	1130	998	38.9	88.3
Beta thalassemia major		52	37	29	55.8	78.4
Congenital hemolysis NOS		1316	1470	1316	100.0	89.5
G6PD		383	336	323	84.3	96.1
HbE trait		434	n/a	0	0.0	.
HbEE disease		107	<3	0	0.0	0.0
HbH disease		52	n/a	0	0.0	.
Hereditary spherocytosis		1289	1230	1224	95.0	99.5
PKD		37	28	28	75.7	100.0
Sickle cell disease		236	251	206	87.3	82.1
Sickle cell trait		635	66	63	9.9	95.5
Thalassemia NOS		267	522	260	97.4	49.8
Residual		1059	690	653	61.5	94.6
	Elliptocytosis	*44*	*42*	*40*		
	HbBart's hydrops foetalis	*<3*	*<3*	*<3*		
	HbC and HbCC disease	*100*	*0*	*0*		
	HbD and HbDD disease	*115*	*<3*	*<3*		
	Other enzymopathy	*405*	*406*	*397*		
	Other hemoglobinopathia	*388*	*235*	*206*		
	Stomatocytosis	*7*	*5*	*5*		

The total number of patients identified by the two models (main and sensitivity) is listed along with the agreement. The recall denotes the number of patients and percentage of patients identified by both models compared with the number identified by the main model—i.e. the probability that at patient identified by the main model will be identified by the sensitivity model. The positive predictive value (PPV) is

calculated as the number of patients identified by both models compared with the numbers of patients identified by the sensitivity model—i.e. the probability that a patient identified by the sensitivity model will be identified by the main model. Cells with less than three persons is anonymized to "<3", hence the Residual total in the main model column do not include the Bart's hydrops foetalis.

G6PD: Glucose-6-phosphate-deficiency, HbH: hemoglobin H, deficiency, HbC: heterozygotic hemoglobin C, HbCC: homozygotic hemoglobin C, HbD: heterozygotic hemoglobin D, HbDD: homozygotic hemoglobin D, HbE: heterozygotic hemoglobin E, HbEE: homozygotic hemoglobin EE, HbS: heterozygotic hemoglobin S, n/a: not applicable, NOS: Not otherwise specified, PKD: Pyruvate kinase

Supplementary table 3 - Characteristics of patients with congenital hemolytic disorders in Denmark 2000-2016

	HbE n=434	HbEE disease n=107	G6PD n=383	PKD n=37	Congenital hemolysis NOS n=1316	Residual n=1061
Women (% [95% CI])	77.9 [73.7; 81.7]	88.8 [81.2; 94.1]	28.5 [24.0; 33.3]	40.5 [24.8; 57.9]	53.8 [51.1; 56.5]	59.0 [56.0; 62.0]
Danish origin (% [95% CI])	14.7 [11.5; 18.4]	6.5 [2.7; 13.0]	29.2 [24.7; 34.1]	89.2 [74.6; 97.0]	92.2 [90.6; 93.6]	63.6 [60.6; 66.5]
Splenectomized after 1977 (% [95% CI])	0.2 [0.0; 1.3]	0.0 [0.0; 3.4]	1.3 [0.4; 3.0]	27.0 [13.8; 44.1]	8.1 [6.6; 9.7]	1.8 [1.1; 2.8]
Age at diagnosis (median (IQR))	32.7 (25.1; 42.6)	35.5 (28.6; 46.9)	6.4 (1.9; 30.2)	18.5 (3.9; 65.2)	67.3 (44.3; 78.0)	50.8 (29.3; 72.8)

Basic description of included patients with congenital hemolysis, subgroups not included in primary section of the article.

Abbreviation: CI: confidence interval, G6PD: Glucose-6-phosphate-deficiency, IQR: interquartile range, HbE: heterozygotic hemoglobin E, HbEE: homozygotic hemoglobin EE, NOS: Not otherwise specified, PKD: Pyruvate kinase.

Supplementary table 4 - Prevalence of other congenital hemolytic disorders in Denmark in 2000, 2007 and 2015

		Prevalence per 100,000 persons [95% CI]		
		2000	**2007**	**2015**
Congenital hemolysis NOS				
	All	5.82 [5.19; 6.50]	5.20 [4.61; 5.84]	5.12 [4.55; 5.75]
	Age < 20	7.76 [6.30; 9.46]	9.05 [7.51; 10.81]	10.95 [9.23; 12.89]
	Age 20-50	4.76 [3.92; 5.72]	4.78 [3.92; 5.77]	4.85 [3.99; 5.84]
	Age > 50	5.84 [4.75; 7.10]	2.92 [2.19; 3.81]	1.70 [1.19; 2.37]
G6PD				
	All	1.80 [1.46; 2.20]	3.34 [2.87; 3.86]	4.52 [3.99; 5.11]
	Age < 20	6.34 [5.02; 7.89]	11.52 [9.77; 13.49]	15.28 [13.24; 17.54]
	Age 20-50	0.59 [0.33; 1.00]	1.02 [0.65; 1.53]	1.75 [1.25; 2.38]
	Age > 50	0.12 [0.01; 0.42]	0.27 [0.09; 0.63]	0.73 [0.41; 1.20]
PKD				
	All	0.21 [0.10; 0.37]	0.29 [0.17; 0.48]	0.42 [0.27; 0.63]
	Age < 20	0.63 [0.27; 1.25]	0.82 [0.41; 1.47]	1.29 [0.75; 2.07]
	Age 20-50	0.08 [0.01; 0.31]	0.09 [0.01; 0.32]	0.13 [0.03; 0.38]
	Age > 50	0.06 [0.00; 0.33]	0.16 [0.03; 0.47]	0.19 [0.05; 0.50]
HbE				
	All	0.41 [0.26; 0.62]	1.67 [1.35; 2.05]	5.65 [5.05; 6.31]
	Age < 20	0.32 [0.09; 0.81]	1.72 [1.09; 2.58]	4.86 [3.75; 6.21]
	Age 20-50	0.76 [0.45; 1.21]	3.01 [2.34; 3.81]	9.39 [8.18; 10.73]
	Age > 50	0.00 [0.00; 0.22]	0.00 [0.00; 0.20]	2.00 [1.43; 2.71]
HbEE disease				
	All	0.04 [0.00; 0.14]	0.40 [0.25; 0.61]	1.27 [1.00; 1.60]
	Age < 20	0.00 [0.00; 0.29]	0.00 [0.00; 0.28]	0.68 [0.31; 1.30]
	Age 20-50	0.08 [0.01; 0.31]	0.93 [0.58; 1.42]	2.31 [1.73; 3.03]
	Age > 50	0.00 [0.00; 0.22]	0.05 [0.00; 0.30]	0.49 [0.23; 0.90]
Residual				
	All	2.05 [1.68; 2.47]	4.20 [3.68; 4.79]	10.16 [9.35; 11.02]
	Age < 20	2.46 [1.67; 3.49]	4.04 [3.03; 5.27]	8.51 [7.01; 10.24]
	Age 20-50	1.57 [1.11; 2.17]	4.03 [3.24; 4.94]	11.44 [10.10; 12.92]
	Age > 50	2.39 [1.72; 3.25]	4.54 [3.62; 5.62]	9.78 [8.48; 11.23]

Prevalence of congenital hemolysis, subgroups not included in primary section of the article.

Estimated as the number of living persons assigned the diagnosis at the latest on the 1st of January each of the years 2000, 2007 and 2015 stratified by age and sex with population denominators derived from census data.

Abbreviation: CI: confidence interval, G6PD: Glucose-6-phosphate-deficiency, IQR: interquartile range, HbE: heterozygotic hemoglobin E, HbEE: homozygotic hemoglobin EE, NOS: Not otherwise specified, PKD: Pyruvate kinase deficiency.

Supplementary table 5 - Table of sex-specific prevalence of congenital hemolytic anemias in Denmark in 2000, 2007 and 2015

		Prevalence per 100,000 persons [95% CI]		
		2000	**2007**	**2015**
Alpha Thalassemia				
Alpha Thalassemia trait				
	Female	0.63 [0.37; 1.01]	10.83 [9.64; 12.14]	28.61 [26.68; 30.64]
	Male	0.30 [0.13; 0.60]	2.60 [2.02; 3.28]	9.71 [8.59; 10.93]
HbH disease				
	Female	0.11 [0.02; 0.33]	0.40 [0.20; 0.72]	0.88 [0.57; 1.30]
	Male	0.00 [0.00; 0.14]	0.15 [0.04; 0.38]	0.60 [0.35; 0.97]
Alpha Thalassemia NOS				
	Female	0.26 [0.10; 0.53]	0.47 [0.25; 0.81]	1.16 [0.80; 1.63]
	Male	0.15 [0.04; 0.39]	0.37 [0.18; 0.68]	0.64 [0.38; 1.01]
Beta Thalassemia				
Beta Thalassemia minor				
	Female	5.90 [5.02; 6.89]	19.02 [17.42; 20.72]	40.79 [38.48; 43.20]
	Male	2.96 [2.34; 3.70]	11.79 [10.53; 13.16]	28.96 [27.00; 31.02]
Beta Thalassemia intermedia				
	Female	0.04 [0.00; 0.21]	0.07 [0.01; 0.26]	0.56 [0.32; 0.91]
	Male	0.00 [0.00; 0.14]	0.11 [0.02; 0.33]	0.32 [0.15; 0.61]
Beta thalassemia major				
	Female	0.04 [0.00; 0.21]	0.51 [0.28; 0.85]	0.98 [0.65; 1.42]
	Male	0.00 [0.00; 0.14]	0.11 [0.02; 0.33]	0.39 [0.20; 0.70]
Thalassemia NOS				
	Female	1.82 [1.34; 2.40]	2.73 [2.14; 3.42]	3.83 [3.14; 4.62]
	Male	1.29 [0.89; 1.80]	2.15 [1.63; 2.78]	2.74 [2.16; 3.42]
Other defined congenital				
Sickle cell trait				
	Female	1.08 [0.72; 1.54]	2.87 [2.27; 3.58]	10.85 [9.67; 12.13]
	Male	0.34 [0.16; 0.65]	1.37 [0.97; 1.89]	5.34 [4.52; 6.26]
Sickle cell disease				
	Female	0.82 [0.51; 1.24]	1.49 [1.07; 2.02]	2.98 [2.38; 3.69]
	Male	0.23 [0.08; 0.50]	0.82 [0.51; 1.24]	2.42 [1.88; 3.07]
Hereditary spherocytosis				
	Female	10.05 [8.89; 11.32]	13.42 [12.08; 14.86]	17.13 [15.64; 18.72]
	Male	10.44 [9.24; 11.75]	14.13 [12.75; 15.62]	18.32 [16.77; 19.97]
Congenital hemolysis NOS				
	Female	6.34 [5.43; 7.37]	5.16 [4.35; 6.09]	4.81 [4.04; 5.69]
	Male	5.28 [4.44; 6.23]	5.23 [4.40; 6.17]	5.44 [4.61; 6.38]
G6PD				
	Female	0.59 [0.34; 0.96]	1.53 [1.10; 2.06]	2.63 [2.07; 3.30]
	Male	3.04 [2.41; 3.78]	5.19 [4.37; 6.13]	6.44 [5.54; 7.45]
PKD				
	Female	0.22 [0.08; 0.48]	0.29 [0.13; 0.57]	0.42 [0.22; 0.74]
	Male	0.19 [0.06; 0.44]	0.30 [0.13; 0.58]	0.43 [0.22; 0.75]
HbE				
	Female	0.67 [0.40; 1.06]	2.62 [2.05; 3.30]	8.57 [7.52; 9.71]
	Male	0.15 [0.04; 0.39]	0.70 [0.42; 1.10]	2.70 [2.13; 3.38]
HbEE disease				
	Female	0.07 [0.01; 0.27]	0.73 [0.44; 1.12]	2.32 [1.79; 2.95]
	Male	0.00 [0.00; 0.14]	0.07 [0.01; 0.27]	0.21 [0.08; 0.46]
Residual				
	Female	2.71 [2.12; 3.40]	5.49 [4.65; 6.44]	12.60 [11.33; 13.98]
	Male	1.37 [0.96; 1.89]	2.89 [2.29; 3.61]	7.68 [6.69; 8.78]

Prevalences of congenital hemolysis stratified for all subgroups. Estimated as the number of living persons assigned the diagnosis up to January each of the years 2000, 2007 and 2015 stratified by age and sex with population denominators derived from census data.

Abbreviation: CI: confidence interval, G6PD: Glucose-6-phosphate-deficiency, IQR: interquartile range, HbH: hemoglobin H, HbE: heterozygotic hemoglobin E, HbEE: homozygotic hemoglobin EE, NOS: Not otherwise specified, PKD: Pyruvate kinase deficiency.

Supplementary table 6 – Prevalence proportion ratio for prevalence of alpha-thalassemic diseases by the main model, Denmark 2000-2016

	Alpha thalassemia trait	Hemoglobin H disease	Alpha thalassemia NOS
PPR			
2000	1.00[a]	1.00[a]	1.00[a]
2001	2.35 [1.47,3.75]	1.99 [0.50,7.97]	1.27 [0.58,2.79]
2002	4.85 [3.15,7.45]	1.99 [0.50,7.94]	1.35 [0.62,2.95]
2003	6.77 [4.45,10.30]	2.64 [0.70,9.95]	1.53 [0.72,3.27]
2004	8.65 [5.72,13.08]	3.29 [0.91,11.96]	1.80 [0.86,3.75]
2005	10.64 [7.06,16.02]	4.27 [1.22,14.98]	1.79 [0.86,3.74]
2006	12.65 [8.42,19.00]	4.58 [1.32,15.95]	2.05 [1.00,4.21]
2007	14.40 [9.61,21.60]	4.89 [1.42,16.90]	2.05 [1.00,4.20]
2008	15.50 [10.34,23.21]	5.19 [1.51,17.82]	2.12 [1.04,4.34]
2009	17.45 [11.66,26.10]	5.16 [1.50,17.70]	2.37 [1.18,4.79]
2010	19.84 [13.28,29.64]	5.78 [1.70,19.62]	2.71 [1.36,5.40]
2011	23.12 [15.50,34.49]	7.35 [2.21,24.47]	3.14 [1.60,6.16]
2012	26.86 [18.02,40.02]	9.23 [2.81,30.31]	3.47 [1.78,6.77]
2013	31.01 [20.83,46.17]	9.20 [2.80,30.19]	3.63 [1.87,7.05]
2014	35.84 [24.09,53.32]	11.05 [3.40,35.93]	3.62 [1.86,7.02]
2015	40.98 [27.57,60.93]	13.18 [4.09,42.54]	4.37 [2.28,8.38]
2016	45.95 [30.92,68.27]	14.63 [4.55,47.01]	4.75 [2.49,9.07]

Exponentiated coefficients from Poisson regression; 95% confidence intervals in brackets.

The overall prevalence of alpha thalassemic diseases calculated on 1st of January each year with census data as denominator.

Abbreviations: [a]Reference value, NOS: not otherwise specified, PPR: Prevalence proportion ratio.

Supplementary table 7 – Prevalence proportion ratio for prevalence of beta-thallassemic diseases by the main model, in Denmark 2000-2016

	Beta thalassemia minor	Beta thalassemia intermedia	Beta thalassemia major	Thalassemia NOS
PPR				
2000	1.00[a]	1.00[a]	1.00[a]	1.00[a]
2001	1.27 [1.07,1.51]	1.99 [0.18,21.98]	1.00 [0.06,15.93]	1.07 [0.79,1.44]
2002	1.57 [1.33,1.84]	1.99 [0.18,21.90]	0.99 [0.06,15.87]	1.17 [0.88,1.57]
2003	1.82 [1.55,2.13]	1.98 [0.18,21.84]	1.98 [0.18,21.84]	1.28 [0.96,1.70]
2004	2.22 [1.90,2.58]	2.96 [0.31,28.48]	6.91 [0.85,56.18]	1.31 [0.98,1.74]
2005	2.58 [2.22,3.00]	2.95 [0.31,28.41]	8.86 [1.12,69.97]	1.45 [1.10,1.91]
2006	3.00 [2.59,3.47]	3.93 [0.44,35.15]	13.75 [1.81,104.55]	1.50 [1.14,1.98]
2007	3.47 [3.01,4.01]	4.89 [0.57,41.88]	16.63 [2.21,125.00]	1.57 [1.19,2.06]
2008	3.79 [3.29,4.37]	4.87 [0.57,41.66]	16.55 [2.20,124.34]	1.61 [1.22,2.11]
2009	4.13 [3.58,4.75]	8.70 [1.10,68.70]	17.41 [2.32,130.40]	1.71 [1.31,2.24]
2010	4.68 [4.07,5.38]	8.67 [1.10,68.41]	20.22 [2.72,150.34]	1.75 [1.34,2.29]
2011	5.28 [4.60,6.06]	13.42 [1.76,102.05]	22.05 [2.98,163.25]	1.89 [1.45,2.47]
2012	5.88 [5.13,6.75]	15.28 [2.03,115.23]	21.97 [2.97,162.66]	1.94 [1.50,2.53]
2013	6.55 [5.71,7.50]	16.17 [2.15,121.52]	30.44 [4.16,222.79]	1.98 [1.53,2.58]
2014	7.28 [6.36,8.33]	21.79 [2.94,161.31]	34.10 [4.68,248.70]	2.07 [1.59,2.68]
2015	7.85 [6.86,8.98]	23.54 [3.19,173.75]	36.73 [5.05,267.33]	2.11 [1.63,2.73]
2016	8.61 [7.53,9.84]	26.15 [3.56,192.19]	42.03 [5.79,304.87]	2.09 [1.62,2.71]

Exponentiated coefficients from Poisson regression; 95% confidence intervals in brackets.

The overall prevalence of beta thalassemic diseases calculated on 1st of January each year with census data as denominator.

Abbreviations: [a]Reference value, NOS: not otherwise specified, PPR: Prevalence proportion ratio.

Supplementary table 8 – Prevalence proportion ratio for prevalence of sickle cell and hereditary spherocytosis by the main model, in Denmark 2000-2016

	Sickle cell trait	Sickle cell disease	Hereditary spherocytosis
PPR			
2000	1.00[a]	1.00[a]	1.00[a]
2001	1.21 [0.78,1.85]	1.14 [0.69,1.89]	1.05 [0.93,1.18]
2002	1.54 [1.03,2.32]	1.24 [0.76,2.04]	1.10 [0.98,1.23]
2003	1.69 [1.13,2.53]	1.49 [0.92,2.40]	1.14 [1.02,1.28]
2004	1.95 [1.32,2.88]	1.80 [1.13,2.85]	1.18 [1.05,1.32]
2005	2.18 [1.48,3.19]	2.04 [1.30,3.20]	1.22 [1.09,1.37]
2006	2.71 [1.87,3.93]	2.07 [1.32,3.24]	1.28 [1.14,1.43]
2007	2.99 [2.07,4.31]	2.20 [1.41,3.44]	1.34 [1.20,1.50]
2008	3.46 [2.41,4.96]	2.43 [1.57,3.77]	1.40 [1.25,1.56]
2009	3.92 [2.75,5.59]	2.52 [1.63,3.90]	1.44 [1.29,1.60]
2010	4.49 [3.16,6.37]	2.96 [1.93,4.53]	1.50 [1.34,1.67]
2011	5.20 [3.68,7.34]	3.25 [2.13,4.96]	1.53 [1.37,1.70]
2012	6.31 [4.49,8.87]	3.68 [2.43,5.58]	1.56 [1.40,1.74]
2013	8.09 [5.78,11.32]	3.91 [2.59,5.91]	1.62 [1.46,1.80]
2014	9.67 [6.93,13.49]	4.53 [3.02,6.81]	1.70 [1.53,1.89]
2015	11.38 [8.17,15.84]	5.15 [3.44,7.70]	1.73 [1.56,1.92]
2016	12.90 [9.28,17.93]	5.57 [3.73,8.31]	1.78 [1.61,1.98]

Exponentiated coefficients from Poisson regression; 95% confidence intervals in brackets.

The overall prevalence of sickle cell disorders and hereditary spherocytosis calculated on 1st of January each year with census data as denominator.

Abbreviations: [a]Reference value, PPR: Prevalence proportion ratio.

Supplementary table 9 – Prevalence proportion ratio for prevalence of other congenital hemolytic anemias by the main model, in Denmark 2000-2016

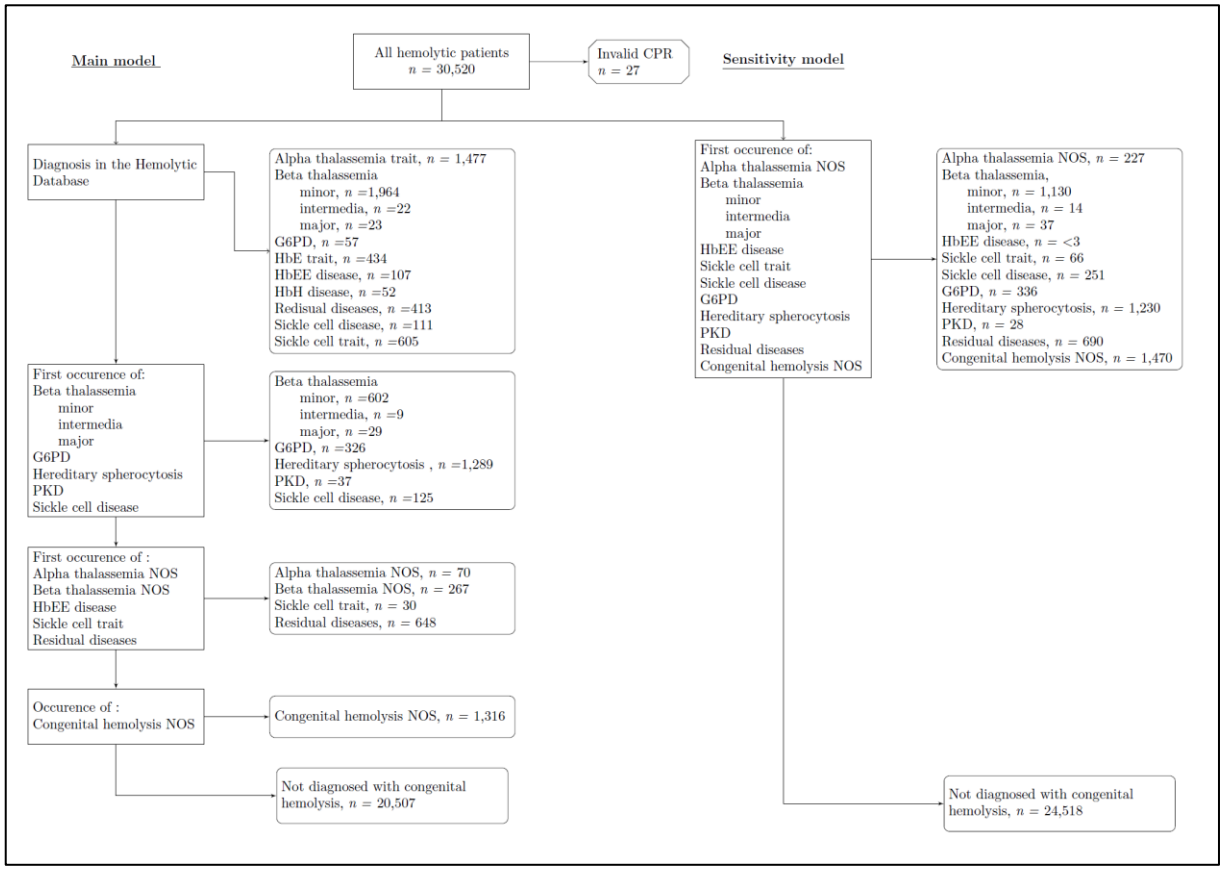
	HbE	HbEE disease	G6PD	PKD	Congenital hemolysis NOS	Residual hemolysis
PPR						
2000	1.00 [a]	1.00 [a]	1.00 [a]	1.00 [a]	1.00 [a]	1.00 [a]
2001	1.40 [0.81,2.42]	1.49 [0.25,8.94]	1.17 [0.89,1.54]	1.27 [0.58,2.79]	0.99 [0.85,1.16]	1.04 [0.80,1.36]
2002	1.81 [1.07,3.04]	2.48 [0.48,12.79]	1.27 [0.97,1.66]	1.26 [0.57,2.78]	0.98 [0.84,1.15]	1.19 [0.93,1.54]
2003	2.21 [1.33,3.65]	2.97 [0.60,14.72]	1.38 [1.06,1.80]	1.17 [0.52,2.61]	0.95 [0.81,1.11]	1.34 [1.05,1.72]
2004	2.74 [1.68,4.46]	4.44 [0.96,20.57]	1.45 [1.12,1.88]	1.17 [0.52,2.60]	0.93 [0.79,1.09]	1.59 [1.25,2.01]
2005	3.18 [1.97,5.13]	6.40 [1.44,28.37]	1.58 [1.22,2.04]	1.43 [0.66,3.09]	0.92 [0.79,1.08]	1.77 [1.40,2.24]
2006	3.57 [2.23,5.72]	8.35 [1.93,36.13]	1.73 [1.35,2.22]	1.34 [0.62,2.92]	0.92 [0.78,1.07]	1.91 [1.52,2.41]
2007	4.05 [2.54,6.45]	10.76 [2.53,45.77]	1.86 [1.45,2.38]	1.42 [0.66,3.07]	0.89 [0.76,1.05]	2.06 [1.64,2.58]
2008	4.47 [2.82,7.09]	11.68 [2.76,49.42]	1.92 [1.50,2.45]	1.50 [0.70,3.21]	0.89 [0.76,1.05]	2.27 [1.81,2.84]
2009	4.88 [3.09,7.71]	13.06 [3.10,54.90]	1.99 [1.56,2.55]	1.76 [0.84,3.67]	0.88 [0.75,1.03]	2.45 [1.96,3.06]
2010	5.38 [3.42,8.48]	14.93 [3.57,62.37]	2.08 [1.63,2.65]	1.93 [0.93,3.97]	0.89 [0.76,1.04]	2.73 [2.19,3.40]
2011	6.19 [3.95,9.69]	17.25 [4.15,71.66]	2.17 [1.70,2.76]	2.09 [1.02,4.27]	0.88 [0.75,1.04]	3.06 [2.47,3.79]
2012	6.82 [4.36,10.65]	21.97 [5.33,90.49]	2.26 [1.78,2.87]	2.00 [0.97,4.10]	0.86 [0.73,1.01]	3.43 [2.77,4.24]
2013	7.65 [4.91,11.92]	25.69 [6.26,105.35]	2.38 [1.88,3.01]	1.99 [0.97,4.08]	0.86 [0.73,1.01]	3.87 [3.14,4.77]
2014	10.16 [6.56,15.73]	30.78 [7.54,125.72]	2.45 [1.93,3.10]	2.24 [1.11,4.53]	0.87 [0.74,1.02]	4.26 [3.46,5.24]
2015	13.70 [8.89,21.10]	33.90 [8.32,138.18]	2.51 [1.99,3.18]	2.05 [1.01,4.19]	0.88 [0.75,1.03]	4.97 [4.05,6.10]
2016	16.17 [10.52,24.86]	40.62 [10.00,165.03]	2.65 [2.10,3.34]	2.12 [1.04,4.31]	0.90 [0.77,1.05]	5.53 [4.52,6.78]

Exponentiated coefficients from Poisson regression; 95% confidence intervals in brackets.

The overall prevalence of other congenital hemolytic disorders calculated on 1st of January each year with census data as denominator. Abbreviations: [a]Reference value, G6PD: Glucose-6-phosphate-deficiency, PKD: Pyruvate kinase deficiency, PPR: Prevalence proportion ratio, NOS: Not otherwise specified, HbE: heterozygotic hemoglobin E, HbEE homozygotic hemoglobin E.

Supplementary figures

Supplementary Figure 1 – flowchart for assigning diagnosis of all congenital hemolytic disorders

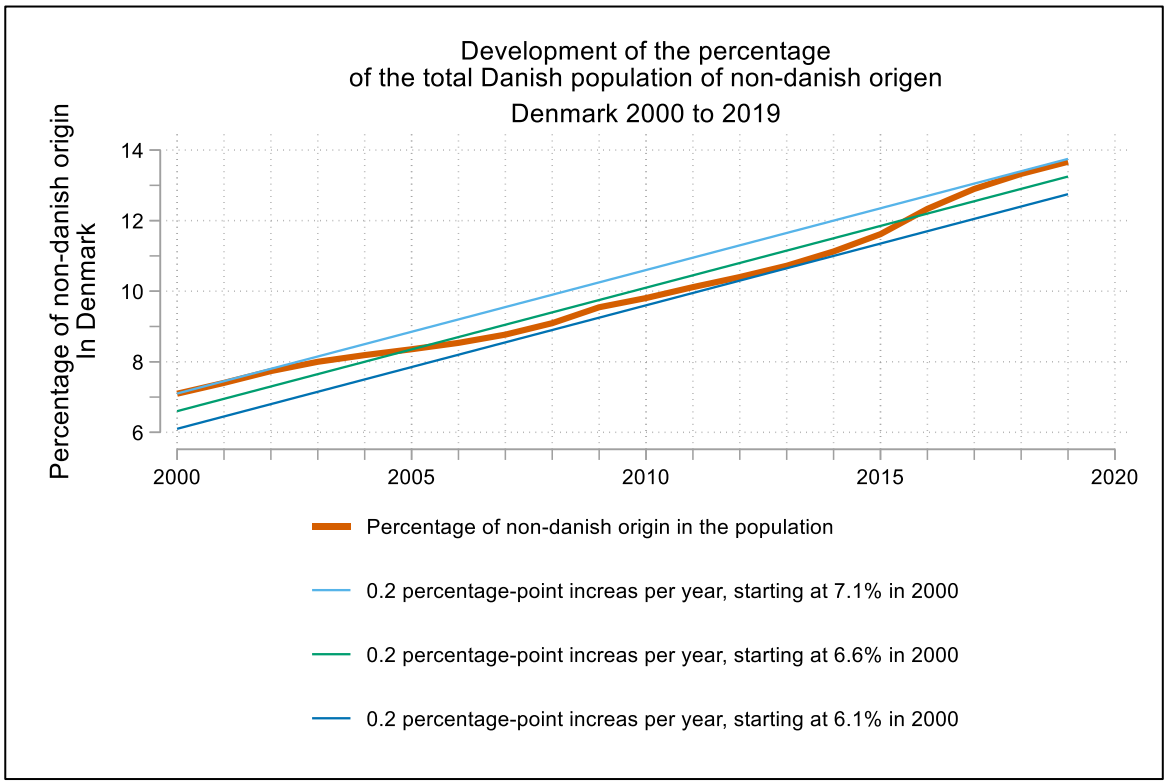


Flow chart illustrating the process of assigning diagnoses of congenital hemolysis to patients. We used the two models consecutively on the cohort of 30,520 patients. The main model, on the left, uses a hierarchy to assign a diagnosis to a patient. Only patients who cannot be assigned a diagnosis proceed from each level. Patients with two equally reliable diagnoses in the Danish National Patient Register were

assigned the chronologically first recorded diagnosis. On the right, results of using the sensitivity model where patients were classified only according to the chronologically first recorded diagnosis code compatible with acquired hemolytic anemias. The sensitivity model only employs the Danish National Patient Register as source for diagnosing, and it is therefore missing all diagnoses not defined in the International Classification of Diseases 8th or 10th revision (e.g. heterozygotic hemoglobin C, D or E).

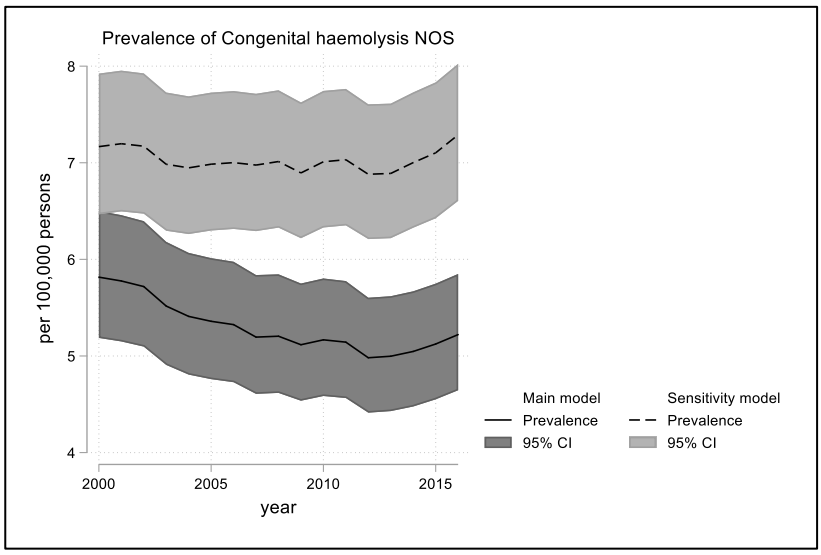
Abbreviations: G6PD: Glucose-6-phosphate-deficiency, HbH: hemoglobin H, deficiency, HbC: heterozygotic hemoglobin C, HbCC: homozygotic hemoglobin C, HbD: heterozygotic hemoglobin D, HbDD: homozygotic hemoglobin D, HbE: heterozygotic hemoglobin E, HbEE: homozygotic hemoglobin EE, HbS: heterozygotic hemoglobin S, NOS: Not otherwise specified, PKD: Pyruvate kinase deficiency.

Supplementary Figure 2 – Development of Citizens on non-Danish origin, 2000 to 2019



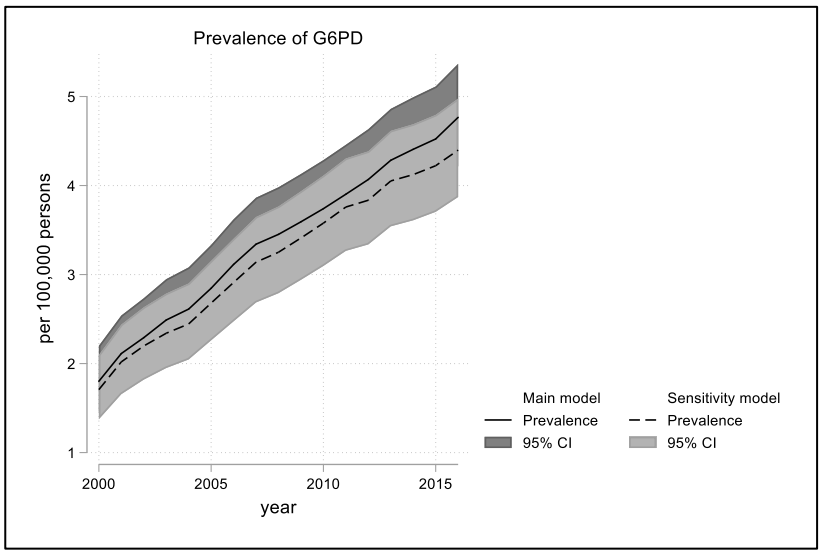
Development in the amount of the inhabitants in Denmark of non-Danish origin. Calculated as the number of people of non-Danish origin living in Denmark on the 1st of January each year, divided by the total population in Denmark on the same date.

Supplementary Figure 3 - Prevalence of congenital hemolysis NOS in Denmark, 2000-2016, according to models for classification of diagnosis (main model vs. sensitivity model)



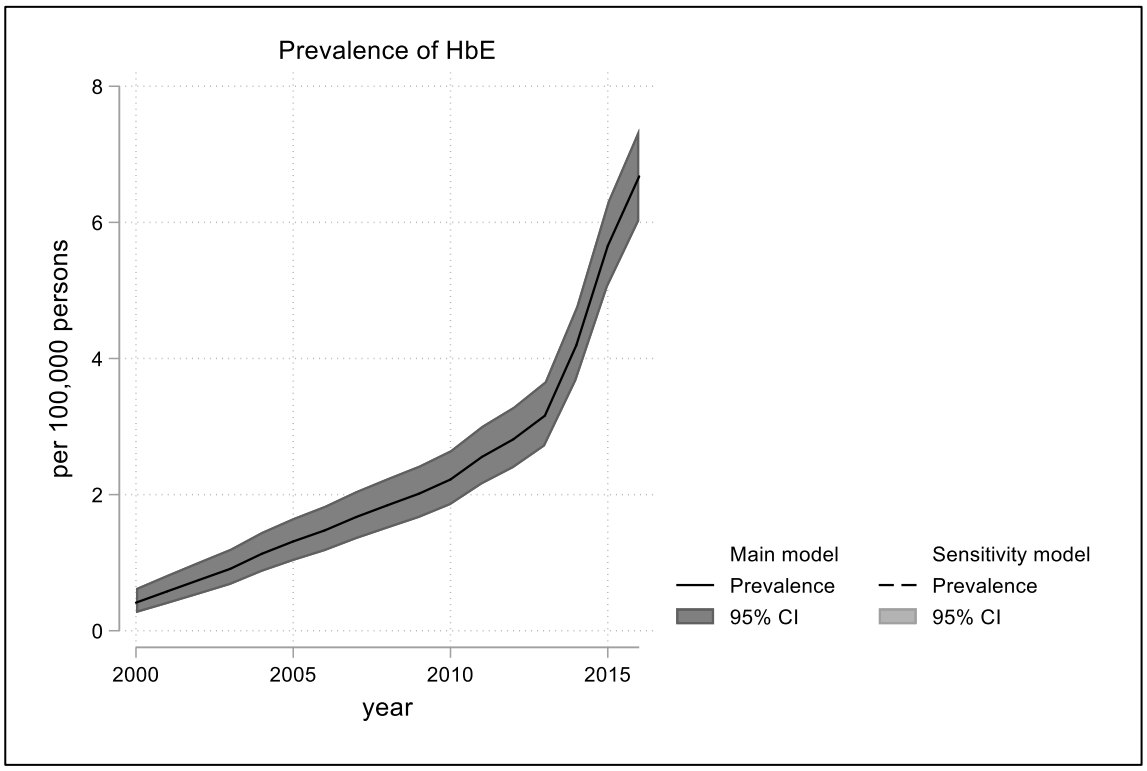
The overall prevalence with 95% confidence intervals for congenital hemolysis NOS calculated on 1st of January each year with census data as denominator. The 95% confidence intervals are calculated using the Clopper-Pearson method. Abbreviation: CI: confidence interval, NOS: not otherwise specified.

Supplementary Figure 4 - Prevalence of Glucose-6-phospahate-deficiency in Denmark, 2000-2016, according to models for classification of diagnosis (main model vs. sensitivity model)



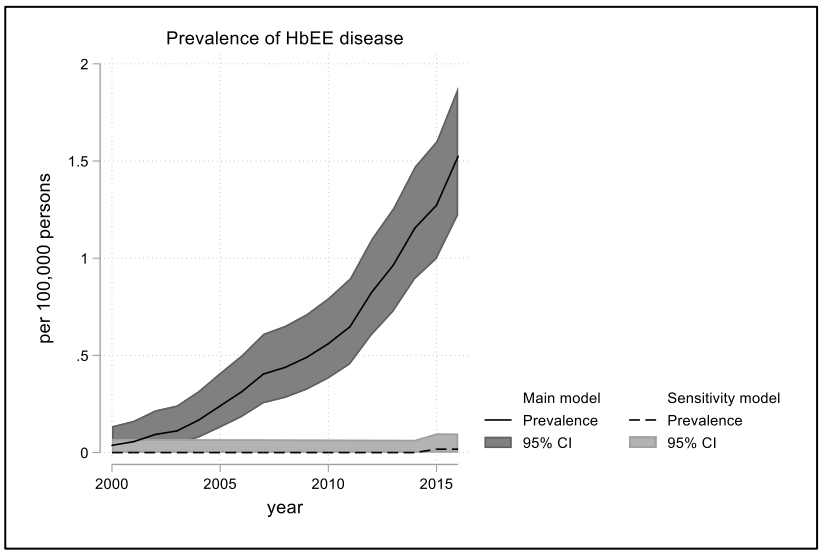
The overall prevalence with 95% confidence intervals for G6PD calculated on 1st of January each year with census data as denominator. The 95% confidence intervals are calculated using the Clopper-Pearson method. Abbreviation: CI: confidence interval, G6PD: Glucose-6-phosphate-deficiency.

Supplementary Figure 5- Prevalence of Hemoglobin E trait disorders in Denmark, 2000-2016, according to models for classification of diagnosis (main model vs. sensitivity model)



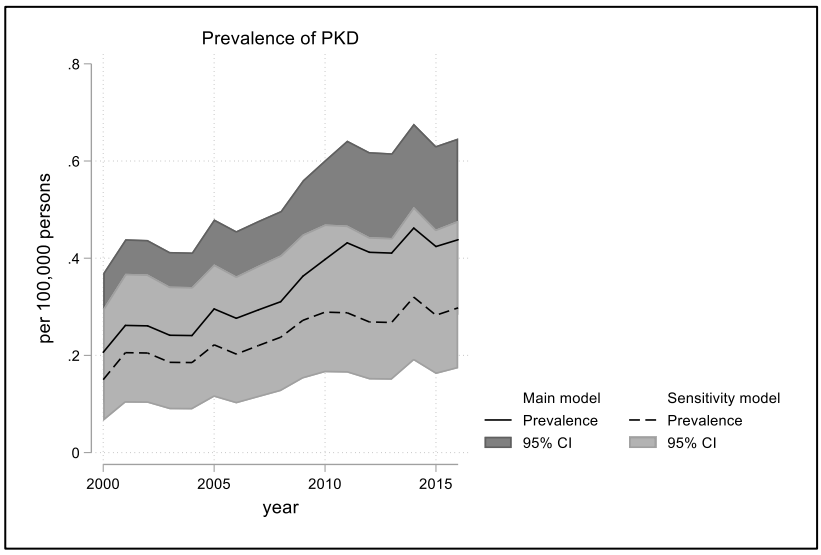
The overall prevalence with 95% confidence intervals for heterozygotic hemoglobin E trait calculated on 1st of January each year with census data as denominator. The 95% confidence intervals are calculated using the Clopper-Pearson method. Abbreviation: CI: confidence interval, HbE: heterozygotic hemoglobin E.

Supplementary Figure 6- Prevalence of hemoglobin E disease in Denmark, 2000-2016, according to models for classification of diagnosis (main model vs. sensitivity model)



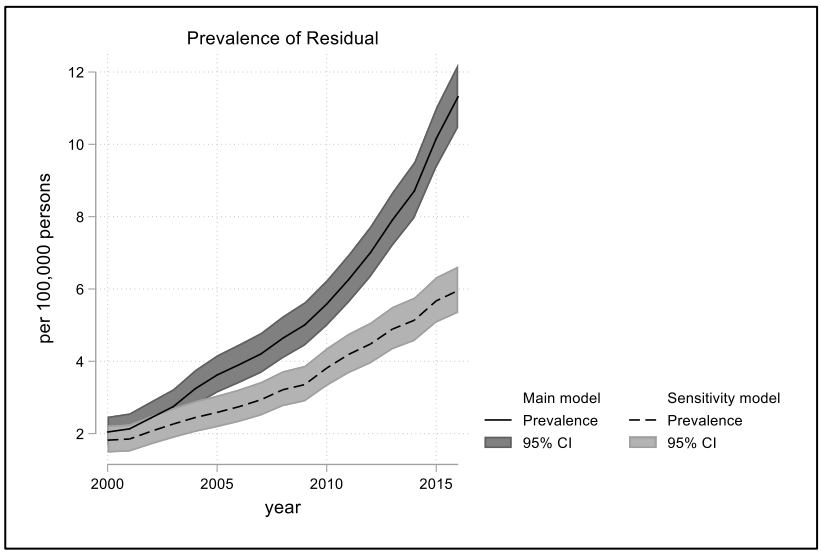
The overall prevalence with 95% confidence intervals for homozygotic hemoglobin E disease calculated on 1st of January each year with census data as denominator. The 95% confidence intervals are calculated using the Clopper-Pearson method. Abbreviation: CI: confidence interval, HbEE: homozygotic hemoglobin E.

Supplementary Figure 7- Prevalence of Pyruvate kinase-deficiency in Denmark, 2000-2016, according to models for classification of diagnosis (main model vs. sensitivity model)



The overall prevalence with 95% confidence intervals for PKD trait calculated on 1st of January each year with census data as denominator. The 95% confidence intervals are calculated using the Clopper-Pearson method. Abbreviation: CI: confidence interval, PKD: pyruvate kinase deficiency.

Supplementary Figure 8 - Prevalence of residual hemolytic disorders in Denmark, 2000-2016, according to models for classification of diagnosis (main model vs. sensitivity model)



The overall prevalence with 95% confidence intervals for the combined group of residual hemolytic disorders calculated on 1st of January each year with census data as denominator. The 95% confidence intervals are calculated using the Clopper-Pearson method. Abbreviation: CI: confidence interval.