Supplementary material for the article:

Increasing incidence and prevalence of acquired hemolytic anemias in Denmark, 1980–2016

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Supplementary methods – detailed description

Data sources and Danish Hemolysis Cohort

Denmark provides universal tax-funded healthcare for all inhabitants. All hospitals, public or private, report to the Patient Register and other administrative registers.[1] The few private hospitals in Denmark do not manage blood disorders.[2]

The Patient Register has recorded all diagnoses from hospitalizations since 1977, and from out-patient contacts since 1994. Diagnoses are classified according to the International Classification of Diseases (ICD) 8th revision until 1994, and 10th revision thereafter.[2]

Established in 1968, the Danish Civil Registration System records sex, vital status, migration status (including country of origin), and birth information for all persons, alive or deceased, who are born in Denmark or who reside in Denmark for at least 3 months.[3] Upon registration, each person receives a unique and permanent Civil Personal Register number (CPR), which enables individual-level linkage across all public registers.[3]

Applying our most conservative validation of the diagnosis codes, PNH and CAD had positive predictive values (PPVs) above 80%, AIHA above 75%, and the remaining codes below 75%.[4] From this foundation we extracted data regarding patients with hemolysis from the Patient Register for the time-period January 1977 through December 2016.[2, 3] Data from all hospital contacts of patients diagnosed with hemolytic anemia or immune-mediated thrombocytopenia were extracted by Statistics Denmark, forming the Danish Hemolysis Cohort (Supplementary Table 1). To improve the PPV, we included only patients registered with discharge diagnoses from departments of hematology, pediatrics, and internal medicine.[4] For cohort members, we also retrieved information about all hospital-registered comorbidities and splenectomy from the Patient Register; and data regarding vital status, migration status, sex, date of birth, and date of death from

the Civil Registration System. Annual data on the Danish population, for age- and sex-specific strata, were obtained from Statistics Denmark.[5]

Statistics – detailed description

Data were managed and analyzed using Stata 15.1.[6] We tabulated general characteristics, such as age, sex, secondary disease, splenectomy, and survival status. Median survival time from the date of hemolysis diagnosis was estimated using the Kaplan-Meier method. Incidence rates were calculated from the cumulative incidences during the time-periods 1980–1993, 1994–2007, and 2008–2016, and were reported as patients per 100,000 person-years for all defined groups, using cumulative stratified annual census data as the denominator. Prevalence proportions were calculated as the number of patients alive with an acquired hemolysis diagnosis on the 1st of January in 1980, 2000, and 2015. Prevalence proportions were reported per 100,000 persons using stratified census data as denominator. For sensitivity testing, we also calculated overall prevalence proportions for each study year. We evaluated changes in overall incidence rates and prevalence proportions using negative binomial regression, estimating incidence rate rations (IRR) and prevalence proportion ratios (PPR).[7] However, if the dispersion parameter was indistinguishable from zero, the regressions were simplified to Poisson regressions.[6]

Sensitivity testing

Our diagnostic model could introduce a survivorship bias if patients died before getting a reliable diagnosis, thereby lowering the incidence of the more specific diagnoses.[8] To address this issue, we calculated incidence and prevalence using a sensitivity model. The sensitivity model assigned patients with their first encountered acquired hemolysis diagnosis in the Patient Register, irrespective of its PPV, and thus did not have a lead time from first registered hemolysis diagnosis to the most reliable diagnosis. We used negative binomial regression or Poisson regression to

compare the overall incidence rates and annual prevalence proportions between the sensitivity model versus the main model.

PNH can be divided into classic PNH and clonal disease frequently associated with myelodysplastic syndrome (MDS) or aplastic anemia (AA). Data on clonesize is not available, but instead we post hoc defined a sensitivity model, excluding all patients with a diagnosis of MDS and/or AA before or within six months after the diagnosis of PNH. We further used this subcategorization of PNH to estimate incidence and prevalence of the two subcategories.

Post hoc we also re-calculated incidence and prevalence for AIHA, as previously described, but this time we classified AIHA into primary AIHA and secondary AIHA. Patients were classified into these two categories based on the presence (secondary AIHA), or absence (primary AIHA) of diagnosis codes for predisposing diseases (see Supplementary Table 2) at any time before and up to 100 days after inclusion date.

Supplementary results

Sensitivity analysis

Supplementary Figure 3 presents a graphical comparison of the annual point estimates of disease prevalence based on the main model and the sensitivity model. Compared to the sensitivity model, the main model included a higher number of affected individuals, and hence higher point prevalence rates—except in the case of acquired hemolysis NOS, where the reverse was true (i.e. the sensitivity model had higher counts and prevalence rates).

As there was no sign of over-dispersion, we used Poisson regression to compare the incidence rates determined using the two models. The main model yielded the highest numbers and hence higher incidence rates for all diseases, except acquired hemolysis NOS. CAD was the only subtype for which the difference between the two models had a major impact on the results—with an incidence rate ratio of 2.63 (95% CI: 2.63; 2.63) between the models, using the sensitivity model as reference (Supplementary Tables 4 and 6). Likewise, we used Poisson regression to compare the prevalence proportions from the two models, and only CAD showed a constant and statistically significant difference in prevalence estimates between the two models (Supplementary Tables 6 and 7).

The post hoc sensitivity model for PNH reviled annual point prevalences lower than, but comparable to the main model, Supplementary Figure 4. The incidence was similar to the main model in the periods 1980-1993 and 1994-2007, but differed in the latest period 2008-2016, Supplementary Figure 5. The post hoc sensitivity model did not show the same steep increase in incidence as the main and the sensitivity model when changing from the 1994-2007 to the 2008-2016 period. Instead the post hoc sensitivity model show a small increment from each period to the subsequent period.

The re-estimation of incidence and prevalence on AIHA subdivided into primary and secondary AIHA revealed that the incidence of primary AIHA had a relatively small increase throughout the study whereas the incidence of secondary AIHA increased more rapidly, especially when comparing 1980-1993 to 1994-2007. In the latest period the incidence of primary and secondary AIHA are equal. The prevalence of primary AIHA rose steadily during the study period, whereas the annual increase in prevalence of secondary AIHA was negligible before the mid-1990s, but increased thereafter. In 2016 secondary AIHA accounted for approximately one third of all prevalent AIHA patients.

References

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SUPPLEMENTARY TABLES

Supplementary Table 1. International Classification of Diseases (ICD) codes for diagnosis as defined in the Danish National Patient Register

Disease	Danish National Patient Register definition	
	ICD 8	ICD 10
Category 1, PPV > 80%		
PNH	28393	D595
CAD	na	D591A
Category 2, PPV > 75%		
AIHA	28309, 28390, 28391	D591
Category 3, PPV <75%		
Drug induced	28392	D590, D592
Acquired hemolysis NOS	28399	D598, D599, D599A
Other defined hemolysis		
PCD	28395	D59
March hemoglobinuria	28394	D594
Other acquired anemia		D594C, D596A
Other included non-acquired hemolytic or non-hemolytic diseases		
Immune thrombocytopenia	28710, 28711, 28718, 28719	D693
Congenital hemolysis	28249, 28250, 28229, 28230, 28209, 28219, 28299, 28239, 28258, 28259	D560, D563, D561C, D563C, D561A, D561B, D56, D568, D569, D582E, D573, D57, D570, D571, D572, D572A, D572B, D572C, D572D, D578, D550,D552,D580, D580A, D581, D581A, D58, D588, D589, D582, D582A, D582B, D582C, D582D, D588A, D55, D551, D553, D558, D559

ICD-8 and ICD-10 codes used to define the extraction of the cohort from the source population in the Patient Register. The suffixes “A”, “B”, “C”, and “D” are a Danish adaptation in the ICD-10 system. CAD diagnosis was not defined before the introduction of the ICD-10 in 1994, and is therefore marked as not applicable (na). The immune thrombocytopenia codes are included to identify patients with Evans syndrome, who were excluded from this study. PPV, positive predictive value; AIHA, autoimmune hemolytic anemia; NOS, not otherwise specified; CAD, cold agglutinin disease; PNH, paroxysmal nocturnal hemoglobinuria; na, not applicable.

Supplementary Table 2. International Classification of Diseases (ICD) diagnosis codes defining secondary underlying diseases in patients with hemolytic anemia

Cause of secondary disease	**ICD-8**	**ICD-10**
Immunodeficiency	27519	D800, D801, D802
Autoimmune disease	135, 24503, 56301, 56319, 4460, 4461, 4462, 4463, 7120, 7121, 716, 7340, 7341, 73490,	D860, D861, D862, D869, E063, K50, K51, M05, M06, M08, M30, M31, M32, DM33, M34, M350, M351, M353, R768B, R768D
Infection	07983, 57193	B171, B182, B20, B200, B200A, B201, B202, B203, B204, B205, B206, B207, B208, B209, B21, B210, B210A, B211, B212, B213, B217, B218, B21, B219, B22, B220, B220A, B221, B222, B227, B23, B230, B231, B232, B238, B24, B240, B249
Hematological malignancies	20019, 20199, 20209, 20220, 20229, 20299, 20399, 20409, 20419, 20499, 20509, 20519, 20519, 20609, 20619, 20699, 20709, 20719, 20729, 20799, 28509	C81, C810, C811, C812, C813, C817, C819, C82, C820, C821, C822, C827, C829, C83, C830, C831, C832, C833, C834, C835, C836, C837, C838, C839, C84, C840, C840A, C840B, C840C, C841, C842, C843, C844, C844A, C844B, C844C, C844D, C844E, C845, C845A, C845B, C845C, C845D, C85, C850, C851, C851A, C851B, C85C, C851D, C851E, C857, C857A, C859, C88, C880, C881, C882, C883, C887, C889, C90, C900, C901, C902, C902A, C91, C910, C911, C912, C913, C914, C914A, C915, C917, C917A, C919, C92, C920, C921, C922, C923, C923A, C923B, C924, C925, C927, C927A, C929, C93, C930, C931, C932, C937, C939, C94
Carcinoma	140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195	C00, C01, C02, C03, C05, C06, C07, C08, C09, C10, C11, C12, C13, C14, C15, C16, C17, C18, C19, C20, C21, C22, C23, C24, C25, C26, C27, C28, C29, C30, C31, C32, C33, C34, C35, C36, C37, C38, C39, C40, C41, C42, C43, C44, C45, C46, C47, C48, C49, C50, C51, C52, C53, C54, C55, C56, C57, C58, C59, C60, C61, C62, C63, C64, C65, C66, C67, C68, C69, C70, C71, C72, C73, C74, C75, C76

Codes recorded before 100 days after diagnosis of hemolysis. The suffixes “A”, “B”, “C” and “D” are a Danish adaptation of the ICD-10 system.

Supplementary Table 3. Description of the population of diagnosis, and agreement of diagnosis between the main model and sensitivity model

Disease	Subgroup	Main model, count	Sensitivity model, count	Agreement	Recall	PPV
AIHA		2715	2372	2319	85.4%	97.8%
Acquired hemolysis NOS		2154	2496	2134	99.1%	85.5%
CAD		112	43	43	38.4%	100.0%
Drug induced		397	414	394	99.2%	95.2%
PNH		116	91	91	78.4%	100.0%
Other defined hemolysis		374	452	374	100.0%	82.7%
	March hemoglobinuria	8	8	8		
	Other acquired anemia	358	430	358		
	PCD	8	14	8		

Description of the population included patients with diagnosis of hemolysis in the Danish National Patient Register. Other defined hemolysis is a composite category combining march hemoglobinuria, other acquired anemia, and PCD. 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 a 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. Cohen's kappa statistics of inter-rater agreement between the two models was 0.865 ± 0.009, indicating an overall good agreement.

AIHA, autoimmune hemolytic anemia; NOS, not otherwise specified; CAD, cold agglutinin disease; PNH, paroxysmal nocturnal hemoglobinuria; PCD, paroxysmal cold hemoglobinuria.

Supplementary Table 4. Incidence rate ratios (IRRs) and 95% confidence intervals for incidences of hemolytic anemia in Denmark, 1980–2016, calculated using the main model

	AIHA	Acquired hemolysis NOS	CAD	Drug induced	Other defined hemolysis	PNH
Main model, IRR:						
1980–1993	1.00[a]	1.00[a]	na	1.00[a]	1.00[a]	1.00[a]
1994–2007	1.77 [1.60; 1.96]	1.23 [1.11; 1.37]	1.00[a]	0.27 [0.20; 0.35]	12.25 [7.24; 20.72]	1.06 [0.65; 1.72]
2008–2016	2.20 [2.00; 2.42]	1.59 [1.43; 1.76]	6.41 [4.05; 10.14]	0.37 [0.29; 0.47]	15.62 [9.28; 26.29]	1.78 [1.15; 2.74]

CAD diagnosis was not defined in the ICD before 1994. Therefore, 1980–1993 is the reference period for all diseases, except CAD for which 1994–2007 is the reference.

[a]Reference value.

IRR, incidence rate ratio; AIHA, autoimmune hemolytic anemia; AHNOS, acquired hemolysis not otherwise specified; CAD, cold agglutinin disease; PNH, paroxysmal nocturnal hemoglobinuria; CI, confidence interval; na, not applicable.

Supplementary Table 5. Prevalence proportions ratios for prevalence of hemolytic anemia in Denmark, 1980–2016, calculated using the main model

	AIHA	Acquired hemolysis NOS	CAD	Drug induced	Other defined hemolysis	PNH
Main model, PPR:						
1980	1.00[a]	1.00[a]	na	1.00[a]	1.00[a]	1.00[a]
1981	1.18 [0.93; 1.49]	1.11 [0.87; 1.41]	na	1.19 [0.79; 1.81]	0.75 [0.17; 3.35]	1.33 [0.56; 3.16]
1982	1.35 [1.07; 1.69]	1.30 [1.03; 1.63]	na	1.42 [0.95; 2.11]	1.25 [0.34; 4.66]	1.56 [0.67; 3.60]
1983	1.42 [1.13; 1.78]	1.41 [1.13; 1.77]	na	1.64 [1.11; 2.41]	1.25 [0.34; 4.66]	1.78 [0.79; 4.03]
1984	1.55 [1.24; 1.94]	1.62 [1.30; 2.01]	na	2.10 [1.45; 3.05]	1.75 [0.51; 5.99]	1.78 [0.79; 4.03]
1985	1.68 [1.35; 2.09]	1.76 [1.41; 2.18]	na	2.08 [1.43; 3.02]	2.00 [0.60; 6.66]	1.45 [0.62; 3.39]
1986	1.72 [1.39; 2.14]	1.75 [1.41; 2.17]	na	2.22 [1.54; 3.21]	2.25 [0.69; 7.31]	1.56 [0.67; 3.60]
1987	1.80 [1.45; 2.23]	1.81 [1.46; 2.24]	na	2.29 [1.59; 3.31]	2.25 [0.69; 7.30]	1.55 [0.67; 3.59]
1988	1.89 [1.53; 2.34]	1.86 [1.50; 2.30]	na	2.19 [1.52; 3.17]	2.50 [0.78; 7.96]	1.66 [0.73; 3.80]
1989	2.07 [1.67; 2.55]	2.13 [1.73; 2.62]	na	2.34 [1.62; 3.37]	2.75 [0.87; 8.62]	2.11 [0.95; 4.66]
1990	2.02 [1.63; 2.49]	2.17 [1.76; 2.68]	na	2.34 [1.62; 3.37]	3.24 [1.06; 9.94]	2.33 [1.07; 5.08]
1991	2.24 [1.82; 2.75]	2.13 [1.73; 2.62]	na	2.28 [1.58; 3.29]	3.48 [1.15; 10.58]	2.32 [1.06; 5.07]
1992	2.24 [1.82; 2.75]	2.31 [1.88; 2.84]	na	2.35 [1.63; 3.38]	3.47 [1.14; 10.55]	2.43 [1.12; 5.27]

	AIHA	Acquired hemolysis NOS	CAD	Drug induced	Other defined hemolysis	PNH
1993	2.37 [1.93; 2.91]	2.28 [1.86; 2.81]	na	2.22 [1.54; 3.21]	3.71 [1.23; 11.17]	2.75 [1.28; 5.88]
1994	2.55 [2.08; 3.13]	2.29 [1.86; 2.82]	1.00 [a]	2.21 [1.53; 3.20]	4.19 [1.41; 12.45]	2.96 [1.39; 6.29]
1995	2.87 [2.35; 3.51]	2.38 [1.93; 2.92]	1.00 [0.00; na]	2.08 [1.44; 3.02]	7.37 [2.59; 20.91]	3.16 [1.50; 6.68]
1996	3.09 [2.53; 3.76]	2.50 [2.04; 3.07]	0.99 [0.00; na]	2.07 [1.43; 3.00]	9.02 [3.22; 25.31]	3.25 [1.54; 6.85]
1997	3.23 [2.65; 3.93]	2.58 [2.11; 3.16]	0.99 [0.00; na]	1.89 [1.30; 2.76]	12.38 [4.47; 34.25]	3.56 [1.70; 7.44]
1998	3.34 [2.74; 4.06]	2.67 [2.18; 3.27]	0.98 [0.00; na]	1.96 [1.35; 2.85]	14.75 [5.36; 40.57]	3.87 [1.86; 8.03]
1999	3.47 [2.85; 4.21]	2.76 [2.26; 3.38]	0.98 [0.00; na]	1.88 [1.29; 2.74]	18.07 [6.61; 49.42]	3.86 [1.86; 8.00]
2000	3.75 [3.09; 4.56]	2.88 [2.36; 3.52]	>200 [na]	1.85 [1.27; 2.70]	18.98 [6.95; 51.82]	3.95 [1.91; 8.19]
2001	3.88 [3.20; 4.71]	2.98 [2.44; 3.63]	>200 [na]	1.77 [1.21; 2.59]	20.11 [7.37; 54.83]	4.04 [1.95; 8.36]
2002	4.02 [3.31; 4.87]	3.14 [2.58; 3.83]	>200 [na]	1.84 [1.26; 2.68]	21.71 [7.98; 59.08]	4.13 [2.00; 8.53]
2003	4.20 [3.47; 5.09]	3.31 [2.72; 4.03]	>200 [na]	1.88 [1.29; 2.74]	23.79 [8.76; 64.62]	4.12 [2.00; 8.51]
2004	4.52 [3.74; 5.46]	3.50 [2.88; 4.25]	>200 [na]	1.81 [1.24; 2.63]	25.38 [9.36; 68.87]	4.43 [2.16; 9.10]
2005	4.72 [3.91; 5.70]	3.51 [2.89; 4.27]	>200 [na]	1.73 [1.18; 2.53]	26.03 [9.60; 70.59]	4.63 [2.26; 9.48]
2006	4.94 [4.09; 5.96]	3.65 [3.01; 4.43]	>200 [na]	1.77 [1.21; 2.59]	28.55 [10.54; 77.30]	4.72 [2.31; 9.65]
2007	5.12 [4.24; 6.17]	3.78 [3.12; 4.59]	>200 [na]	1.70 [1.16; 2.49]	28.92 [10.68; 78.27]	4.91 [2.41; 10.02]
2008	5.32 [4.41; 6.42]	4.00 [3.30; 4.84]	>200 [na]	1.67 [1.14; 2.44]	30.87 [11.42; 83.47]	4.78 [2.34; 9.77]

	AIHA	Acquired hemolysis NOS	CAD	Drug induced	Other defined hemolysis	PNH
2009	5.40 [4.48; 6.50]	4.06 [3.35; 4.91]	>200 [na]	1.63 [1.11; 2.39]	33.92 [12.56; 91.59]	5.06 [2.49; 10.30]
2010	5.47 [4.54; 6.59]	4.24 [3.50; 5.13]	>200 [na]	1.69 [1.16; 2.48]	33.32 [12.34; 89.98]	5.24 [2.58; 10.65]
2011	5.77 [4.79; 6.95]	4.29 [3.55; 5.19]	>200 [na]	1.71 [1.17; 2.50]	34.54 [12.80; 93.24]	5.63 [2.78; 11.39]
2012	6.04 [5.02; 7.27]	4.57 [3.78; 5.52]	>200 [na]	1.66 [1.13; 2.43]	37.86 [14.04; 102.08]	5.61 [2.77; 11.35]
2013	6.20 [5.15; 7.46]	4.59 [3.80; 5.55]	>200 [na]	1.72 [1.18; 2.51]	40.45 [15.02; 108.98]	6.09 [3.02; 12.28]
2014	6.52 [5.42; 7.84]	4.75 [3.93; 5.73]	>200 [na]	1.86 [1.28; 2.71]	42.78 [15.89; 115.17]	5.97 [2.96; 12.03]
2015	6.76 [5.62; 8.12]	4.97 [4.12; 5.99]	>200 [na]	1.88 [1.29; 2.72]	42.31 [15.71; 113.91]	5.93 [2.94; 11.96]
2016	6.92 [5.76; 8.31]	5.13 [4.25; 6.18]	>200 [na]	1.95 [1.35; 2.82]	42.85 [15.92; 115.35]	6.08 [3.02; 12.25]

Exponentiated coefficients; 95% confidence intervals in brackets.

CAD diagnosis was not defined in the ICD before 1994. Therefore, 1980 is the reference year for all diseases, except CAD for which 1994 is the reference. CAD incidence was very low in 1994, but increases drastically from 2000. Therefore, the PPR for the years 2000 and onward is extremely large compared to 1994, and has been truncated to >200 without confidence intervals.

[a]Reference value.

PPR, prevalence proportion ratio; AIHA, autoimmune hemolytic anemia; NOS, not otherwise specified; CAD, cold agglutinin disease; PNH, paroxysmal nocturnal hemoglobinuria; CI, confidence intervals; na, not applicable.

Supplementary Table 6. IRR for comparison of the incidence of hemolytic anemia in Denmark, 1980–2016, calculated using both models

	AIHA	Acquired hemolysis NOS	CAD	Drug induced	Other defined hemolysis	PNH
IRR:						
1980–1993	1.00[a]	1.00[a]	na	1.00[a]	1.00[a]	1.00[a]
1993–2007	1.77 [1.59; 1.97]	1.26 [1.14; 1.39]	1.00[a]	0.28 [0.21; 0.36]	12.61 [7.81; 20.37]	0.71 [0.40; 1.27]
2008–2016	2.19 [1.98; 2.43]	1.61 [1.46; 1.77]	6.45 [3.07; 13.54]	0.39 [0.31; 0.50]	15.16 [9.42; 24.39]	1.74 [1.09; 2.77]
Sensitivity model	1.00[a]	1.00[a]	1.00[a]	1.00[a]	1.00[a]	1.00[a]
Main model	1.15 [1.02; 1.29]	0.87 [0.78; 0.97]	2.62 [1.16; 5.93]	0.97 [0.81; 1.17]	0.83 [0.42; 1.65]	1.15 [0.69; 1.92]
1980–1993 # sensitivity model	1.00 [1.00; 1.00]	1.00 [1.00; 1.00]	Na	1.00 [1.00; 1.00]	1.00 [1.00; 1.00]	1.00 [1.00; 1.00]
1980–1993 # main model	1.00 [1.00; 1.00]	1.00 [1.00; 1.00]	Na	1.00 [1.00; 1.00]	1.00 [1.00; 1.00]	1.00 [1.00; 1.00]
1994–2007 # sensitivity model	1.00 [1.00; 1.00]	1.00 [1.00; 1.00]	1.00 [1.00; 1.00]	1.00 [1.00; 1.00]	1.00 [1.00; 1.00]	1.00 [1.00; 1.00]
1980–1993 # main model	1.00 [0.87; 1.16]	0.98 [0.84; 1.14]	1.00 [1.00; 1.00]	0.96 [0.65; 1.43]	0.97 [0.48; 1.98]	1.48 [0.70; 3.15]
2008–2016 # sensitivity model	1.00 [1.00; 1.00]	1.00 [1.00; 1.00]	1.00 [1.00; 1.00]	1.00 [1.00; 1.00]	1.00 [1.00; 1.00]	1.00 [1.00; 1.00]
2008–2016 # main model	1.00 [0.87; 1.16]	0.99 [0.86; 1.13]	0.99 [0.42; 2.38]	0.94 [0.67; 1.33]	1.03 [0.51; 2.09]	1.02 [0.54; 1.94]

Exponentiated coefficients; 95% confidence intervals in brackets.

CAD diagnosis was not defined in the ICD before 1994. Therefore, the period 1980–1993 is the reference interval for all diseases, except CAD for which 1994–2007 is the reference.

[a]Reference value.

IRR, incidence rate ratio; AIHA, autoimmune hemolytic anemia; NOS, not otherwise specified; CAD, cold agglutinin disease; PNH, paroxysmal nocturnal hemoglobinuria; CI, confidence intervals; na, not applicable. The # represents the interaction-term.

Supplementary Table 7. PPR for comparison of prevalence of hemolytic anemia in Denmark, 1980-2016, using both models

	AIHA	Acquired hemolysis NOS	CAD	Drug induced	Other defined hemolysis	PNH
PPR:						
1980	1.00[a]	1.00[a]	na	1.00[a]	1.00[a]	1.00[a]
1981	1.16 [0.91;1.49]	1.13 [0.90;1.41]	na	1.17 [0.77;1.76]	0.86 [0.29;2.55]	1.22 [0.51;2.95]
1982	1.35 [1.07;1.71]	1.29 [1.04;1.60]	na	1.41 [0.95;2.09]	1.14 [0.41;3.15]	1.45 [0.62;3.38]
1983	1.41 [1.11;1.78]	1.41 [1.14;1.74]	na	1.64 [1.12;2.41]	1.14 [0.41;3.16]	1.67 [0.73;3.81]
1984	1.56 [1.24;1.96]	1.60 [1.30;1.97]	na	2.10 [1.45;3.03]	1.43 [0.54;3.76]	1.56 [0.67;3.60]
1985	1.65 [1.31;2.07]	1.71 [1.40;2.10]	na	2.12 [1.47;3.06]	1.57 [0.61;4.06]	1.34 [0.56;3.17]
1986	1.69 [1.35;2.11]	1.74 [1.42;2.13]	na	2.26 [1.57;3.26]	1.57 [0.61;4.06]	1.45 [0.62;3.38]
1987	1.76 [1.41;2.20]	1.81 [1.47;2.21]	na	2.31 [1.61;3.32]	1.57 [0.61;4.05]	1.55 [0.67;3.59]
1988	1.83 [1.47;2.29]	1.89 [1.55;2.32]	na	2.23 [1.55;3.22]	1.85 [0.74;4.65]	1.66 [0.73;3.80]
1989	1.98 [1.59;2.46]	2.18 [1.79;2.65]	na	2.38 [1.66;3.41]	2.00 [0.81;4.95]	2.11 [0.95;4.66]
1990	1.93 [1.55;2.40]	2.25 [1.85;2.74]	na	2.37 [1.66;3.41]	2.28 [0.94;5.54]	2.33 [1.07;5.08]
1991	2.11 [1.70;2.61]	2.25 [1.85;2.74]	na	2.35 [1.64;3.37]	2.42 [1.00;5.83]	2.32 [1.06;5.07]
1992	2.10 [1.69;2.61]	2.44 [2.01;2.95]	na	2.41 [1.68;3.45]	2.55 [1.07;6.11]	2.43 [1.12;5.27]
1993	2.26 [1.82;2.79]	2.41 [1.99;2.93]	na	2.28 [1.59;3.28]	2.68 [1.13;6.38]	2.64 [1.23;5.67]
1994	2.42 [1.96;2.99]	2.44 [2.01;2.96]	1.00[a]	2.25 [1.57;3.24]	2.96 [1.26;6.96]	2.85 [1.33;6.08]
1995	2.64 [2.14;3.25]	2.55 [2.11;3.09]	1.00 [0.00; na]	2.13 [1.48;3.07]	5.05 [2.25;11.35]	2.95 [1.39;6.26]
1996	2.88 [2.34;3.54]	2.68 [2.22;3.25]	0.99 [0.00; na]	2.09 [1.45;3.01]	5.99 [2.70;13.32]	2.93 [1.38;6.22]
1997	3.01 [2.45;3.69]	2.79 [2.31;3.37]	0.99 [0.00; na]	1.90 [1.31;2.75]	8.32 [3.80;18.21]	2.91 [1.37;6.19]
1998	3.13 [2.55;3.83]	2.88 [2.39;3.48]	0.98 [0.00; na]	1.96 [1.35;2.83]	9.95 [4.58;21.62]	3.01 [1.42;6.38]
1999	3.23 [2.64;3.96]	2.98 [2.48;3.60]	0.98 [0.00; na]	1.86 [1.28;2.70]	12.39 [5.74;26.74]	3.11 [1.47;6.56]
2000	3.50 [2.86;4.28]	3.13 [2.60;3.77]	>200 [na]	1.88 [1.29;2.72]	13.04 [6.05;28.10]	3.10 [1.47;6.54]
2001	3.62 [2.96;4.42]	3.26 [2.71;3.92]	>200 [na]	1.85 [1.27;2.68]	13.82 [6.42;29.72]	3.09 [1.46;6.52]
2002	3.77 [3.09;4.60]	3.39 [2.82;4.07]	>200 [na]	1.89 [1.30;2.73]	14.86 [6.92;31.90]	3.29 [1.56;6.90]
2003	3.98 [3.26;4.85]	3.56 [2.96;4.27]	>200 [na]	1.90 [1.31;2.76]	15.90 [7.42;34.09]	3.28 [1.56;6.88]
2004	4.29 [3.52;5.22]	3.74 [3.12;4.49]	>200 [na]	1.83 [1.26;2.66]	16.95 [7.91;36.28]	3.48 [1.67;7.27]
2005	4.47 [3.68;5.44]	3.78 [3.15;4.53]	>200 [na]	1.74 [1.19;2.53]	17.98 [8.41;38.46]	3.68 [1.77;7.66]
2006	4.66 [3.84;5.67]	3.91 [3.26;4.68]	>200 [na]	1.78 [1.22;2.58]	19.95 [9.35;42.58]	3.67 [1.76;7.63]
2007	4.84 [3.98;5.88]	4.01 [3.35;4.81]	>200 [na]	1.72 [1.18;2.51]	20.28 [9.51;43.28]	3.76 [1.81;7.81]
2008	4.99 [4.11;6.05]	4.28 [3.58;5.13]	>200 [na]	1.69 [1.16;2.47]	21.65 [10.16;46.13]	3.74 [1.80;7.77]
2009	5.02 [4.14;6.10]	4.35 [3.63;5.20]	>200 [na]	1.66 [1.14;2.42]	23.50 [11.04;50.01]	4.03 [1.95;8.31]
2010	5.09 [4.20;6.18]	4.53 [3.78;5.41]	>200 [na]	1.74 [1.20;2.53]	23.27 [10.93;49.52]	4.32 [2.10;8.87]
2011	5.37 [4.43;6.52]	4.64 [3.88;5.54]	>200 [na]	1.78 [1.22;2.58]	24.21 [11.38;51.50]	4.50 [2.20;9.22]
2012	5.69 [4.70;6.89]	4.90 [4.10;5.85]	>200 [na]	1.75 [1.20;2.54]	26.22 [12.34;55.72]	4.59 [2.24;9.39]
2013	5.84 [4.82;7.07]	4.97 [4.16;5.93]	>200 [na]	1.78 [1.23;2.59]	27.43 [12.92;58.24]	5.08 [2.50;10.33]
2014	6.08 [5.02;7.36]	5.14 [4.31;6.13]	>200 [na]	1.95 [1.35;2.81]	29.13 [13.73;61.80]	5.06 [2.49;10.28]

	AIHA	Acquired hemolysis NOS	CAD	Drug induced	Other defined hemolysis	PNH
2015	6.22 [5.14;7.52]	5.36 [4.50;6.39]	>200 [na]	1.94 [1.34;2.80]	29.22 [13.77;61.99]	5.03 [2.47;10.22]
2016	6.40 [5.29;7.74]	5.50 [4.61;6.55]	>200 [na]	2.05 [1.43;2.95]	29.36 [13.84;62.28]	5.09 [2.50;10.33]
Sensitivity model	1.00[a]	1.00[a]	1.00[a]	1.00[a]	1.00[a]	1.00[a]
Main model	1.07 [0.83;1.37]	0.89 [0.70;1.13]	1.00 [0.00; na]	0.98 [0.63,1.50]	0.57 [0.17,1.95]	1.00 [0.40,2.52]
1980 # Sensitivity model	1.00 [1.00;1.00]	1.00 [1.00;1.00]	na	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]
1980 # Main model	1.00 [1.00;1.00]	1.00 [1.00;1.00]	na	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]
1981 # Sensitivity model	1.00 [1.00;1.00]	1.00 [1.00;1.00]	na	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]
1981 # Main model	1.01 [0.72;1.42]	0.98 [0.71;1.36]	na	1.02 [0.57;1.84]	0.88 [0.14;5.58]	1.09 [0.32;3.75]
1982 # Sensitivity model	1.00 [1.00;1.00]	1.00 [1.00;1.00]	na	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]
1982 # Main model	1.00 [0.72;1.39]	1.00 [0.73;1.38]	na	1.01 [0.57;1.77]	1.09 [0.21;5.76]	1.08 [0.33;3.55]
1983 # Sensitivity model	1.00 [1.00;1.00]	1.00 [1.00;1.00]	na	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]
1983 # Main model	1.01 [0.73;1.40]	1.00 [0.74;1.37]	na	0.99 [0.58;1.72]	1.09 [0.21;5.76]	1.07 [0.33;3.41]
1984 # Sensitivity model	1.00 [1.00;1.00]	1.00 [1.00;1.00]	na	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]
1984 # Main model	1.00 [0.73;1.37]	1.01 [0.74;1.36]	na	1.00 [0.59;1.69]	1.23 [0.26;5.85]	1.14 [0.35;3.68]
1985 # Sensitivity model	1.00 [1.00;1.00]	1.00 [1.00;1.00]	na	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]
1985 # Main model	1.02 [0.74;1.39]	1.02 [0.76;1.38]	na	0.98 [0.58;1.65]	1.27 [0.28;5.87]	1.08 [0.32;3.64]
1986 # Sensitivity model	1.00 [1.00;1.00]	1.00 [1.00;1.00]	na	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]
1986 # Main model	1.02 [0.75;1.40]	1.00 [0.75;1.35]	na	0.98 [0.58;1.65]	1.43 [0.32;6.49]	1.08 [0.33;3.55]
1987 # Sensitivity model	1.00 [1.00;1.00]	1.00 [1.00;1.00]	na	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]
1987 # Main model	1.02 [0.75;1.39]	1.00 [0.74;1.34]	na	0.99 [0.59;1.66]	1.43 [0.32;6.49]	1.00 [0.31;3.27]
1988 # Sensitivity model	1.00 [1.00;1.00]	1.00 [1.00;1.00]	na	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]
1988 # Main model	1.03 [0.76;1.40]	0.98 [0.73;1.32]	na	0.98 [0.58;1.65]	1.35 [0.31;5.91]	1.00 [0.31;3.22]
1989 # Sensitivity model	1.00 [1.00;1.00]	1.00 [1.00;1.00]	na	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]
1989 # Main model	1.04 [0.77;1.41]	0.98 [0.73;1.30]	na	0.98 [0.59;1.64]	1.37 [0.32;5.92]	1.00 [0.33;3.07]
1990 # Sensitivity model	1.00 [1.00;1.00]	1.00 [1.00;1.00]	na	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]
1990 # Main model	1.05 [0.77;1.42]	0.97 [0.73;1.29]	na	0.98 [0.59;1.64]	1.42 [0.34;5.94]	1.00 [0.33;3.02]
1991 # Sensitivity model	1.00 [1.00;1.00]	1.00 [1.00;1.00]	na	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]
1991 # Main model	1.06 [0.79;1.43]	0.95 [0.71;1.26]	na	0.97 [0.58;1.63]	1.44 [0.35;5.95]	1.00 [0.33;3.02]
1992 # Sensitivity model	1.00 [1.00;1.00]	1.00 [1.00;1.00]	na	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]
1992 # Main model	1.07 [0.79;1.44]	0.95 [0.71;1.26]	na	0.97 [0.58;1.63]	1.36 [0.33;5.59]	1.00 [0.33;2.99]
1993 # Sensitivity model	1.00 [1.00;1.00]	1.00 [1.00;1.00]	na	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]
1993 # Main model	1.05 [0.78;1.41]	0.95 [0.71;1.26]	na	0.97 [0.58;1.63]	1.38 [0.34;5.62]	1.04 [0.35;3.07]
1994 # Sensitivity model	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]
1994 # Main model	1.05 [0.79;1.41]	0.94 [0.71;1.25]	1.00 [1.00;1.00]	0.98 [0.59;1.65]	1.42 [0.35;5.66]	1.04 [0.36;3.03]
1995 # Sensitivity model	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]
1995 # Main model	1.09 [0.81;1.45]	0.93 [0.70;1.23]	1.00 [0.00; na]	0.98 [0.58;1.65]	1.46 [0.39;5.46]	1.07 [0.37;3.11]
1996 # Sensitivity model	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]

	AIHA	Acquired hemolysis NOS	CAD	Drug induced	Other defined hemolysis	PNH
1996 # Main model	1.07 [0.81;1.43]	0.93 [0.71;1.23]	1.00 [0.00; na]	0.99 [0.59;1.67]	1.51 [0.41;5.55]	1.11 [0.38;3.21]
1997 # Sensitivity model	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]
1997 # Main model	1.07 [0.81;1.43]	0.93 [0.70;1.22]	1.00 [0.00; na]	1.00 [0.59;1.70]	1.49 [0.41;5.37]	1.22 [0.43;3.51]
1998 # Sensitivity model	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]
1998 # Main model	1.07 [0.80;1.42]	0.93 [0.70;1.22]	1.00 [0.00; na]	1.00 [0.59;1.69]	1.48 [0.41;5.31]	1.29 [0.45;3.67]
1999 # Sensitivity model	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]
1999 # Main model	1.07 [0.81;1.42]	0.93 [0.70;1.22]	1.00 [0.00; na]	1.01 [0.60;1.72]	1.46 [0.41;5.17]	1.24 [0.44;3.53]
2000 # Sensitivity model	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]
2000 # Main model	1.07 [0.81;1.42]	0.92 [0.70;1.21]	1.00 [0.00; na]	0.99 [0.58;1.68]	1.46 [0.41;5.15]	1.28 [0.45;3.62]
2001 # Sensitivity model	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]
2001 # Main model	1.07 [0.81;1.42]	0.91 [0.70;1.20]	1.00 [0.00; na]	0.96 [0.56;1.64]	1.46 [0.41;5.14]	1.31 [0.46;3.72]
2002 # Sensitivity model	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]
2002 # Main model	1.07 [0.81;1.41]	0.93 [0.71;1.21]	1.50 [0.00; na]	0.98 [0.57;1.66]	1.46 [0.41;5.15]	1.26 [0.45;3.55]
2003 # Sensitivity model	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]
2003 # Main model	1.06 [0.80;1.39]	0.93 [0.71;1.22]	1.33 [0.00; na]	0.99 [0.58;1.67]	1.50 [0.43;5.26]	1.26 [0.45;3.55]
2004 # Sensitivity model	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]
2004 # Main model	1.05 [0.80;1.38]	0.94 [0.72;1.22]	1.67 [0.00; na]	0.99 [0.58;1.68]	1.50 [0.43;5.26]	1.27 [0.45;3.57]
2005 # Sensitivity model	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]
2005 # Main model	1.05 [0.80;1.38]	0.93 [0.71;1.21]	2.25 [0.00; na]	1.00 [0.58;1.70]	1.45 [0.41;5.07]	1.26 [0.45;3.50]
2006 # Sensitivity model	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]
2006 # Main model	1.06 [0.81;1.39]	0.93 [0.72;1.22]	2.00 [0.00; na]	1.00 [0.59;1.70]	1.43 [0.41;5.00]	1.29 [0.46;3.58]
2007 # Sensitivity model	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]
2007 # Main model	1.06 [0.81;1.39]	0.94 [0.72;1.23]	1.86 [0.00; na]	0.98 [0.58;1.68]	1.43 [0.41;4.98]	1.31 [0.47;3.62]
2008 # Sensitivity model	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]
2008 # Main model	1.07 [0.82;1.40]	0.93 [0.72;1.21]	2.33 [0.00; na]	0.98 [0.58;1.68]	1.43 [0.41;4.98]	1.28 [0.46;3.55]
2009 # Sensitivity model	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]
2009 # Main model	1.07 [0.82;1.41]	0.93 [0.72;1.21]	2.44 [0.00; na]	0.98 [0.57;1.68]	1.44 [0.41;5.03]	1.26 [0.46;3.47]
2010 # Sensitivity model	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]
2010 # Main model	1.07 [0.82;1.40]	0.94 [0.72;1.22]	2.27 [0.00; na]	0.97 [0.57;1.66]	1.43 [0.41;4.99]	1.21 [0.44;3.33]
2011 # Sensitivity model	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]
2011 # Main model	1.07 [0.82;1.40]	0.93 [0.71;1.20]	2.36 [0.00; na]	0.96 [0.56;1.64]	1.43 [0.41;4.97]	1.25 [0.46;3.42]
2012 # Sensitivity model	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]
2012 # Main model	1.06 [0.81;1.39]	0.93 [0.72;1.21]	2.73 [0.00; na]	0.95 [0.56;1.62]	1.44 [0.42;5.02]	1.22 [0.45;3.34]
2013 # Sensitivity model	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]
2013 # Main model	1.06 [0.81;1.39]	0.92 [0.71;1.20]	2.83 [0.00; na]	0.96 [0.57;1.64]	1.47 [0.42;5.12]	1.20 [0.44;3.25]
2014 # Sensitivity model	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]
2014 # Main model	1.07 [0.82;1.40]	0.92 [0.71;1.20]	2.89 [0.00; na]	0.96 [0.57;1.61]	1.47 [0.42;5.09]	1.18 [0.44;3.20]
2015 # Sensitivity model	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]
2015 # Main model	1.09 [0.83;1.42]	0.93 [0.72;1.20]	2.81 [0.00; na]	0.97 [0.57;1.63]	1.45 [0.42;5.02]	1.18 [0.44;3.20]

	AIHA	Acquired hemolysis NOS	CAD	Drug induced	Other defined hemolysis	PNH
2016 # Sensitivity model	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]	1.00 [1.00;1.00]
2016 # Main model	1.08 [0.83;1.41]	0.93 [0.72;1.21]	2.56 [0.00; na]	0.95[0.57;1.59]	1.46 [0.42;5.06]	1.20 [0.44;3.24]

Exponentiated coefficients; 95% confidence intervals in brackets.

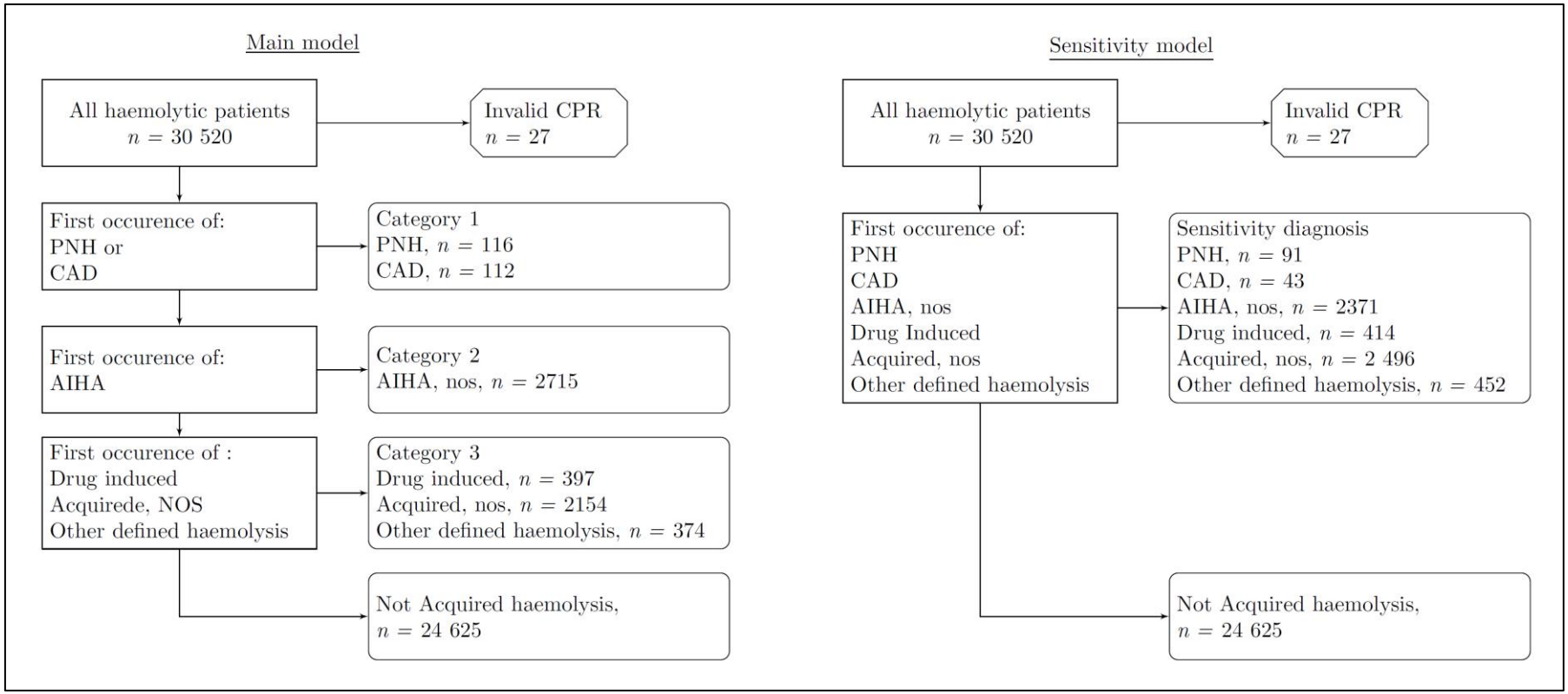
CAD diagnosis was not defined in the ICD before 1994. Therefore, 1980 is the reference year for all diseases, except CAD for which 1994 is the reference. CAD incidence was very low in 1994, but increased drastically from 2000. Therefore, the PPR for the years 2000 and onward are extremely large compared to 1994, and have been truncated to >200 without confidence intervals.

[a]Reference value.

PPR, prevalence proportion ratio; AIHA, autoimmune hemolytic anemia; NOS, not otherwise specified; CAD, cold agglutinin disease; PNH, paroxysmal nocturnal hemoglobinuria; CI, confidence intervals; na, not applicable. The # represents the interaction-term.

SUPPLEMENTARY FIGURES

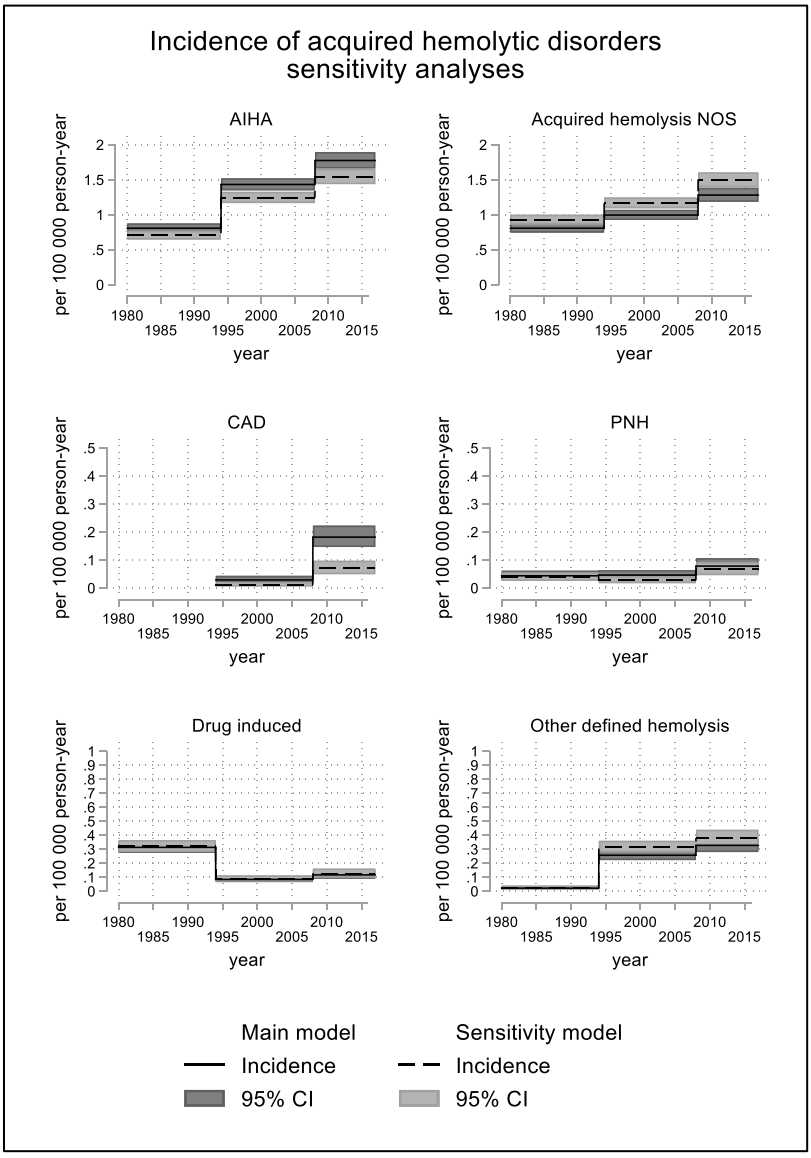
Supplementary Figure 1. Flowchart describing the process of assigning diagnoses using the two models



Flowchart illustrating the process of assigning diagnoses using the two models. The left panel depicts the main model, which uses a hierarchy to assign the diagnosis to patients. Only patients who are not assigned a diagnosis proceed to next level. Patients with two equally reliable diagnoses, (e.g. PNH and CAD) are assigned the first recorded of these. The right panel depicts the sensitivity model, in which patients were classified only according to the first recorded diagnosis code of acquired hemolytic anemia. PNH, paroxysmal nocturnal

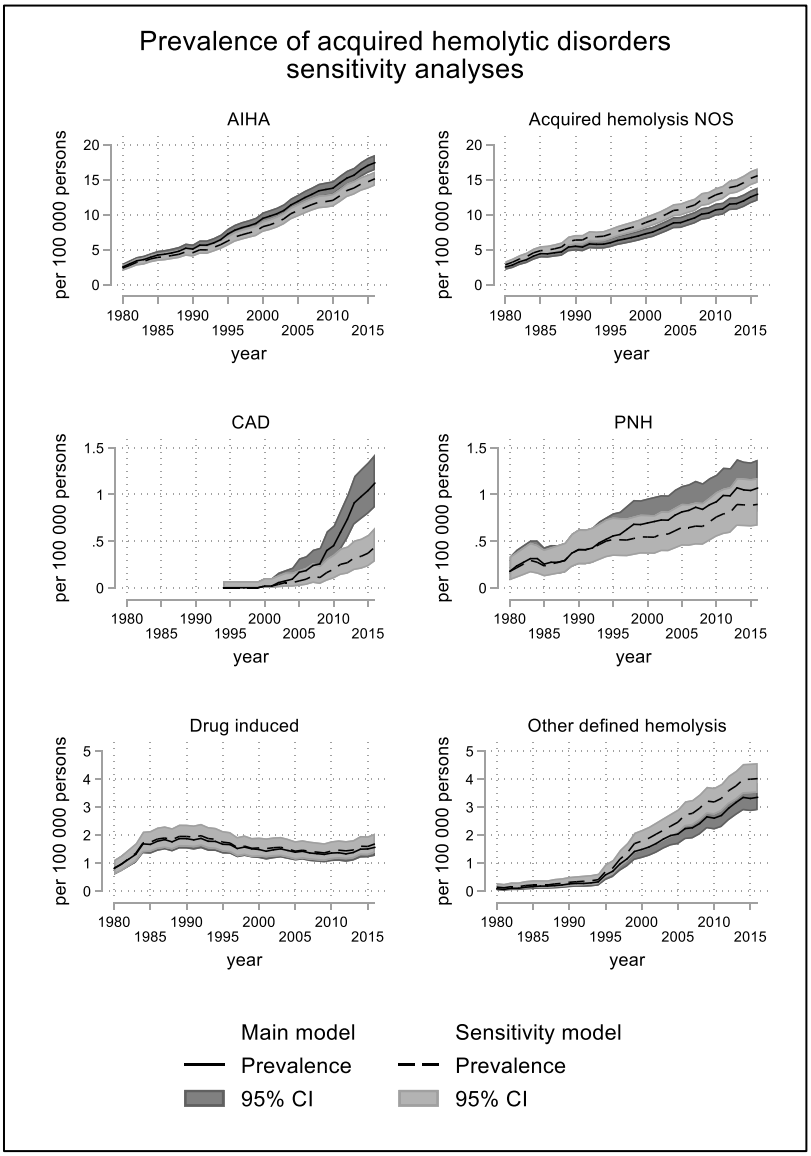
hemoglobinuria; CAD, cold agglutinin disease; AIHA, autoimmune hemolytic anemia; NOS, not otherwise specified; CPR, civil registration number.

Supplementary Figure 2. Incidence of acquired hemolytic diseases in Denmark, 1980–2016, according to the model used for classification of diagnosis (main model vs sensitivity analysis model).



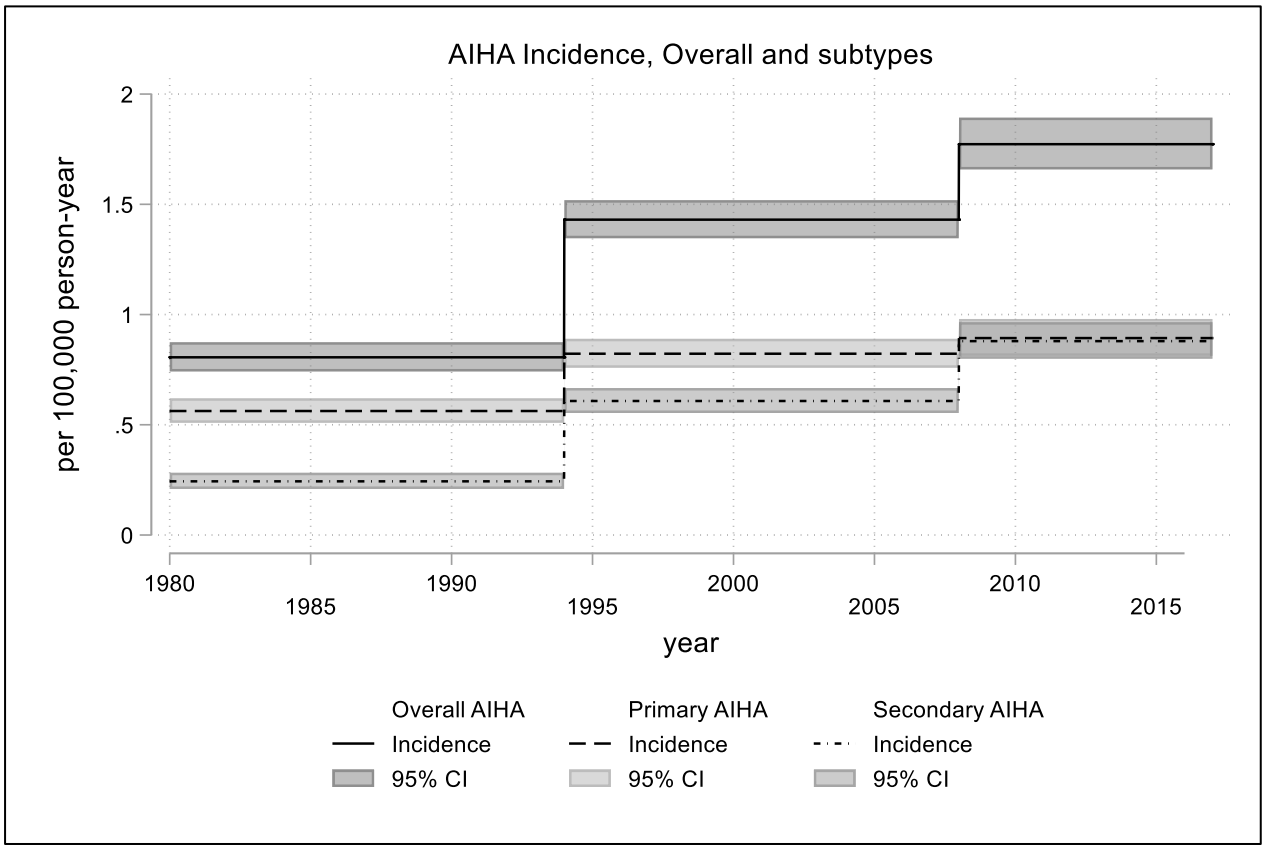
Period incidence of acquired hemolytic diseases estimated on 1 January, 1980–2016. The main model (full line; darker shading) utilizes the best available diagnosis in the Danish National Patient Register. The sensitivity model (broken line; lighter shading) uses the first encountered diagnosis. CAD was not defined in the ICD before 1994. AIHA, autoimmune hemolytic anemia; CAD, cold agglutinin disease; CI, confidence interval; NOS, not otherwise specified; PNH, paroxysmal nocturnal hemoglobinuria.

Supplementary Figure 3. Prevalence of acquired hemolytic diseases in Denmark, 1980–2016, according to the model used for classification of diagnosis (main model vs. sensitivity analysis model).



Point prevalence of acquired hemolytic diseases estimated on 1 January, 1980–2016. The main model (full line; darker shading) utilizes the best available diagnosis in the Danish National Patient Register. The sensitivity model (broken line; lighter shading) uses the first encountered diagnosis. CAD was not defined in the ICD before 1994. AIHA, autoimmune hemolytic anemia; CAD, cold agglutinin disease; CI, confidence interval; NOS, not otherwise specified; PNH, paroxysmal nocturnal hemoglobinuria.

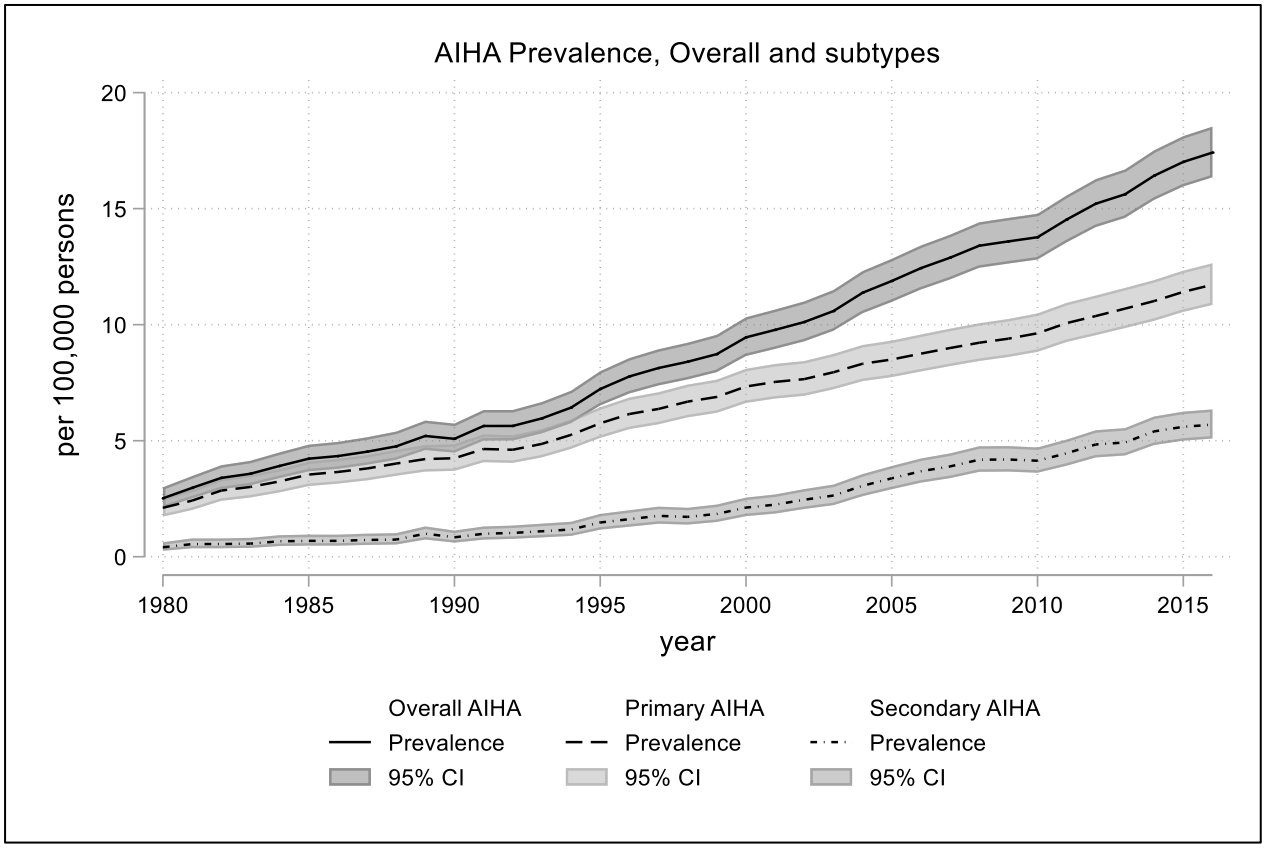
Supplementary Figure 4. Comparing incidence of AIHA and subtypes in Denmark, 1980–2016.



Period incidence of AIHA estimated on 1 January, 1980–2016. The overall AIHA (full line; darker shading) is based on the AIHA diagnosis in the Danish National Patient Register. The primary AIHA (broken line; lighter shading) are patients without predisposing diseases before or until 100 days post AIHA diagnosis. The broken and dotted are secondary AIHA, being patients with one or more of the predisposing conditions diagnosed before or at the latest 100 days after the diagnosis of AIHA (se supplementary table 2 for predisposing condition).

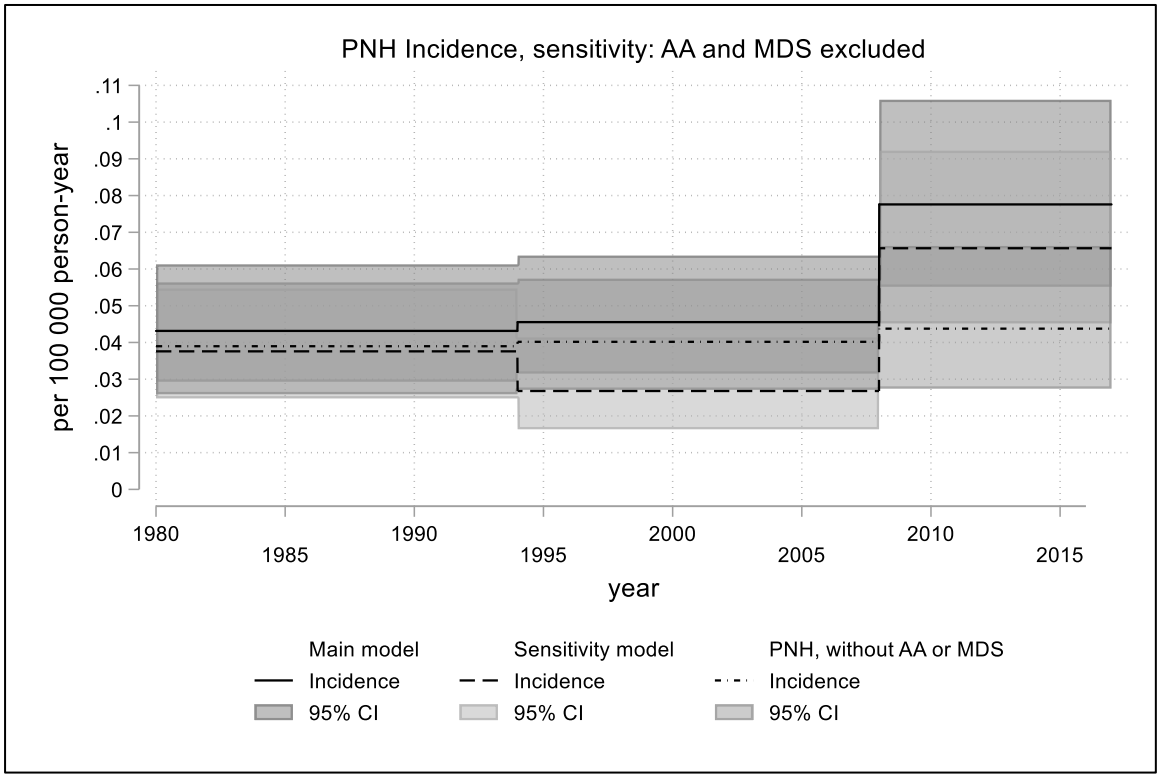
AIHA, autoimmune hemolytic anemia; CI, confidence interval

Supplementary Figure 5. Comparing prevalence of AIHA and subtypes in Denmark, 1980–2016.



Point prevalence of AIHA and subtypes estimated on 1 January, 1980–2016. The overall AIHA (full line; darker shading) is based on the AIHA diagnosis in the Danish National Patient Register. The primary AIHA (broken line; lighter shading) are patients without predisposing diseases before or until 100 days post AIHA diagnosis. The broken and dotted are secondary AIHA, being patients with one or more of the predisposing conditions diagnosed before or at the latest 100 days after the diagnosis of AIHA (se supplementary table 2 for predisposing condition).

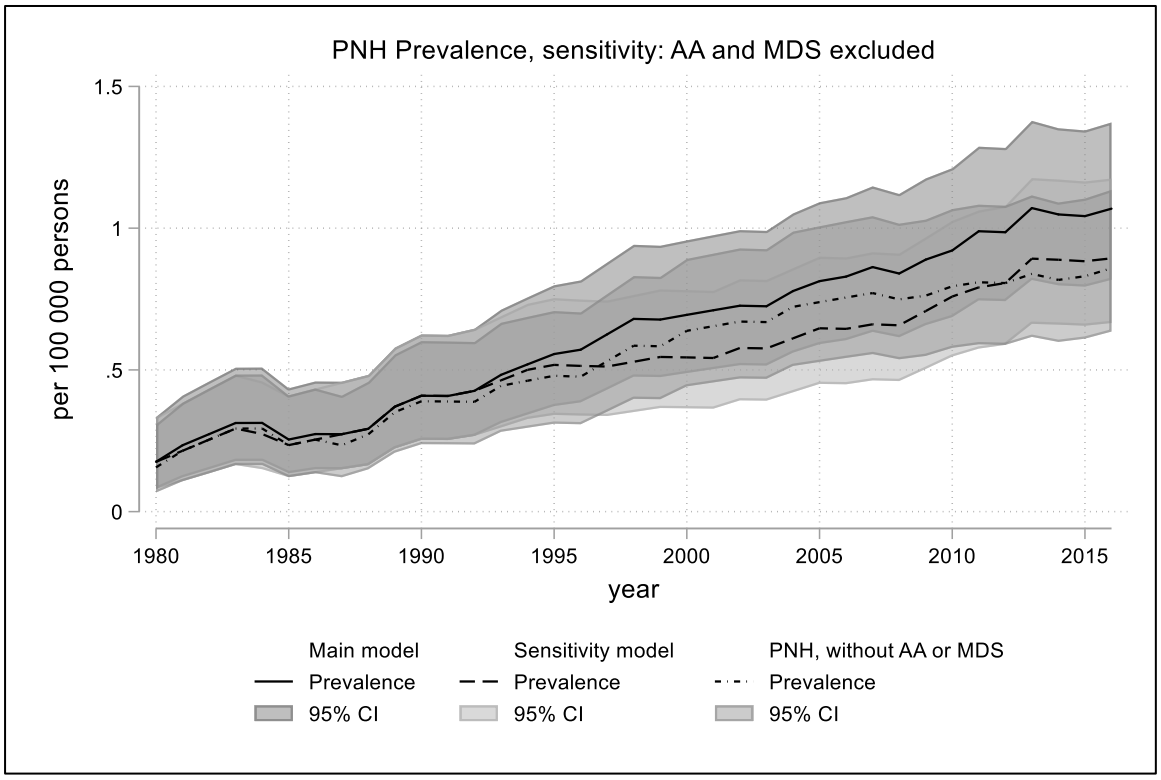
Supplementary Figure 6. Sensitivity test of PNH incidence in Denmark, 1980–2016, Aplastic anemia and Myelodysplastic syndrome excluded.



Period incidence of PNH estimated 1980–2016. The main model (full line; darker shading) utilizes the best available diagnosis in the Danish National Patient Register. The sensitivity model (broken line; lighter shading) uses the first encountered diagnosis. The broken and dotted line represents the model where all patients with PNH and myelodysplastic syndrome or aplastic anemia before or within 6 months after diagnosis of PNH are excluded.

PNH, paroxysmal nocturnal hemoglobinuria; MDS: Myelodysplastic syndrome; AA: aplastic anemia; CI, confidence interval.

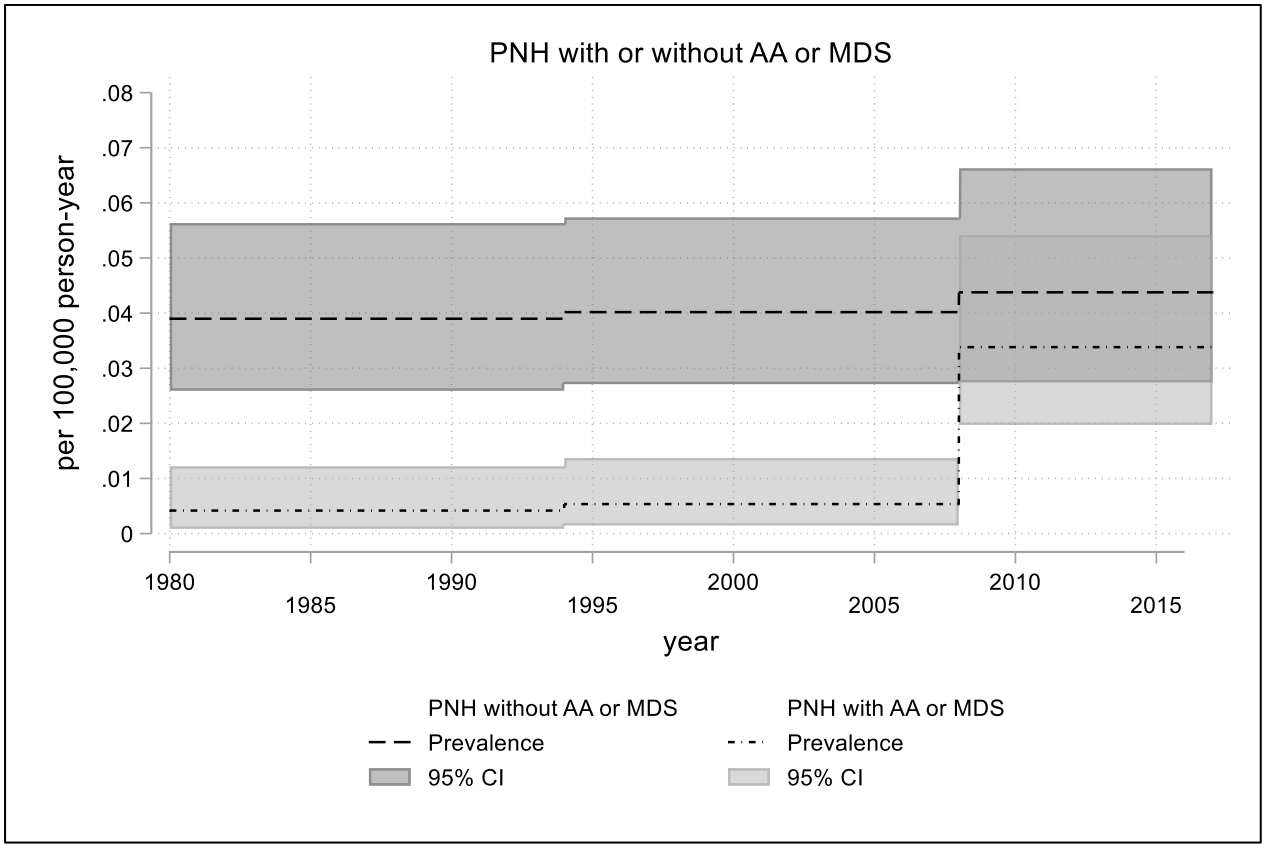
Supplementary Figure 7. Sensitivity test of PNH prevalence in Denmark, 1980–2016, Aplastic anemia and Myelodysplastic syndrome excluded.



Point prevalence of PNH estimated on 1 January, 1980–2016. The main model (full line; darker shading) utilizes the best available diagnosis in the Danish National Patient Register. The sensitivity model (broken line; lighter shading) uses the first encountered diagnosis. The broken and dotted line represents the model where all patients with PNH and myelodysplastic syndrome or aplastic anemia before or within 6 months after diagnosis of PNH are excluded.

PNH, paroxysmal nocturnal hemoglobinuria; MDS: Myelodysplastic syndrome; AA: aplastic anemia; CI, confidence interval.

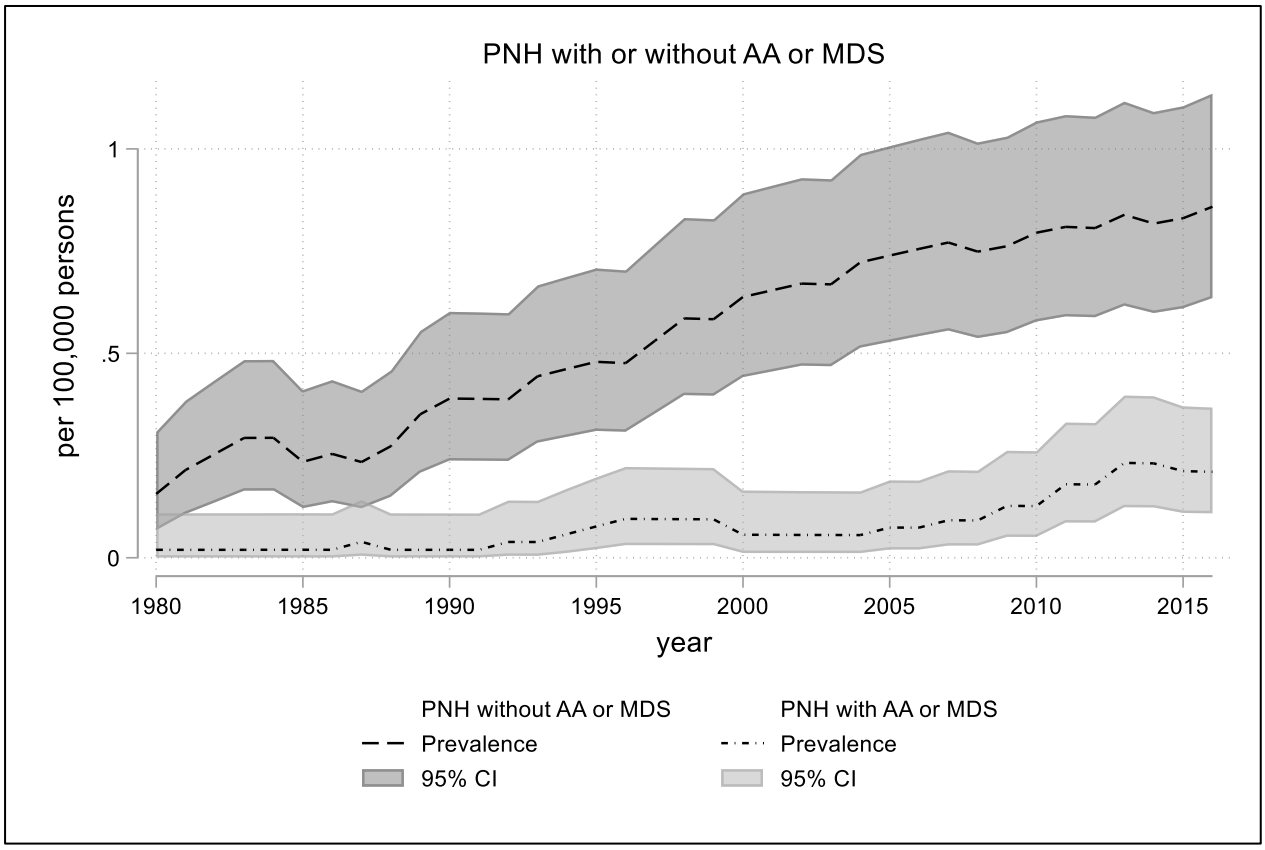
Supplementary Figure 8. Sensitivity test of PNH with or without AA or MDS incidence in Denmark, 1980–2016.



Period incidence of PNH estimated 1980–2016. The broken line represents PNH without association to AA or MDS. The broken and dotted line represents incidence of PNH associated with AA or MDS before or within 6 months after diagnosis of PNH. Both estimates utilize the best available diagnosis in the Danish National Patient Register.

PNH, paroxysmal nocturnal hemoglobinuria; MDS: Myelodysplastic syndrome; AA: aplastic anemia; CI, confidence interval.

Supplementary Figure 9. Sensitivity test of PNH with or without association to AA or MDS prevalence in Denmark, 1980–2016.



Point prevalence of PNH estimated on 1 January, 1980–2016. The broken line represents PNH without association to AA or MDS. The broken and dotted line represents incidence of PNH associated with AA or MDS before or within 6 months after diagnosis of PNH. Both estimates utilize the best available diagnosis in the Danish National Patient Register.

PNH, paroxysmal nocturnal hemoglobinuria; MDS: Myelodysplastic syndrome; AA: aplastic anemia; CI, confidence interval.