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ORIGINAL ARTICLE

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Risk for incident comorbidities, nonhepatic cancer and mortality in acute hepatic porphyria: A matched cohort study in 1244 individuals

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Abstract

The acute hepatic porphyrias (AHP) are associated with long-term complications such as primary liver cancer, hypertension, and chronic kidney disease. Data on other related comorbidities are scarce. In this register-based, matched cohort study, we assessed the risks of nonhepatic cancers, cardiovascular diseases, renal diseases, psychiatric disorders, and mortality in relation to porphyria type, sex, and biochemical disease activity. All patients in the Swedish porphyria register with a verified AHP diagnosis during 1987–2015 were included. The biochemical activity of acute intermittent porphyria was assessed using recorded maximal urinary porphobilinogen (U-PBG). Data on incident comorbidities and mortality were collected from national health registries. Cumulative incidences, rates, and hazards were compared to reference individuals from the general population, matched 1:10 by age, sex, and county. We identified 1244 patients with AHP with a median follow-up of 19 years. Health registries identified 149 AHP-subjects (12.0%) with nonhepatic cancer, similar to 1601 (13.0%) in the matched reference population ($n = 12\,362$). Patients with AHP had a higher risk of kidney cancer (0.8% vs. 0.2%, $p < 0.001$), hypertension, and chronic kidney disease but no increase in risk for cardiovascular disease, except for cerebrovascular disease in patients with elevated U-PBG, (aHR = 1.40 [95% CI:1.06–1.85]). Mortality risk during follow-up was higher among patients with AHP (21% vs. 18%, $p = 0.001$), and associated with primary liver cancer, female sex, and biochemical activity. In conclusion, AHP is associated with an increased risk of kidney cancer, hypertension, chronic kidney disease, and mortality but not with cardiovascular disease or other nonhepatic cancers.

KEYWORDS

acute intermittent porphyria, chronic kidney disease, hereditary coproporphyria, inherited disease, kidney cancer, variegate porphyria

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1 | INTRODUCTION

The porphyrias are a group of rare metabolic diseases related to altered functions in the eight enzymatic steps in the heme synthesis pathway.[1] Based on symptoms and mainly affected organ, the porphyrias are characterized as either acute or cutaneous and erythropoietic or hepatic. Acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP) are together commonly labeled acute hepatic porphyria (AHP). They are all inherited in an autosomal dominant manner but are caused by different pathogenic variants in genes corresponding to either the third (AIP), sixth (HCP), or seventh (VP) step of the heme synthesis pathway. Another extremely rare autosomal recessive form of AHP, ALAD-deficient porphyria, was not included in this study.

AIP is the least rare AHP with an estimated prevalence of symptomatic disease in Europe of 5.9 per million inhabitants.[2] Due to a founder mutation effect, Sweden has the world's highest prevalence with approximately 23 cases of symptomatic AIP per million[3] and thereby a large, well characterized cohort available for detailed study.

Patients with AHP are at risk of acute porphyria attacks that involve severe abdominal pain, gastrointestinal and neurological symptoms, and mental status changes. Triggers such as drugs, fasting, or hormonal changes induce the first and rate limiting enzyme of the heme synthesis pathway, aminolevulinic acid synthase 1 (ALAS1), in the liver and cause downstream accumulation of 5-aminolevulinic acid (ALA) and porphobilinogen (PBG), cytotoxic porphyrin precursors associated with acute porphyria attacks. Symptomatic disease is most common in females of reproductive age.[4,5] Phenotypic disease expression varies significantly. Most carriers of pathogenic gene variants never experience attacks and most symptomatic patients have only one or few attacks during their life, while a minority suffers from recurrent attacks resulting in severe morbidity and low quality of life[1,6] . Biochemical activity, defined as elevated levels of ALA and PBG, which are always increased during and after attacks, also occurs in asymptomatic patients with AIP.[7]

Patients with AHP are also at risk of several long-term complications including primary liver cancer (PLC),[8–13] systemic arterial hypertension (HT),[14–16] renal disease,[14–18] and neurological conditions.[19–21] In our previous study on the same cohort, we found a 38-fold increase in PLC risk, mainly affecting patients with biochemically active AIP.[12] Based on the high risk of PLC and studies identifying ALA as cytotoxic and potentially carcinogenic, an increased risk of other cancer forms and malignancy in general has been hypothesized.[22,23] Results from previous studies are however diverging. HT and renal disease are common in patients with AHP, particularly AIP with a history of acute symptoms, compared to the general population.[14–18] It is, however, unknown what impact these common risk factors have on the risk of cardiovascular diseases in patients with AHP. Neuropsychiatric symptoms are common in symptomatic AHP but data on long-term psychiatric risks are scarce. Some studies have reported increased risks of schizophrenia and bipolar disease in AHP cohorts, and an increased prevalence of AHP in psychiatric patient cohorts.[24,25]

Our current knowledge about AHP-related nonhepatic cancer risk, cardiovascular, and psychiatric comorbidity is limited, and it is unknown whether AHP-type or biochemical porphyria activity are associated with differences in risk. With modern medical management, few patients die from acute attacks but our knowledge about how long-term conditions impact mortality is limited.[26,27] In this large nationwide register-based matched cohort study we aimed to assess these risks in AHP patients, in relation to sex, AHP type and, for AIP, to biochemical disease activity.

2 | PATIENTS AND METHODS

This register-based cohort study is based on the same AHP-patient cohort and register-data as described in our previous study on AHP-related PLC.[12] In short, we used the nationwide Swedish porphyria register to assemble all patients alive and 18 years or older from 1987 to 2015 with a verified AHP diagnosis. For patients with AIP, we included biochemical data on maximal U-PBG levels categorized as ever elevated (U-PBG >1.6 mmol/mol creatinine, the upper limit of normal [U-PBG positive]) or never elevated (U-PBG ≤1.5 mmol/mol creatinine [U-PBG negative]). The AHP patients were matched by age, sex, and county of residence with up to 10 randomly selected non-AHP comparators from the general population. A detailed description of the study population, baseline variables, inclusion and exclusion criteria, registers and definition of outcomes is available in Appendix and in our previous publication.[12]

Given the large number of possible outcomes, we used a predefined set of outcomes based on previous study findings, clinical relevance, and general population incidence. The number of outcomes used for further analysis was limited depending on number of outcomes in each category.

2.1 | Nonhepatic cancers

All cancer forms and related ICD-codes are listed in Table S1. We used the Swedish cancer register and the

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cause of death register to identify incident cancers. The cancer register relies on mandatory reporting of histopathological samples and has excellent accuracy and coverage in general.[28] For some cancer forms, for example, lung cancer and pancreatic cancer where a proportion of patients are diagnosed in late palliative stages, the cancer register coverage is lower. We used the reported main and first contributing cause of death in the cause of death register to define cancer-related deaths not captured in the cancer register. After an initial assessment of number of outcomes, we proceeded with further analysis of the 10 most common cancer forms in Sweden, cancer forms that were identified in five or more AHP patients, and also cancer forms suggested to be more common in previous studies on AHP.

2.2 | Renal, cardiovascular, neurological, and psychiatric diseases

All studied diagnoses and related ICD codes are listed in Table S1. We used the Swedish National Patient Registers (NPR), which include (1) healthcare-related data for all hospitalizations nationwide since 1987, and (2) data on specialized outpatient care since 2001. Primary care visits are not included in the NPR and conditions typically managed by primary care physicians may therefore to a lesser extent be included in the NPR. Also, healthcare in Sweden is tax-funded, with activity-related compensation based on reporting the main diagnosis related to the visit. If a patient with, for instance, HT or moderate renal impairment visits a specialized outpatient clinic focusing on other diseases, HT/renal disease will not necessarily be reported to the NPR. Furthermore, different ICD-code distinctions between the ICD-9 (1987–1998) and ICD-10 (1997–2015) eras makes capture and labeling of some conditions such as atrial fibrillation and advanced stage chronic kidney disease (CKD) different between time periods. In the available registry data, superficial thrombophlebitis is included in the venous thrombosis disease category and cannot be separated from deep venous thrombosis. Suicide was assessed using the cause of death register only.

2.3 | Statistical analysis

Continuous variables were summarized as medians and interquartile ranges (IQRs), and categorical variables as counts and percentages. For each outcome, total numbers of events, proportions, and incidence rates per 1000 person-years were calculated. The hazards of developing the different outcomes, including subgroup analyses for patients with AIP based on U-PBG status, were computed by using Cox proportional hazards models comparing persons with porphyria to their matched controls, adjusted for age and sex, where applicable. The results are presented as hazard ratios (HR) with 95% confidence intervals (CI). Differences in median age at the time of diagnosis of the different outcomes between patients with AHP and the reference population were assessed using quantile regression.

As our previous paper[12] found a higher rate of PLC in patients with porphyria, excess mortality might be driven by this increased risk. Therefore, in a sensitivity analysis of the non-PLC mortality outcomes, we censored patients at a diagnosis of PLC. This sensitivity analysis thus examines mortality in patients who theoretically could not develop liver cancer, in a way to better examine if excess mortality was driven by the higher risk of liver cancer.

Mortality rate was depicted using the Kaplan–Meier method and the log-rank test for equality of survivor functions. p-values <0.05 were considered statistically significant. The Pearson's Chi^2 test was used to test for independence in proportions of CKD between patients with HT, and for differences in recorded causes of death between patients with AHP and the reference population.

STATA Statistical Software Release 15 (StataCorp LLC, College Station, TX) was used to perform all statistical analyses.

3 | RESULTS

The study cohort included 1244 patients with AHP and 12 362 matched comparators from the general population (Table 1). Due to a founder mutation effect, the Swedish AHP cohort has a large proportion of patients with AIP, $n = 1063$ (85%) compared to VP, $n = 125$ (10%) and HCP, $n = 56$ (5%). Among patients with AIP, 494 (46%) were U-PBG-positive and 345 (33%) were U-PBG-negative. Data on U-PBG were missing in 224 (21%) patients with AIP.

3.1 | Nonhepatic cancers

During follow-up (1987–2015), 149 (12%) patients with AHP and 1601 (13%) matched comparators had a nonhepatic cancer diagnosis registered (Table 2). No significant increase in over-all nonhepatic cancer risk was identified in any subgroup analysis by AHP type, sex, or in AIP by biochemical disease activity (U-PBG). A decreased risk was noticed in male AHP patients compared to the male reference population. We found no increased risks of the most common cancer forms: prostate, breast, skin,

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colorectal, and lung cancer (Table 3, Figure 1). The potential high-risk group, AIP patients with a reported elevated U-PBG, had similar risks as the matched reference population. Patients with AHP had a nonsignificant trend towards lower rates of two cancer forms that are related to smoking, lung cancer, and bladder cancer (Table 3), compared to the matched comparators.

TABLE 1 Characteristics of the study population

	AHP	Reference population
Total study population	1244	12 362
Sex, female, *n* (%)	654 (53)	6514 (53)
Age at study entry, median (IQR)	36 (19–53)	36 (19–52)
Birthyear males, median (IQR)	1962 (1941–1977)	1962 (1941–1977)
Birthyear females, median (IQR)	1954 (1938–1972)	1954 (1938–1972)
AHP type:		
Acute intermittent porphyria, *n* (%)	1063 (85)	–
Variegate porphyria, *n* (%)	125 (10)	–
Hereditary coproporphyria, *n* (%)	56 (5)	–
U-PBG, highest value, AIP only:		
- no data, *n* (%)	224 (21)	–
- negative, never elevated, *n* (%)	345 (33)	–
- positive (>1.6 mmol/mol creatinine) *n* (%)	494 (46)	

Abbreviations: AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; IQR, interquartile range; U-PBG, urinary porphobilinogen.

3.2 | Kidney cancer

The risk of kidney cancer was significantly increased among patients with AHP, 10 (0.8%) cases compared to 27 (0.2%) among the comparators (aHR = 3.92 [95% CI = 1.90–8.11]; Figure 1). The median age at kidney cancer diagnosis in patients with AHP was 75 years (IQR 65–82) not significantly different from 70 years (IQR 63–77) in the reference population, $p = 0.380$. Eight (80%) of the AHP patients with kidney cancer were females compared to 12 (44%) in the reference population. Two of the AHP kidney cancer patients had VP, and eight had AIP. Among those with AIP, all with recorded U-PBG tests ($n = 6$) were U-PBG positive. Tumor classification data were available for six patients in the AHP cohort; four of these were clear-cell and two were chromophobe renal carcinomas. Six of the AHP patients with kidney cancer died during follow-up, five of them from kidney cancer as main cause of death. The median survival after kidney cancer diagnosis was 11 months (range 0–75 months).

3.3 | Chronic kidney disease

CKD and kidney diseases overall (see Table S1 for ICD codes) were more common among patients with AHP and particularly in U-PBG positive AIP patients compared to the reference population (Table 4, Figure 2A,B). The HR of advanced CKD, here defined as CKD stage 4–5 (glomerular filtration rate [GFR] < 30 ml/min), was

TABLE 2 Nonhepatic cancer incidence and relative risk

	n (%)	IR/1000 (95% CI)	aHR (95% CI)	*p*
Reference ($n = 12\,362$)	1601 (13.0)	7.51 (7.14–7.89)	ref	–
AHP ($n = 1244$)	149 (12.0)	7.14 (6.08–8.38)	0.95 (0.81–1.13)	0.265
Female ref ($n = 6514$)	942 (14.5)	8.22 (7.71–8.76)	ref	–
Female AHP ($n = 654$)	101 (15.4)	9.15 (7.53–11.12)	1.15 (0.94–1.42)	0.168
Male ref ($n = 5848$)	659 (11.3)	6.68 (6.19–7.21)	ref	–
Male AHP ($n = 590$)	48 (8.1)	4.88 (3.68–6.47)	0.70 (0.53–0.94)	0.019
AIP ($n = 1063$)	125 (11.8)	6.83 (5.73–8.14)	0.94 (0.78–1.13)	0.497
U-PBG positive ($n = 494$)	82 (16.6)	8.87 (7.15–11.01)	1.03 (0.82–1.28)	0.816
U-PBG negative ($n = 345$)	27 (7.8)	4.49 (3.08–6.54)	0.81 (0.56–1.19)	0.292
VP and HCP ($n = 181$)	24 (13.2)	9.31 (6.24–13.90)	1.25 (0.84–1.88)	0.266

Abbreviations: AHP, acute hepatic porphyria; aHR, adjusted hazard ratio; AIP, acute intermittent porphyria; HCP, hepatic coproporphyria; IR, incidence rate; U-PBG, urinary porphobilinogen; VP, variegate porphyria.

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4.88 (95% CI = 2.59–9.17) in patients with any AHP and 7.06 (95% CI = 3.54–14.06) in U-PBG positive AIP patients. Among the 14 AHP-patients who had a diagnosis of advanced CKD, none were U-PBG negative, 11 (79%) were U-PBG positive AIP patients and 13 (93%) were women, compared to 10 (32%) women in the reference

TABLE 3 Incidence and relative risk, individual cancer by site

	Ref		AHP			
Cancer category (no. at risk AHP/Ref)	***n* (%)**	**IR/1000 person years (95% CI)**	***n* (%)**	**IR/1000 person years (95% CI)**	**aHR (95% CI)**	***p***
Prostate (590/5848)	239 (4.1)	2.38 (2.10–2.70)	20 (3.4)	2.00 (1.29–3.10)	0.79 (0.50–1.25)	0.318
Breast (654/6514)	228 (3.5)	1.91 (1.68–2.18)	21 (3.2)	1.82 (1.19–2.79)	1.00 (0.64–1.57)	0.994
Non melanoma skin cancer (1244/12 362)	175 (1.4)	0.79 (0.68–0.91)	16 (1.3)	0.74 (0.45–1.20)	0.99 (0.59–1.65)	0.963
Melanoma skin cancer (1244/12 362)	82 (0.7)	0.37 (0.30–0.46)	7 (0.6)	0.32 (0.15–0.67)	0.91 (0.42–1.98)	0.820
Upper GI (1244/12 362))	47 (0.4)	0.19 (0.14–0.25)	6 (0.6)	0.27 (0.12–0.61)	1.30 (0.56–3.05)	0.543
Lower GI (1244/12 362)	202 (1.6)	0.91 (0.79–1.05)	23 (1.8)	1.06 (0.70–1.59)	1.22 (0.79–1.88)	0.359
Lung (1244/12 362)	106 (0.9)	0.48 (0.39–0.58)	4 (0.3)	0.18 (0.07–0.49)	0.40 (0.15–1.08)	0.070
Urinary bladder (1244/12 362)	56 (0.5)	0.25 (0.19–0.33)	2 (0.2)	0.09 (0.02–0.37)	0.37 (0.09–1.52)	0.169
Kidney (1244/12 362)	27 (0.2)	0.12 (0.08–0.18)	10 (0.8)	0.46 (0.25–0.85)	3.92 (1.90–8.11)	<0.001
Lymphoma (1244/12 362)	71 (0.6)	0.32 (0.25–0.40)	4 (0.3)	0.18 (0.07–0.49)	0.61 (0.22–1.67)	0.336
Leukemia (1244/12 362)	25 (0.2)	0.11 (0.08–0.17)	1 (0.1)	0.05 (0.01–0.33)	0.41 (0.06–3.04)	0.385
Uterus (corpus) (654/6514)	51 (0.8)	0.42 (0.32–0.56)	7 (1,1)	0.60 (0.29–1.26)	1.54 (0.70–3.40)	0.282
Uterus (cervix) (654/6514)	137 (2.1)	1.15 (0.97–1.36)	18 (2.7)	1.56 (0.98–2.47)	1.33 (0.82–2.18)	0.252
CNS, PNS (1244/12 362)	62 (0.5)	0.28 (0.22–0.36)	6 (0.5)	0.27 (0.12–0.61)	1.01 (0.44–2.33)	0.988

Abbreviations: AHP, acute hepatic porphyria; aHR, adjusted hazard ratio; CNS, central nervous system; GI, gastro-intestinal tract; IR, incidence rate; PNS, peripheral nervous system.

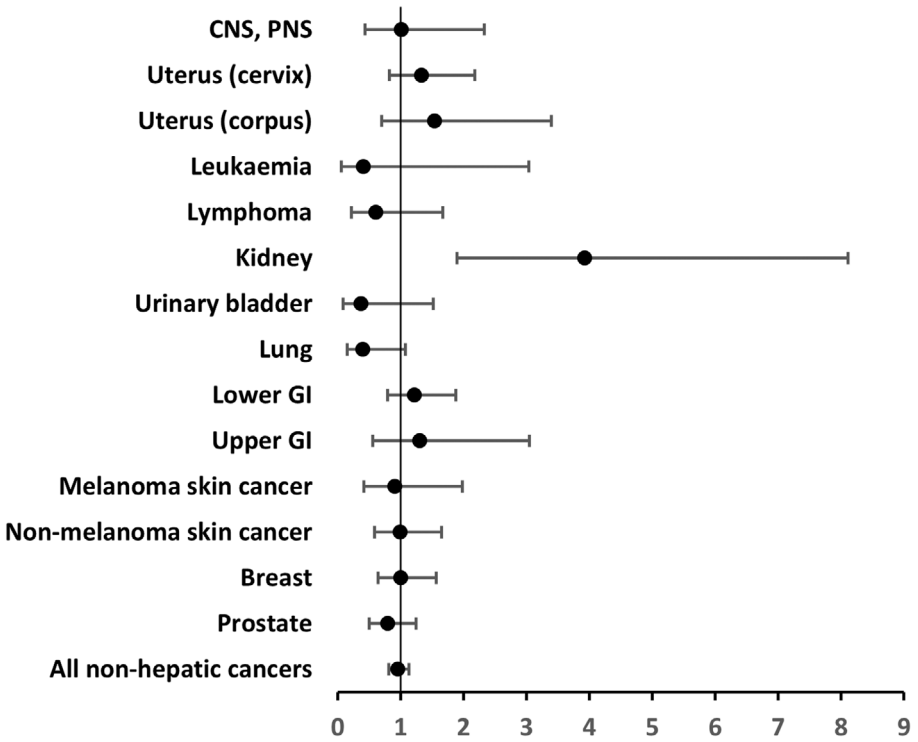

FIGURE 1 Forest plot with adjusted hazard ratios (aHR) and 95% CIs illustrating cancer risks. Patients with acute hepatic porphyria (AHP) versus the matched reference population

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TABLE 4 Renal disease, incidence, relative risk, and median age at kidney disease diagnosis

Category (no. at risk)	*n* (%)	IR (95% CI)	aHR (95% CI)	*p*	Age at diagnosis	*p* (age difference)
Any kidney disease						
Reference ($n = 12\,362$)	466 (3.8)	2.11 (1.93–2.31)	ref		74	
AHP ($n = 1244$)	90 (7.2)	4.21 (3.42–5.18)	2.10 (1.67–2.63)	<0.001	69	0.009
U-PBG positive ($n = 494$)	59 (11.9)	6.25 (4.85–8.07)	2.67 (2.04–3.50)	<0.001	68	0.011
All CKD						
Reference ($n = 12\,362$)	170 (1.4)	0.76 (0.66–0.89)	ref		76	
AHP ($n = 1244$)	45 (3.6)	2.09 (1.56–2.79)	2.89 (2.08–4.01)	<0.001	66	<0.001
U-PBG positive ($n = 494$)	34 (6.9)	3.56 (2.54–4.98)	4.14 (2.87–5.99)	<0.001	63	<0.001
Advanced CKD, stage 4–5						
Reference ($n = 12\,362$)	31 (0.3)	0.14 (0.10–0.20)	ref		75	
AHP ($n = 1244$)	14 (1.1)	0.64 (0.38–1.08)	4.88 (2.59–9.17)	<0.001	73	0.517
U-PBG positive ($n = 494$)	11 (2.2)	1.13 (0.62–2.03)	7.06 (3.54–14.06)	<0.001	76	0.834

Abbreviations: AHP, acute hepatic porphyria; aHR, adjusted hazard ratio; CKD, chronic kidney disease; IR, incidence rate; U-PBG, urinary porphobilinogen.

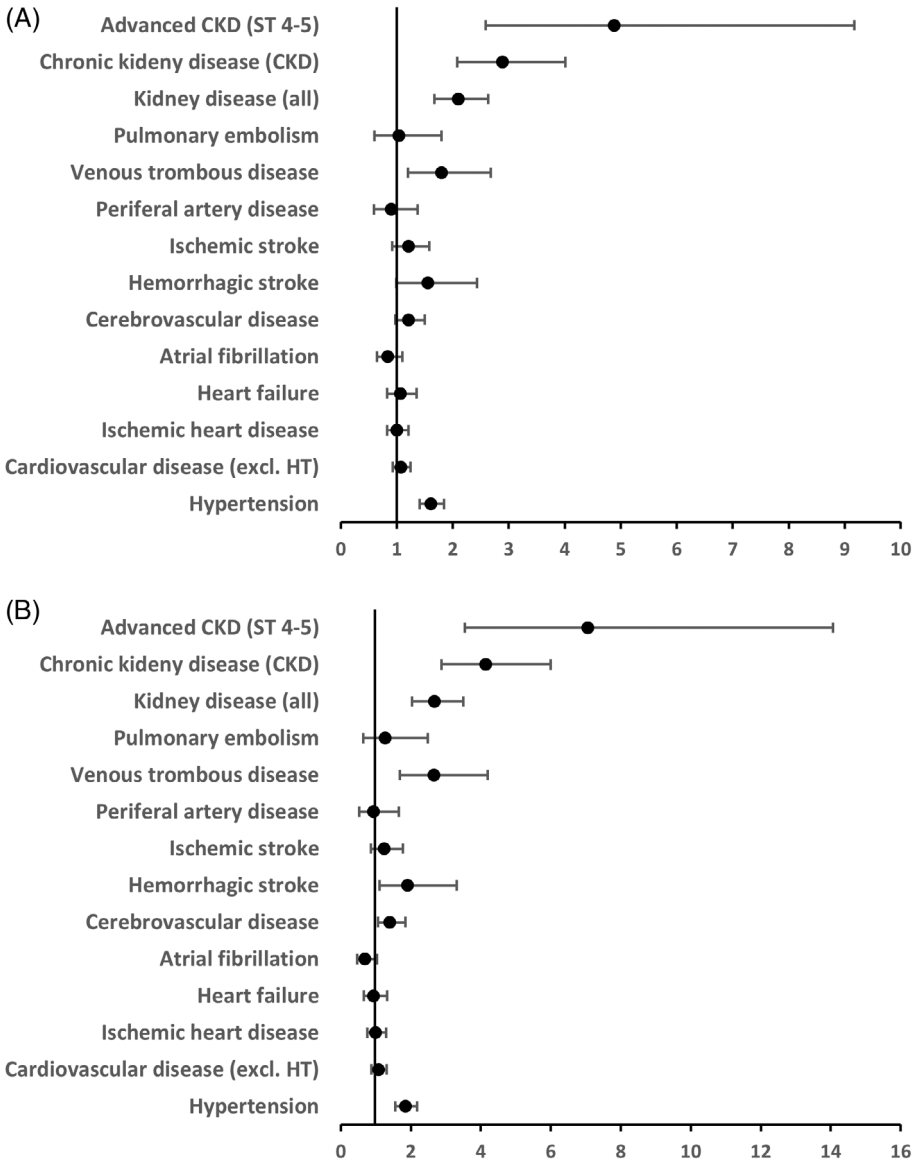

FIGURE 2 Forest plot with adjusted hazard ratios (aHR) and 95% CIs illustrating renal and cardiovascular risks. Patients with acute hepatic porphyria (AHP) (A) and urinary porphobilinogen (U-PBG) positive AIP (B) versus the matched reference population

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population. Six (0.5%) patients with AHP received a kidney transplant, three of whom had a combined liver-kidney transplantation. Fourteen (0.1%) were kidney transplanted in the reference population. CKD severity by stage was not specified in the ICD-system until 1998 and are apparently not systematically reported. Only one (17%) AHP patient who received a kidney transplantation had a specific advanced CKD diagnosis compared to six (43%) of those transplanted in the reference population. Rates of advanced CKD in this study are thus probably significantly underestimated, particularly in patients with AHP.

The median ages at diagnosis of CKD (66 years) in patients with AHP were lower compared to the reference population (76 years), but age at diagnosis of advanced CKD was similar between the groups. Patients with HT and AHP had a higher risk of CKD (16.5%) than comparators with HT (7.5%), $p < 0.001$.

3.4 | Cardiovascular disease

HT was more common among patients with AHP ($n = 253$, 20%), and particularly in the U-PBG-positive AIP subgroup ($n = 148$, 30%) than among the comparators ($n = 1834$, 15%; Table 5, Figure 2A,B). The rate of cerebrovascular disease was increased in U-PBG positive AIP (aHR = 1.40 [95% CI = 1.06–1.85]), mainly related to an increased rate of hemorrhagic stroke (aHR = 1.91 [95% CI = 1.11–3.31]), but not in AHP in general. The risk of other cardiovascular conditions commonly associated with HT such as heart failure, atrial fibrillation, ischemic heart disease, and peripheral artery disease did not differ between the AHP groups and comparators. Venous thrombosis disease occurred in 28 (2.2%) of the patients with AHP compared to 164 (1.3%) in the reference population (aHR = 1.80 [95% CI = 1.20–2.68]). The incidence of pulmonary embolism was not different between groups. Common risk factors for cardiovascular disease that could be assessed using registers (diabetes, obesity, hyperlipidaemia, and alcohol addiction) did not differ significantly between groups (Table S2). Data on smoking was not available in the registers.

3.5 | Neurological and Psychiatric diseases

Neuropathy is common in acute porphyria attacks.[19] The number of AHP patients with a recorded diagnosis of mononeuropathy or polyneuropathy was low, but the proportion was increased ($n = 16$, 1.3%), compared to the reference population ($n = 60$, 0.5%; Table 6). Psychiatric disease overall was more common among patients with AHP, aHR = 1.23 (95% CI = 1.04–1.47), $p = 0.017$, but in the main diagnosis categories risks were similar in patients with any AHP, U-PBG positive AIP patients and the reference population (Table 6). We found no increase in incidence of opiate addiction or addiction overall. No suicides were registered among patients with AHP during follow-up. In the behavioral disorders category, a difference in relative risk was noticed based on eight (0.6%) AHP-patients ($p = 0.015$). These patients had diagnosis

TABLE 5 Cardiovascular diseases

Category	Reference ($n = 12\,362$) n (%)	AHP ($n = 1244$)			AIP U-PBG positive ($n = 494$)		
		n (%)	aHR (95% CI)	p	n (%)	aHR (95% CI)	p
Any cardiovascular disease (excluding hypertension)	1932 (15.6)	203 (16.3)	1.07 (0.93–1.24)	0.350	102 (20.6)	1.07 (0.88–1.31)	0.483
Hypertension	1834 (14.8)	253 (20.3)	1.61 (1.41–1.84)	<0.001	148 (30.0)	1.85 (1.56–2.18)	<0.001
Ischemic heart disease	1172 (9.5)	117 (9.4)	1.00 (0.83–1.21)	0.969	57 (11.5)	0.99 (0.76–1.29)	0.943
Heart failure	723 (5.8)	73 (5.9)	1.06 (0.83–1.35)	0.642	32 (6.5)	0.93 (0.65–1.32)	0.681
Atrial fibrillation	737 (6.0)	59 (4.7)	0.84 (0.65–1.10)	0.212	26 (5.3)	0.69 (0.47–1.03)	0.067
Cerebrovascular disease	790 (6.4)	90 (7.3)	1.21 (0.97–1.50)	0.087	53 (10.7)	1.40 (1.06–1.85)	0.018
Hemorrhagic stroke	150 (1.2)	22 (1.7)	1.55 (0.99–2.43)	0.055	14 (2.8)	1.91 (1.11–3.31)	0.020
Ischemic stroke	521 (4.2)	59 (4.7)	1.21 (0.92–1.58)	0.171	31 (6.3)	1.23 (0.86–1.77)	0.256
Peripheral artery disease	269 (2.2)	23 (1.8)	0.90 (0.59–1.37)	0.617	12 (2.4)	0.93 (0.52–1.66)	0.803
Venous thrombosis disease	164 (1.3)	28 (2.2)	1.80 (1.20–2.68)	0.004	21 (4.3)	2.66 (1.69–4.19)	<0.001
Pulmonary embolism	143 (1.2)	14 (1.1)	1.04 (0.60–1.80)	0.884	9 (1.8)	1.26 (0.64–2.48)	0.499

Abbreviations: AHP, acute hepatic porphyria; aHR, adjusted hazard ratio; IQR, interquartile range; U-PBG, urinary porphobilinogen.

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TABLE 6 Neuropathy and psychiatric disease

	n (%)	IR (95% CI)	aHR (95% CI)	*p*
Neuropathy (all)				
Reference ($n = 12\,362$)	60 (0.5)	0.27 (0.21–0.35)		
AHP ($n = 1244$)	16 (1.3)	0.74 (0.45–1.20)	2.80 (1.61–4.87)	<0.001
Psychiatric diagnosis (all)				
Reference ($n = 12\,362$)	1218 (9.9)	5.69 (5.38–6.02)		
AHP ($n = 1244$)	143 (11.5)	6.93 (5.89–8.17)	1.23 (1.04–1.47)	0.017
Dementia/amnesia				
Reference ($n = 12\,362$)	377 (3.0)	1.70 (1.54–1.88)		
AHP ($n = 1244$)	38 (3.1)	1.75 (1.27–2.41)	1.11 (0.79–1.55)	0.551
Addiction				
Reference ($n = 12\,362$)	402 (3.3)	1.83 (1.66–2.02)		
AHP ($n = 1244$)	33 (2.7)	1.53 (1.09–2.16)	0.83 (0.58–1.18)	0.303
Alcohol addiction				
Reference ($n = 12\,362$)	231 (1.9)	1.04 (0.92–1.19)		
AHP ($n = 1244$)	17 (1.4)	0.78 (0.49–1.26)	0.74 (0.45–1.22)	0.238
Opiate addiction				
Reference ($n = 12\,362$)	25 (0.2)	0.11 (0.08–0.17)		
AHP ($n = 1244$)	4 (0.3)	0.18 (0.07–0.49)	1.61 (0.56–4.63)	0.377
Psychosis				
Reference ($n = 12\,362$)	101 (0.8)	0.46 (0.37–0.55)		
AHP ($n = 1244$)	14 (1.1)	0.64 (0.38–1.09)	1.41 (0.81–2.47)	0.226
Mood disorders				
Reference ($n = 12\,362$)	326 (2.6)	1.48 (1.33–1.64)		
AHP ($n = 1244$)	36 (2.9)	1.67 (1.21–2.32)	1.14 (0.81–1.61)	0.447
Neurotic disorders				
Reference ($n = 12\,362$)	315 (2.5)	1.43 (1.28–1.60)		
AHP ($n = 1244$)	33 (2.7)	1.53 (1.09–2.15)	1.07 (0.75–1.54)	0.699
Behavioral disorders				
Reference ($n = 12\,362$)	31 (0.3)	0.14 (0.10–0.20)		
AHP ($n = 1244$)	8 (0.6)	0.37 (0.18–0.74)	2.62 (1.20–5.69)	0.015
Suicide				
Reference ($n = 12\,362$)	28 (0.2)	0.13 (0.09–0.18)		
AHP ($n = 1244$)	0 (0.0)	0	NA	

Abbreviations: AHP, acute hepatic porphyria; IR, incidence rate; aHR, adjusted hazard ratio.

codes related to unspecific symptoms that could represent features of symptomatic porphyria such as "other and unspecified psychological symptoms," "psychalgia," and "other and unspecified disorders of eating."

3.6 | Mortality

The overall mortality rate was higher among patients with AHP compared to the reference population (Figure 3A). During follow-up, 265 (21%) deaths were recorded among patients with AHP compared to 2201 (18%) in the reference population (Table 7). The mortality rate was higher among females with AHP (aHR = 1.64 [95% CI = 1.39–1.95]) and U-PBG positive patients with AIP (aHR = 1.30 [95% CI = 1.10–1.55]) compared to females in the reference population and U-PBG negative patients with AIP. The difference in mortality between the AHP and the reference population was no longer significant after censoring patients with PLC at the time of PLC diagnosis

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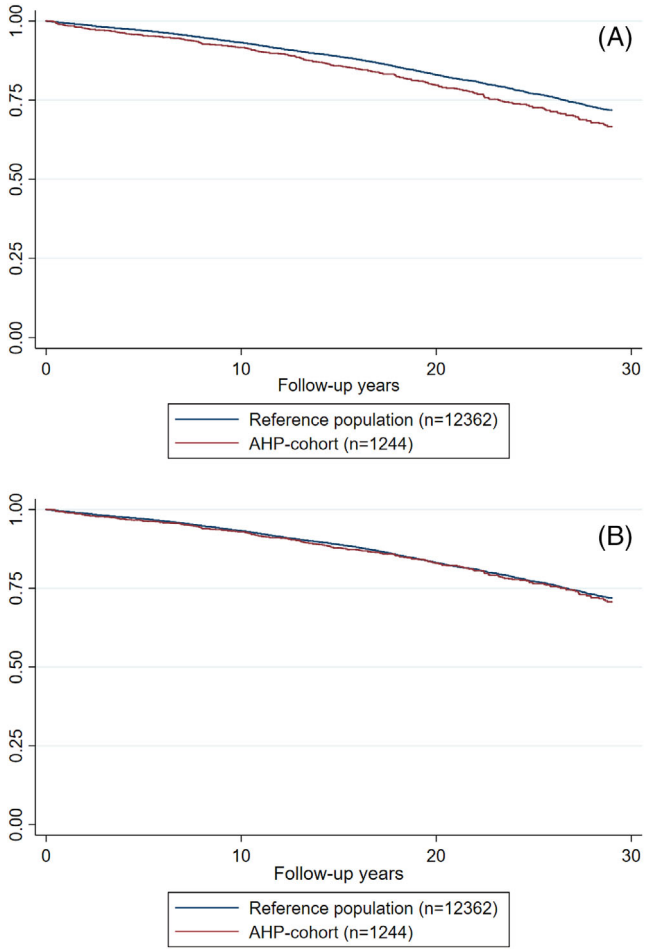

FIGURE 3 (A) Kaplan–Meier plot illustrating overall survival in patients with acute hepatic porphyria (AHP) and the matched reference population. Log-rank test for equality of survivor functions: $p = 0.001$. (B) Kaplan–Meier plot illustrating overall survival in patients with acute hepatic porphyria (AHP) and the matched reference population. Patients with primary liver cancer (PLC) in both groups censored at PLC diagnosis. Log-rank test for equality of survivor functions: $p = 0.549$

(Figure 3B). However, among females with AHP, the adjusted mortality hazard remained increased after censoring patients with PLC (aHR = 1.36 [95% CI:1.12–1.64]; Table 7). Based on the recorded causes of death, AHP patients had a higher risk of death related to renal disease ($n = 12$ [1.0%] vs. ref, $n = 37$ [0.3%], $p < 0.001$), PLC ($n = 54$ [4.3%] vs. ref, $n = 20$ [0.2%], $p < 0.001$) and porphyria ($n = 10$ [0.8%] vs. ref, $n = 0$).

3.7 | Variegate porphyria and hereditary coproporphyria

We found no increased risk of nonhepatic cancer in VP and HCP patients (Table 2). Two female patients with VP developed kidney cancer (aHR = 11.07 [95% CI = 2.60–47.15]). Three patients with VP (2.4%) developed CKD (one with advanced CKD) resulting in a borderline significant CKD risk increase (aHR = 3.09 [95% CI = 0.98–9.72]). One patient in the HCP group developed advanced CKD. The incidence of HT was increased among patients with VP, $n = 26$ (21%), (aHR =2.18 [95% CI = 1.48–3.21], $p < 0.001$), while the risks of cardiovascular diseases did not differ compared to the reference population. No associations to HT or other cardiovascular diseases were noticed in the HCP group. We observed no differences in the risks of neuropathy, psychiatric disorders (data not shown), or mortality in the VP or HCP groups compared to the reference population.

4 | DISCUSSION

In this cohort study, the largest hitherto published, we found no increase in overall cancer risk, and with the exception of kidney cancer, no increased risk of any specific form of cancer in patients with AHP compared to matched controls from the general population. High AHP-related risks of HT and CKD were confirmed but with the exception of hemorrhagic stroke in the subgroup with U-PBG positive AIP, we did not find an increased risk of HT-related cardiovascular diseases. Similarly, risks of specified forms of psychiatric disorders such as mood disorders, psychosis, and addiction were not different from the matched reference population. The mortality rate was increased in patients with AHP, mainly related to the high incidence of PLC. The risks of HT, CKD, kidney cancer, and mortality were all higher in females and in AIP-patients with elevated U-PBG in their clinical records.

Patients with AIP have a high risk of developing PLC. In our previous study on this patient cohort, we reported a strong association between PLC risk and biochemical disease activity (elevated U-PBG).[12] The mechanisms behind the association between elevated PBG and ALA and hepatic carcinogenesis are unknown. Several preclinical studies indicate that accumulation of ALA, the first intermediary in the heme biosynthesis pathway, is an important factor. ALA is associated with oxidative stress and DNA damage, is cytotoxic in vitro, and is elevated in tyrosinemia type 1, which has also been associated with a high risk of liver cancer.[22,23,29,30] Furthermore, studies have proposed that the disease-associated gene in AIP, *HMBS* (hydroxymethylbilane synthase), has a tumor suppressor function.[31] These associations have led to an assumption that AHP might be associated not only with hepatic cancers, but also with some specific cancer forms or even with cancer in general. Previous studies have

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TABLE 7 Mortality by category, mortality rates, median age at death, and adjusted hazard ratios

	n (%)	Mortality rate/1000 p. years (95% CI)	Age at death (iqr)	ahr* (95% CI)	*p*	aHR** (PLC censored) (95% CI)	*p*
Reference ($n = 12\,362$)	2201 (17.8)	9.87 (9.47–10.29)	79 (69–86)	ref	–	ref	–
AHP ($n = 1244$)	265 (21.3)	12.13 (10.75–13.68)	77 (68–83)	1.27 (1.12–1.45)	<0.001	1.06 (0.92–1.22)	0.441
Female ref ($n = 6514$)	1113 (17.1)	9.19 (8.67–9.75)	81 (72–87)	ref	–	ref	–
Female AHP ($n = 654$)	150 (22.9)	12.79 (10.90–15.01)	77 (69–84)	1.64 (1.39–1.95)	<0.001	1.36 (1.12–1.64)	0.002
Male ref ($n = 5848$)	1088 (18.6)	10.68 (10.06–11.33)	77 (67–84)	ref	–	ref	–
Male AHP ($n = 590$)	115 (19.5)	11.37 (9.47–13.65)	75 (66–81)	1.00 (0.83–1.22)	0.975)	0.84 (0.68–1.04)	0.101
Aip ($n = 1063$)	240 (22.6)	12.55 (11.06–14.25)	76 (67–83)	1.33 (1.16–1.52)	<0.001	1.09 (0.94–1.26)	0.259
U-PBG positive ($n = 494$)	137 (27.7)	14.00 (11.84–16.55)	75 (66–81)	1.30 (1.10–1.55)	0.003	1.00 (0.82–1.23)	0.976
U-PBG negative ($n = 345$)	40 (11.6)	6.46 (4.74–8.81)	82 (70–85)	0.88 (0.64–1.20)	0.421	0.89 (0.65–1.21)	0.452
Vp ($n = 125$)	14 (11.2)	7.95 (4.71–13.43)	80 (77–85)	1.11 (0.66–1.88)	0.693	1.03 (0.60–1.79)	0.891
Hcp ($n = 56$)	11 (19.6)	11.33 (6.27–20.45)	80 (65–89)	0.76 (0.42–1.37)	0.354	0.69 (0.37–1.29)	0.242

Note: *Adjusted for sex and birthyear; **adjusted for sex, birthyear, patients with PLC censored at PLC diagnosis.
Abbreviations: AHP, acute hepatic porphyria; aHR, adjusted hazard ratio; AIP, acute intermittent porphyria; HCP, hepatic coproporphyria; IQR, interquartile range; PLC, primary liver cancer; U-PBG, urinary porphobilinogen; VP, variegate porphyria.

indeed reported small numbers of lymphoma, breast, prostate, colon, kidney, and uterus cancer but none of these studies have been able to confirm or dismiss an association to nonhepatic cancer risk.[9,27,32] In this, the largest cohort study to date, we found no association between overall incidence of nonhepatic cancer and AHP. We did, however, find an association with kidney cancer.

The risk of kidney cancer was increased almost four-fold among patients with AHP with a strong association to female sex and biochemical activity. Although surveillance bias could influence this finding, it is supported by biological hypotheses. ALA and PBG are synthesized and accumulated in the liver in biochemically active AHP, but the kidneys are also highly exposed to ALA and PBG, which are both excreted into urine. In one long-term study on a cohort of selected patients with symptomatic AIP, >50% developed porphyria associated kidney disease.[18] Both preclinical and histological findings indicate that ALA and PBG cause cellular damage, apoptosis, and scarring in proximal tubular cells, which are the cells from which renal cell carcinoma originate.[18] Previous Scandinavian studies have also reported cases of kidney cancer among patients with AHP.[9,27] The cumulative risk of kidney cancer in patients with AHP is, however, low, <1% and in our opinion does not merit regular surveillance.

Renal functional impairment is common in patients with AIP,[14–18] and development of end stage renal disease is a feared complication for which kidney transplantation might be the only curative treatment option.[33–35] Studies on the risk of advanced CKD in unselected AHP populations and the risk of renal impairment in VP and HCP are however scarce. We found 45 (3.6%) patients with any AHP and 34 (6.9%) with U-PBG positive AIP who developed CKD of any stage, compared to 170 (1.4%) in the reference population.

Previous studies have shown AIP to be independently associated with CKD. This is important since HT is highly prevalent in AHP and an important risk factor for developing CKD.[18] Among our patients with HT and AHP, the risk of CKD was significantly higher (16.5%) than among comparators with HT (7.5%). Advanced CKD (defined as stage 4–5) was reported in 14 (1.1%) patients

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with AHP of whom 13 were women and 11 (2.2%) were patients with U-PBG positive AIP. However, the incidence of advanced CKD in this study is underestimated due to under-reporting of specific CKD-stage to the NPR, as described in the results. Six patients with AHP received kidney transplants of which three were combined liver kidney transplantations.[33,35] Only one (2.0%) patient with HCP and three (2.4%) patients with VP developed CKD. Results regarding VP and HCP should be interpreted with caution since the number of outcomes is low and the relative risk estimates are only borderline significant. Considering the common AHP pathophysiology and a few previous publications,[36,37] it appears plausible to assume that patients with VP have an increased risk of developing CKD. Further studies with larger VP and HCP cohorts would be required for more precise risk assessments.

HT is a well-known comorbidity in AHP.[14–16] We found a significantly higher presence of HT among patients with AHP, particularly U-PBG positive AIP patients, compared to the reference population (20%, 30%, and 15%, respectively). The difference in HT risk did not correlate to any significant difference in risk of developing cardiovascular disease in general (aHR = 1.07 [95% CI:0.93–1.24]) or by specific disease categories (Table 5). Similarly, U-PBG positive AIP patients had no significant risk difference of any specific form of cardiovascular diseases, except for a 1.4-fold increased risk of cerebrovascular diseases. The risk of cerebrovascular disease in U-PBG positive patients with AIP was mainly associated to an increased risk of hemorrhagic stroke (aHR = 1.91 [95% CI = 1.11–3.31]), which might be related to the high frequency of HT in these patients. Possible surveillance bias and reporting bias aspects must be considered when comparing proportions of individuals with a registered HT diagnosis. Our main aim was not to establish a precise estimate of the incidence or prevalence of hypertension in patients with AHP, but rather to assess if the high rates of HT and CKD influence the risk of secondary cardiovascular diseases in relation to AHP type and U-PBG status. While HT is mainly handled in primary care (not included in the registers available for this study), the cardiovascular diseases listed in Table 5 commonly involve inpatient and specialized outpatient care (included in the NPR). Results should be interpreted with some caution since aspects of unmeasured confounding such as smoking and socioeconomic factors might influence the results. Some risk factors could be estimated from registers, such as diabetes, obesity, hyperlipidemia, and alcohol addiction, although numbers are often underestimated due to under-reporting. None of these risk factors differed between groups (Table S2). The reason why the increased risk of hypertension and CKD does not result in a higher risk of cardiovascular complications is unclear. One possible explanation might be lower rates of smoking among patients with AHP.[14] Lower rates of smoking might also contribute to the lower rates of lung and urinary bladder cancer among AHP patients in our study.

Our study results do not support the previously reported increased risk of atrial fibrillation in AHP.[38] Our results do, however, support clinical observations of an increased risk of venous thrombosis complications in AHP,[39] that may be related to treatment with exogenous heme. We found no increased risk of pulmonary embolism.

Previous studies have suggested an increased incidence of psychiatric disorders in AHP as well as the inverse, an increased prevalence of acute porphyria in psychiatric patient cohorts.[24,25] Psychiatric symptoms are commonly associated with acute and recurrent attacks, and analgesic addiction has been described.[6] Most studies are, however, small with limited follow-up and many lack a reference population for relative risk estimates. Overall, psychiatric diagnoses were more common in patients with AHP compared to the reference population, aHR = 1.23 (95% CI = 1.04–1.47), but we found no difference in risk of bi-polar disease, depression, psychosis, addiction, dementia, or suicide. These results indicate similar risks of severe psychiatric disorders among patients with AHP and the rest of the population. Our study does, however, not reflect primary care management of psychiatric symptoms, which may differ between groups.

Acute porphyria attacks are potentially life-threatening, and many AHP-related comorbidities might significantly affect life-expectancy. With generally improved management of acute attacks; the introduction of exogenous heme treatment in the 1980s,[40] liver transplantation for patients with recurrent attacks[33] and recently givosiran, an mRNA silencing treatment,[41,42] the risk of dying from acute attacks has decreased over the past decades.[11,26,27] Our knowledge about how long-term conditions impact mortality is, however, limited. Many studies report an increased risk of PLC-related deaths, but results are not consistent regarding overall mortality risk. We found a significant difference in overall mortality risk that was mainly related to PLC. As expected, the risk difference was thereby related to female sex and U-PBG status. Except for deaths due to PLC and porphyria per se, a higher risk of death due to renal diseases was also detected, confirming previous results from a regional single center cohort.[14]

The strengths of this study include the unprecedented cohort size, the randomly matched population-based reference cohort, the long follow-up period, and the high quality of data from the national registers. The linking of data on biochemical activity for the AIP cohort to outcomes was also an advantage.

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This study has limitations. The assessment of biochemical activity in AIP is based on the highest recorded U-PBG value, regardless of when the test was performed. U-PBG data was not available for 244 (21%) of the patients with AIP and was by study design not included for patients with VP or HCP. The assessment of the different study outcomes has certain limitations. We compared randomly selected matched comparators from the general population to AHP-patients, a group with a known medical risk, and therefore a higher probability of medical attention. This could lead to surveillance bias and lead-time bias. Detection of outcomes depends on reporting of diagnoses to the registers. While the cancer register is based on mandatory tissue-based reporting and is highly reliable, the NPR is based on main and supporting diagnoses from inpatient and specialized outpatient care. In this study, rates of diseases such as cerebrovascular disease and heart failure are probably accurate since both reflect primary causes of care. Other conditions, such as HT or early stages of CKD, are often secondary conditions, and these diagnosis codes may therefore be less reliable for study.

In conclusion, patients with AHP do not have an increased risk of nonhepatic cancers in general, cardiovascular diseases, or severe psychiatric diseases. We did find increased risks of hypertension, CKD, and kidney cancer. As the mortality risk associated with acute porphyria attacks is now low, attention could be focused on improving care for long-term AHP complications, mainly renal complications, HT and PLC.

AUTHOR CONTRIBUTIONS

Study conception and design: ML, DV, YF, ES, PH, and SW. Extraction of data: ML, DV, YF, and SW. Statistical data analysis: ML and JY. Data interpretation and manuscript preparation: ML. All authors contributed to the interpretation of the results and revised the manuscript.

FUNDING INFORMATION

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CONFLICT OF INTEREST

Mattias Lissing has consulted for and received grants from Alnylam Pharmaceuticals. Pauline Harper, Eliane Sardh, Daphne Vassiliou, and Staffan Wahlin have received grants from Alnylam Pharmaceuticals. Hannes Hagström, Ylva Floderus, and Jacinth Yan declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The original data of this register study are not publicly available as it contains information that could compromise the privacy of participants.

ETHICS STATEMENT

This study was approved by the Regional Ethical Review Board in Stockholm (Dnr: 2017/117–31). Individual informed consent was waived due to the observational nature of the study.

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SUPPORTING INFORMATION

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

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APPENDIX

Data sources

Patients with AHP were identified from the Swedish Porphyria Register, which includes all patients with a

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confirmed porphyria diagnosis in Sweden since 1976. The Swedish Total Population Register, administered by Statistics Sweden, contains demographic information on all Swedish residents, including their sex, year of birth, death, migration status, and place of residence.

Four national health registers administered by the National Board of Health and Welfare provided information about diseases and outcomes: (1) the Swedish National Patient Register (NPR) has collected healthcare-related data for all hospitalizations nationwide since 1987. (2) The outpatient NPR contains information about specialized outpatient care since 2001. Primary care visits are not included in the register. (3) The cancer register contains data on all malignancies reported from autopsies and morphological or other laboratory examinations since 1958. (4) The Cause of Death Register contains data on causes of death, how these were assessed, and relevant underlying diseases, since 1961.

Healthcare in Sweden is tax-funded, with activity-based compensation, which ensures virtually complete registration of the population. Register-based research is facilitated by the 12-digit Swedish personal identity number (PIN), which has been maintained by the Swedish Tax Agency since 1947 for all individuals who reside in Sweden. In this study, the PIN was used to link individuals' data in the registers.

Study population

We identified all patients with AIP, VP, and HCP, aged 18 years or older within the study period (1987–2015), in the Swedish Porphyria Register. The AHP diagnoses were verified by a confirmed pathogenic mutation in *HMBS*, *PPOX*, or *CPOX*, by being an obligate carrier of a pathogenic mutation in these genes, or by having biochemical findings consistent with AHP and having family members carrying a known pathogenic mutation.

A reference population was created using the total population register. For each patient with AHP, up to 10 reference individuals matched by sex, birth year, and county of residence were randomly identified. Dates of death or migration were collected for the entire study population. The time of study inclusion was defined as the AHP diagnosis date (or, for the reference population, the corresponding matched date), age 18 years, or January 1, 1987. No individual in the study population had a study baseline before the age of 18 years or January 1, 1987. For instance, a patient with a recorded AIP diagnosis at age 15 would have a study baseline at age 18 years, or, if this was before 1987, on January 1, 1987. The end of the study was either the date of incident PLC, death, migration, or December 31, 2015.

Data collection

Patients with AIP were categorized based on biochemical activity, as defined by U-PBG levels. Both PBG and ALA accumulate during an acute attack. Urinary concentrations of PBG and ALA were measured during routine monitoring and in diagnosis of acute porphyria attacks by ion-exchange chromatography, using the Bio-Rad Laboratories, Inc (Hercules, CA, USA) PBG/ALA-test. The concentrations of U-PBG and urinary ALA are reported in millimoles excreted per mole of creatinine, that is, normalized to the creatinine concentration of the specimen. The inter-assay variation for the ion exchange chromatography method was 3.7% for U-PBG. The analyses were performed using a validated method at the Porphyria Centre Sweden, an accredited laboratory conforming to internationally recognized standards.

We grouped the patients based on their highest recorded U-PBG in the porphyria register. Only the highest recorded value was used, regardless of the number of samples collected from each individual patient over time. The dates of the individual U-PBG samples were not included in the dataset. Clinical practice regarding U-PBG testing in patients with known AIP, both symptomatic and asymptomatic, varies significantly over time and between hospitals. Some centers have relied mainly on clinical symptoms in diagnosing acute attacks and have not routinely assessed U-PBG in asymptomatic patients. Other centers assessed U-PBG both during attacks and regularly in asymptomatic patients. The highest recorded U-PBG value, dated at any time in the patient's history, was used to define each patient's U-PBG group status: U-PBG-negative, patients with U-PBG levels that never exceeded the upper limit of normal (ULN; 1.6 mmol/mol creatinine) and U-PBG-positive; patients with U-PBG >1.6, mmol/mol creatinine. Patients with no documented U-PBG values in the porphyria register formed a third group, the U-PBG-unknown. The time at risk was calculated from the study baseline.

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