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Clinical Research Article

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Increased Mortality Risk in Patients With Primary and Secondary Adrenal Insufficiency

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Abbreviations: CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; HR, hazard ratio; ONS, Office for National Statistics.

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Abstract

Context: Mortality data in patients with adrenal insufficiency are inconsistent, possibly due to temporal and geographical differences between patients and their reference populations.

Objective: To compare mortality risk and causes of death in adrenal insufficiency with an individually matched reference population.

Methods: A retrospective cohort study was done using a UK general practitioner database (CPRD). A total of 6821 patients with adrenal insufficiency (primary, 2052; secondary, 3948) were compared with 67564 individually-matched controls (primary, 20366; secondary, 39134). Main outcomes were all-cause and cause-specific mortality, and hospital admission from adrenal crisis.

Results: With follow-up of 40 799 and 406 899 person-years for patients and controls respectively, the hazard ratio (HR [95% CI]) for all-cause mortality was 1.68 [1.58-1.77]. HRs were greater in primary (1.83 [1.66-2.02]) than in secondary (1.52 [1.40-1.64]) disease; primary versus secondary disease (1.16 [1.03-1.30]). The leading cause of death was cardiovascular disease (HR 1.54 [1.32-1.80]), along with malignant neoplasms and respiratory disease. Deaths from infection were also relatively high (HR 4.00 [2.15-7.46]). Adrenal crisis contributed to 10% of all deaths. In the first 2 years following diagnosis, the patients' mortality rate and hospitalization from adrenal crisis were higher than in later years.

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Conclusion: Mortality was increased in adrenal insufficiency, especially primary, even with individual matching and was observed early in the disease course. Cardiovascular disease was the major cause but mortality from infection was also high. Adrenal crisis was a common contributor. Early education for prompt treatment of infections and avoidance of adrenal crisis hold potential to reduce mortality.

Key Words: death, adrenal crisis, adrenal failure, Addison's disease, Hypopituitarism

Increased mortality has been reported in patients with Addison's disease (primary adrenal insufficiency) (1, 2) and pituitary disorders (associated with secondary adrenal insufficiency) (3-11). Results have however been inconsistent in both primary (12) and secondary disease (13-17). Study methodology may have contributed to this, since reported mortality was generally based on comparisons between patients and unmatched national data for which the period and location of care in study patients and the reference population may have differed (5, 18)

The main causes of excess death previously reported have been cardiovascular disease (1, 4, 5, 16), neoplasia (1, 2, 4, 5), infections (1, 2, 9, 10), and respiratory disease (1, 2, 4, 6, 10). However, without matching controls, reliable risk assessment for specific causes of death remained unavailable. It is also unclear whether mortality differs between primary and secondary adrenal insufficiency. The risk could differ as life-threatening adrenal crisis may be more common in primary than secondary disease (19), although underdiagnosed (10, 20, 21). By contrast, additional pituitary hormone deficiencies might elevate mortality in secondary disease (6, 7, 9, 10, 22).

We evaluated mortality in adrenal insufficiency relative to controls matched for sex, age, geographical location, and period of care. Causes of death and roles of adrenal crisis on death were also evaluated.

Materials and Methods

Data Source

We retrospectively investigated adrenal insufficiency patients from 1987 to 2017 in the Clinical Practice Research Datalink (CPRD), which collects data from general practitioners across the UK. The dataset (CPRD GOLD database) contains information for 15 354 125 deceased and living patients from 734 practices. Data are encoded as medical codes (Read codes) for diagnoses and product codes for prescribed medications. For participants registered after 1997, the CPRD provides linkage to Office for National Statistics (ONS) cause of death records and Hospital Episode Statistics (HES) for diagnoses during hospital admissions. Diagnostic codes in HES and ONS data have been formatted using the International Classification of Diseases, 10th or 9th revision (ICD-10 or ICD-9).

Study Population and Period

We extracted adrenal insufficiency patients aged <100 years using medical codes for primary and secondary adrenal insufficiency (Appendix A (23)) in combination with product codes for oral glucocorticoids if recorded within 3 months of the first medical codes (Appendix B (23)). Patients were excluded if they had a diagnosis of acromegaly, Cushing disease, Cushing syndrome, congenital adrenal hyperplasia, and malignancy of the adrenal or pituitary glands (Appendix C (23)), or a follow-up period of <1 month. We initially included 6825 patients, classified as primary, secondary, or unspecified adrenal insufficiency (Appendix A (23)).

For controls, we randomly matched the study patients with controls without adrenal insufficiency from the same dataset, by sex, 5-year strata of year of birth, general practitioner (GP) practice (representing place of care and degree of deprivation), and 5-year strata of year at onset of follow-up. Up to 10 controls were selected for each patient in order to enhance statistical power. Review of the number of potential controls available for each patient identified 10 as a working maximum that could detect important risk differences and be applied to the great majority of participants. The substantial number of matched controls for each patient could also represent better the variation in other potential confounding factors that were not matched and would need to be taken into account in multivariable analysis. The final numbers of patients and matched controls were 6821 and 67 564, respectively (Fig. 1 (23)).

Follow-up began at the most recent date of (1) practice registration; (2) first record of adrenal insufficiency (for patients), or (3) date at which CPRD considered that the practice could provide research-standard information. The follow-up ended at the earliest date of (1) death, (2) exit from the practice or CPRD, or (3) December 31, 2017.

We also extracted a subset of the participants who had linkage information (with HES and ONS) and follow-up from January 1, 1997. The study was approved by the CPRD Independent Scientific Advisory Committee (Protocol number 18_179).

Outcomes and Comorbidities

Primary outcomes were all-cause mortality rates and hazard ratios (HRs). All-cause mortality was from the CPRD record. Mortality was categorized by date of study entry and diagnosis of adrenal insufficiency. Comorbidities (cardiovascular disease and diabetes) were accepted if observed in CPRD at any time before or during follow-up. HRs were categorized by type of adrenal insufficiency, year of study, sex, age, and comorbidities.

Secondary outcomes were cause-specific mortality rates, the HRs of cause-specific mortality, the rate of adrenal crisis-related deaths, and the incidence of hospital admission for adrenal crisis (for those with concordant CPRD and ONS linked data). The cause of death was evaluated by organ system and particular disease, using ICD-10 and ICD-9 (Appendix D (23)). Adrenal crisis (ICD 10: E27.2) was analyzed as the principal or an associated cause of death, if it contributed to hospital admissions, and if it was associated with mortality in the patients who had comorbid cardiovascular disease. Comorbid cardiovascular disease consisted of ischemic heart disease, congestive heart failure, aortic dissection/aneurysm, atrial fibrillation, cerebrovascular disease, transient ischemic attack, and peripheral arterial disease.

Statistical Analysis

We investigated the hazard of all-cause mortality in adrenal insufficiency patients relative to controls using univariable Cox regression models. Effect modification was investigated in strata of age, sex, any history of cardiovascular disease or diabetes. We quantified incident mortality at 1-year intervals for the first 5 years of follow-up and then in 5-year intervals up to >20 years. The HR relative to controls in participants with a follow-up period of 2 years or less was compared with that in those with a follow-up period of more than 2 years. Incidence rates for the underlying cause of death were reported and the HR derived, using univariable Cox regression models.

Mortality rates from adrenal crises were reported. Hospital admissions from adrenal crisis were evaluated using multiple failure analysis. The association of death from adrenal crisis with comorbid cardiovascular disease were examined using logistic regression analysis.

Subcohorts of primary and secondary adrenal insufficiency patients with their matched controls were also analyzed and the mortality rate of primary adrenal insufficiency patients was directly compared with that of secondary adrenal insufficiency patients using univariable Cox regression models.

All analyses were performed by using Stata SE version 15.1.

Sensitivity Analyses

For ONS-linked participants, we validated the death recorded in CPRD using the death recorded by ONS as reference, from which false positive and false negative rates were calculated. We validated the diagnosis of adrenal insufficiency recorded in CPRD using the linked HES data. For primary adrenal insufficiency patients who were admitted to hospital, we extracted those with ICD-10 codes describing primary adrenal insufficiency or adrenal crisis (Appendix E (23)). Positive predictive value for the diagnosis of primary adrenal insufficiency was the proportion of those having codes for primary adrenal insufficiency or adrenal crisis to the total number of primary adrenal insufficiency patients who were admitted. Similarly, secondary adrenal insufficiency patients were extracted using codes describing hypopituitarism, disorders of pituitary glands, and adrenal crisis (Appendix E (23)) and positive predictive value for secondary adrenal insufficiency was calculated.

Results

Baseline characteristics for 6821 patients with adrenal insufficiency (2052 primary and 3948 secondary) and 67 564 matched controls (20 366 matched for primary and 39 134 for secondary) were comparable (Table 1). Baseline characteristics of the subgroup of 3547 patients (1015 primary and 2136 secondary) and 34 944 matched controls (10 025 matched for primary; 20 991 for secondary Table 1) with linkage to ONS mortality and HES data were also comparable. The proportions of men and the ages at diagnosis and start of follow-up were higher in secondary than in primary adrenal insufficiency. Fludrocortisone was prescribed in 75% and 2.8% of patients with primary and secondary adrenal insufficiency, respectively.

All-cause Mortality

There were 40 799 and 406 899 person-years of follow-up, respectively in patients with adrenal insufficiency of any cause and their matched controls. Patients had a higher mortality rate than controls (35.2 [95% CI, 33.4-37.0] vs 21.0 [20.6-21.5] per 1000 person-years; $P < .0001$; Fig. 1A; Table 1 (23)). The mortality rate relative to matched controls was higher in both primary and secondary adrenal insufficiency (35.8 [32.7-39.2] vs 19.6 [18.8-20.3];

Table 1. Baseline characteristics of adrenal insufficiency patients and controls, and the subcohort forfurther analysis of causes of death and hospital admissions

	All adrenal insufficiency		Primary adrenal insufficiency		Secondary adrenal insufficiency	
	Patients n = 6821	Controls n = 67 564	Patients n = 2052	Controls n = 20 366	Patients n = 3948	Controls n = 39 134
The whole CPRD cohort						
Male	3173 (46.5)	31 283 (46.3)	860 (41.9)	8483 (41.7)	1971 (49.9)	19 474 (49.8)
Age (years) at start of follow-up	53 (38-68)	53 (37-68)	51 (36.5-67)	51 (36-67)	54 (38-68)	53 (38-67)
Age (years) at diagnosis	52 (36-67)	—	50 (35-66)	—	53 (37-67)	—
Follow-up period (years)	4.3 (1.7-8.8)	4.0 (1.6-9.0)	4.6 (1.7-9.6)	4.3 (1.7-10.0)	4.4 (1.8-8.9)	4.0 (1.6-8.9)
	Patients n = 3547	Controls n = 34 944	Patients n = 1015	Controls n = 10 025	Patients n = 2136	Controls n = 20 991
The subcohort linked to the causes of death and hospital admissions						
Male	1629 (45.9)	16 059 (46.0)	410 (40.4)	4077 (40.7)	1054 (49.3)	10 343 (49.3)
Age (years) at start of follow-up	53 (36-68)	52 (37-67)	51 (36-67)	51 (35-66)	53 (38-67)	53 (38-67)
Age (years) at diagnosis	51 (36-67)	—	48 (35-65)	—	52 (36.5-66)	—
Follow-up period (years)	3.8 (1.4-7.9)	3.5 (1.5-7.7)	3.9 (1.4-8.3)	3.8 (1.5-8.4)	3.9 (1.6-8.0)	3.5 (1.5-7.6)

Data are median (interquartile range) or n (%).

$P < .0001$ and 31.3 [29.1-33.6] vs 20.8 [20.2-21.3]; $P < .0001$, respectively; Fig. 1B; Table 1(23)). The HR was 1.68 (95% CI, 1.58-1.77) for all adrenal insufficiency, 1.83 (1.66-2.02) for primary, and 1.52 (1.40-1.64) for secondary. Patients with primary adrenal insufficiency had a significantly higher risk of death than those with secondary (HR 1.16 [1.03-1.30]; Fig. 1B). Among patients with primary adrenal insufficiency, the HR was elevated both in patients taking glucocorticoid plus mineralocorticoid replacement (HR 1.66 [1.47-1.88]) and in those taking glucocorticoids alone (HR 2.37 [1.99-2.82]), but the elevation was lower in those using both forms of replacement therapy (*P* for HR difference = .0010).

All-cause mortality in adrenal insufficiency relative to controls remained increased whether or not participants received recent care (after mid-2007). Thus the HRs (95% CI) for mortality in all adrenal insufficiency patients studied before and after mid-2007 were 1.72 (1.61-1.84) and 1.57 (1.41–1.74), respectively (*P* for interaction = .13). In primary adrenal insufficiency, these ratios were 1.77 (1.58-1.99) and 2.00 (1.65-2.41), respectively (*P* for interaction = .29). In secondary adrenal insufficiency, the ratio was reduced in those receiving care in more recent years (HR 1.63 [1.49-1.79] vs 1.26 [1.08-1.47]; *P* for interaction = .0030; Table 2 (23)).

Mortality Risk Stratified by Sex, Age, Cardiovascular Disease, and Diabetes Status

In adrenal insufficiency of any cause, the HR (95% CI) relative to controls was 1.59 (1.48-1.72) in men and 1.77 (1.64-1.92) in women (*P* for interaction = .070; Fig. 2 and Table 1 (23)). Although the mortality rate in younger patients was lower than in older age ranges, the risk relative to matched controls was higher (HR 3.53 [2.92-4.26] vs 1.66 [1.56–1.76]; Fig. 3 and Table 1(23)). In the subgroup of pediatric participants aged less than 12, there were 11 (5.1%) and 2 (0.1%) deaths of 218 patients and 2198 controls, respectively, giving a markedly increased HR (HR, 55.21 [95% CI, 12.23-249.16]; $P < .0001$). In older children aged 12-18, the mortality rates were 2.4% (5/207) and 0.4% (7/1961) for the patients and controls, respectively, resulting in a lower HR of 5.45 (95% CI, 1.72-17.24; $P = .0040$). The very low mortality rates in controls contributed to the increased HRs in pediatric patients.

Similarly, patients without cardiovascular disease had a lower mortality rate than those with cardiovascular disease but when compared with controls, the mortality risk was higher in those without cardiovascular disease (HR 1.70 [1.56-1.85] vs 1.45 [1.35-1.57]; Fig. 4 and Table 1 (23)). In the analysis stratified by diabetes status, the mortality rate in adrenal insufficiency patients without

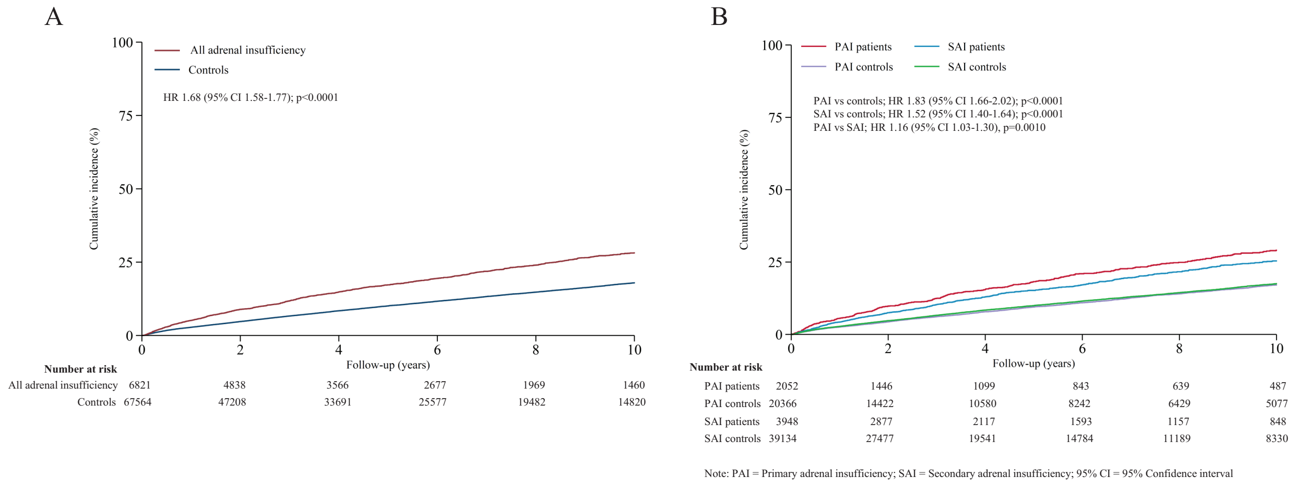


Figure 1. (A) All-cause mortality of patients with adrenal insufficiency of any cause relative to matched controls. (B) All-cause mortality separately of patients with primary and secondary adrenal insufficiency relative to matched controls.

diabetes was lower but the mortality risk relative to controls was higher than in those with adrenal insufficiency plus diabetes (HR 1.72 [1.61-1.83] vs 1.25 [1.10-1.42]; Fig. 5 and Table 1 (23)). Adrenal insufficiency patients without diabetes had a similar mortality rate to controls with diabetes (33.7 [31.8-35.7] vs 34.0 [32.2-35.8] per 1000 person-years; Table 1 (23)) and cumulative mortality profiles (Fig. 5 (23)).

Mortality Rates by Time From Diagnosis

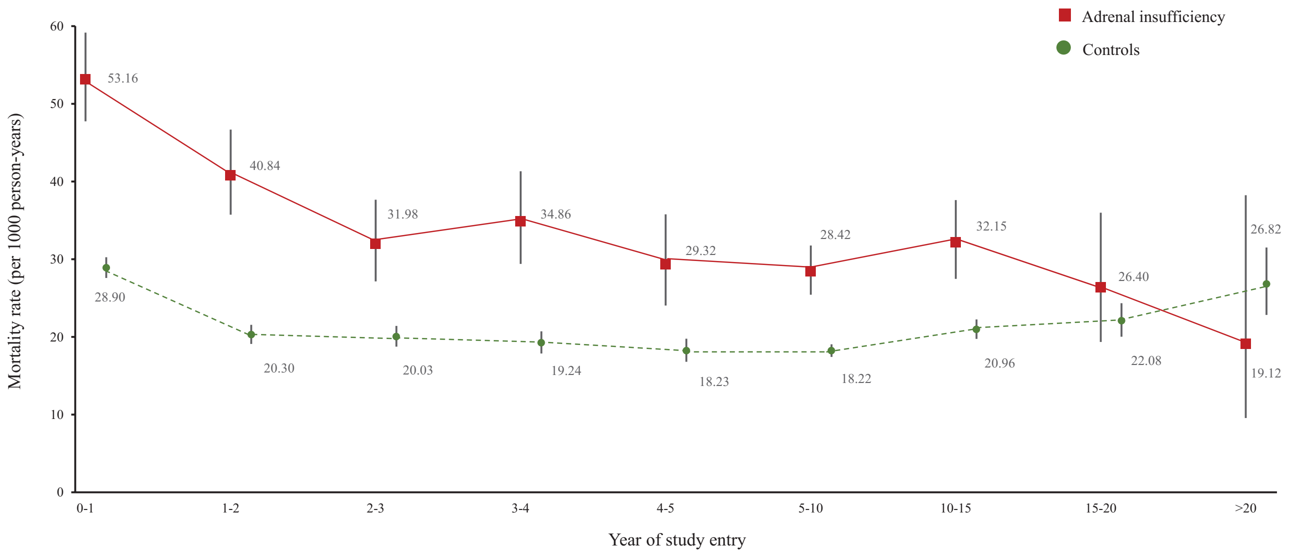
The highest all-cause mortality rate in patients was observed during the first year of follow-up (for adrenal insufficiency of any cause, 53.2 [95% CI, 47.8-59.2]; for primary, 58.3 [48.4-70.3]; and for secondary, 44.0 [37.7-51.3] per 1000 person-years, respectively) and was significantly higher than in controls (Fig. 2; and Table 3 (23)). Mortality rates declined over time and were similar to controls after 15 years (Fig. 2; and Table 3 (23)). Thus in adrenal insufficiency of any cause with a follow-up period of 2 years or less (1980 patients and 20 325 controls), the HR relative to controls was 2.03 (95% CI, 1.86-2.23), which was significantly higher than the HR in those with a follow-up period of more than 2 years (HR, 1.56 [95% CI, 1.45-1.67]; *P* for HR difference <.0001). In primary adrenal insufficiency, the HR of those with shorter follow-up periods was also significantly higher than in those with longer follow-up periods (HR 2.31 [1.96-2.71] vs 1.62 [1.42-1.83]; *P* for HR difference = .0010). In secondary adrenal insufficiency, the HR of those with shorter follow-up periods was slightly higher than in those with longer follow-up periods, although significance remained (HR 1.82 [1.60-2.08] vs 1.48 [1.34-1.62]; *P* for HR difference = .011). The mortality rate was also highest in the first year after diagnosis, then declined as the duration of disease progressed (Table 4 (23)).

Cause of Death

This analysis included 632 (207 primary; 340 secondary adrenal insufficiency) deaths from a total of 3547 (1015 primary; 2136 secondary) patients and 3643 deaths from 34 994 controls. The leading causes of deaths in patients and controls were disease of the circulatory system, neoplasm of any kind, and respiratory system. The mortality rates per 1000 person-years (95% CI) of all patients vs controls were 9.9 (8.6-11.4) vs 6.4 (6.1-6.8) for circulatory system; 8.1 (6.9-9.5) vs 5.6 (5.3-6.0) for neoplasm of any kind; and 6.6 (5.5-7.8) vs 2.8 (2.5-3.0) for respiratory system (Fig. 3; Figs 6 and 7 (23)).

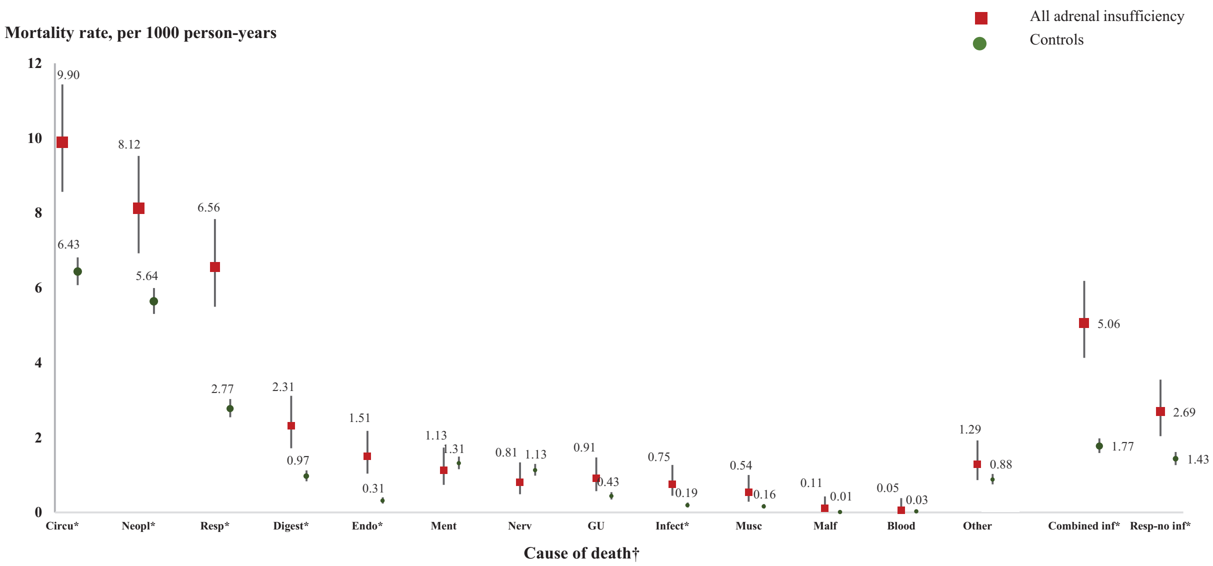
Regarding specific diseases, ischemic heart disease, malignant neoplasm, and respiratory infection were the leading causes of death in both patients and controls. The mortality rates per 1000 person-years of all patients vs controls were 4.9 (4.0-6.1) vs 2.7 (2.5-3.0; $P < .0001$) for ischemic heart disease; 6.8 (5.7-8.1) vs 5.5 (5.2-5.8; $P = .014$) for malignancy; and 3.9 (3.1-4.9) vs 1.3 (1.2-1.5; $P < .0001$) for respiratory infection.

When mortality risk was considered relative to controls, death from cardiovascular disease was increased (HR 1.54 [95% CI, 1.32-1.80]) but death from infection was predominant (HR 4.00 [95% CI, 2.15-7.46]; Table 2). Increased HRs for infection was observed in both primary and secondary adrenal insufficiency (Table 2). When deaths from respiratory and urinary tract infections were combined, infection became a leading cause of death in the patients (Fig. 3). The HR of combined infections for adrenal insufficiency of any type remained increased (HR 2.86 [95%



Note: For mortality rate difference between patients and controls: from year 0-1 to 10-15, p< 0.0001; in year 15-20, p =0.14; and after year 20, p=0.17

Figure 2. All-cause mortality rates of patients with adrenal insufficiency of any cause and matched controls, according to years of follow-up.



Note: †Analysis based on the primary (main) cause of death; Circu= Diseases of the circulatory system; Neopl= Neoplasms; Resp= Diseases of the respiratory system; Digest = Diseases of the digestive system; Endo = Endocrine, nutritional and metabolic diseases; Ment= Mental and behavioural disorders; Nerv= Diseases of the nervous system; GU = Diseases of the genitourinary system; Infect = Certain infections and parasitic diseases; Musc= Diseases of the musculoskeletal system and connective tissue; Malf= Congenital malformations, deformations and chromosomal abnormalities; Blood = Diseases of the blood and blood-forming organs andcertain disorders involving the immune mechanism; Other = Other causes of death; Combined inf= combined infectious disease with lower respiratory tract and upper urinary tract infections; Resp-no inf= Diseases of the respiratory system without infections; * p for mortality rate difference <0.001

Figure 3. Cause-specific mortality rates of patients with adrenal insufficiency of any causes and matched controls, according to ICD-10 organ systems and combined infectious diseases.

CI, 2.27-3.60], *P* < .0001), including for primary (HR 4.14 [95% CI, 2.78-6.18]; *P* < .0001) and secondary adrenal insufficiency (HR 2.25 [95% CI, 1.63-3.10]; *P* < .0001).

The HRs for neoplasm of any kind were significantly increased in patients with adrenal insufficiency of any cause and secondary adrenal insufficiency but not primary adrenal insufficiency (Table 2). When the cause of death was restricted to malignant neoplasm, the HRs were 1.41 (95% CI, 0.99-2.00; *P* = .054) for primary and 1.16 (95% CI, 0.91-1.47; *P* = .22) for secondary adrenal insufficiency.

Role of Adrenal Crisis in Increased Mortality

Adrenal crisis was specified as an associated cause of death in 66 patients (61 primary; 3 secondary; 2 unspecified adrenal insufficiency) from a total of 632 deaths (207

Table 2. The hazard ratios of cause-specific mortality in patients with adrenal insufficiency of any cause, primary, and secondary adrenal insufficiency relative to matched controls

Causes of death (ICD-10)	All adrenal insufficiency			Primary adrenal insufficiency			Secondary adrenal insufficiency		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Endocrine system (E00-E89)	4.85	3.08-7.64	<.0001	9.93	4.85-20.30	<.0001	2.22	1.03-4.80	.042
Infectious disease (A00-B99)	4.00	2.15-7.46	<.0001	4.06	1.27-12.95	.018	3.14	1.33-7.38	.0090
Musculoskeletal system (M00-M99)	3.46	1.68-7.12	.001	5.93	2.15-16.31	.001	1.46	0.33-6.46	.61
Digestive system (K00-K92)	2.39	1.71-3.34	<.0001	3.59	1.99-6.48	<.0001	2.13	1.38-3.29	.0010
Respiratory system (J00-J99)	2.38	1.95-2.90	<.0001	3.77	2.75-5.17	<.0001	1.48	1.08-2.02	.014
Genitourinary system (N00-N99)	2.11	1.25-3.57	.0050	1.35	0.41-4.53	.62	2.21	1.11-4.39	.024
Circulatory system (I00-I99)	1.54	1.32-1.80	<.0001	1.76	1.33-2.33	<.0001	1.51	1.23-1.85	<.0001
Neoplasm (C00-D48)	1.44	1.22-1.71	<.0001	1.38	0.98-1.95	.065	1.50	1.21-1.85	<.0001
Mental and behavioral disorders (F00-F99)	0.87	0.55-1.35	.52	0.80	0.32-1.99	.62	0.39	0.17-0.89	.025
Nervous system (G00-G99)	0.72	0.43-1.21	.21	0.70	0.25-1.92	.48	0.82	0.43-1.56	.54

primary; 340 secondary; 85 unspecified adrenal insufficiency). Adrenal crisis-related mortality rates (95% CI) were 3.5 (2.8-4.5), 11.1 (8.7-14.3), and 0.3 (0.1-0.8) per 1000 person-years for all, primary, and secondary adrenal insufficiency, respectively. The principal cause of death among patients with associated adrenal crisis was circulatory system disease. In adrenal insufficiency patients, adrenal crisis-related mortality was higher in those with concomitant cardiovascular disease than those without cardiovascular disease (odds ratio, 2.82 [95% CI, 1.73-4.59]; $P < .0001$). This association was significant in primary (3.77 [2.22-6.38]; $P < .0001$) but not secondary adrenal insufficiency (1.48 [0.13-16.5]; $P = .74$; Table 5 (23)).

From the date of diagnosis, 223 of 3547 patients (6.3%) were admitted to hospital with adrenal crises (14.8% of primary and 1.7% of secondary adrenal insufficiency; $P < .0001$). Of those admitted with adrenal crises, 73 (33%) had recurrent admissions. Admission rates (95% CI) from adrenal crises were 16.0 (14.4-17.7), 38.3 (34.0-43.3), and 3.4 (2.6-4.6) per 1000 patient-years for all, primary, and secondary adrenal insufficiency, respectively. The admission rate in the first year following diagnosis of adrenal insufficiency was higher than in later years (17.8 [13.8-23.0] vs 8.5 [7.3-10.0] per 1000 patient-years; Table 3).

Validation of Death and the Diagnosis of Adrenal Insufficiency Recorded in CPRD

Sixty of 4336 participants who were recorded by ONS as having died were not recorded as having died in CPRD, giving a false negative rate of 1.4%. One hundred and seven of 34 155 participants who were not recorded by ONS as having died were recorded in CPRD, giving a false positive rate of 0.31%. False negative and positive rates were comparable between patients and controls (Table 6 (23)).

To validate recording of adrenal insufficiency, we extracted 1030 primary and 2060 secondary adrenal insufficiency patients having linkage with HES and valid ICD-10 codes. Of these, 933 primary and 1612 secondary adrenal insufficiency cases had at least 1 record in the HES dataset. Positive predictive value for CPRD records was 90.6% (933/1030), for primary and 78.3% (1612/2060), for secondary adrenal insufficiency.

Discussion

With substantial numbers of cases and controls matched for key variables (sex, age, geographical location, and period of care), our study is a rigorous examination of mortality in adrenal insufficiency. Mortality was increased in adrenal insufficiency of any cause. Primary adrenal insufficiency carries a higher mortality risk than secondary disease. The major cause of death was cardiovascular disease but the greatest risk relative to controls was with infectious disease. Adrenal crisis was a significant factor in the increased mortality, especially in those with comorbid cardiovascular disease. Peak mortality rates and adrenal crisis requiring hospitalization were observed in the first few years after diagnosis, and this was predominantly in patients with primary adrenal insufficiency.

Our study has strengths and limitations. To minimize differences in standard of care between patients and controls, we matched for time in healthcare and GP practice. We used a large sample size from a real-world, quality-controlled database with sex, age, and ethnicity representative of the UK population (24). Nevertheless, controls were people registered with GPs, who might have not represented a "healthy" UK population and this could cause underestimation of the mortality risk. We used the diagnosis of adrenal insufficiency based on the GP coding system which

Table 3. Hospital admissions from adrenal crisis after the diagnosis of adrenal insufficiency in patients with adrenal insufficiency of any cause, primary, and secondary adrenal insufficiency

	All adrenal insufficiency				Primary adrenal insufficiency				Secondary adrenal insufficiency			
Time from diagnosis	No. at risk	No. events	Patient-years	Incidence per 1000 patient-years (95% CI)	No. at risk	No. events	Patient-years	Incidence per 1000 patient-years (95% CI)	No. at risk	No. events	Patient-years	Incidence per 1000 patient-years (95% CI)
0-1 years	3547	58[a]	3257	17.8 (13.8-23.0)	1015	36	927	38.9 (28.0-53.9)[b]	2136	11	1988	5.5 (3.1-10.0)[b]
After 1 year	2957	159	18 625	8.5 (7.3-10.0)	845	113	5370	21.0 (17.5-25.3)[b]	1821	26	11 529	2.3 (1.5-3.3)[b]
All including recurrent episodes	3547	364	22 768	16.0 (14.4-17.7)	1015	265	6911	38.3 (34.0-43.3)[b]	2136	47	13 661	3.4 (2.6-4.6)[b]

[a]Six events from 6 patients (1 primary; 5 unspecified adrenal insufficiency) were excluded from the analysis since adrenal crisis occurred on the date of diagnosis.
[b]*P* for incidence rate difference between primary and secondary adrenal insufficiency <.0001.

might have included misclassifications. As all identifiable patient data including hospital numbers were not available in CPRD and its linked dataset, it was not feasible to explore medical records or biochemical testing in the hospitals. We therefore used the in-hospital diagnostic codes as a reference standard to validate the GP diagnosis of adrenal insufficiency, accepting that this could not categorically exclude or confirm adrenal insufficiency. However, our validation yielded acceptable positive predictive value. Similarly, we validated the death records, with acceptable false positive and negative results. Immediate precipitants of death, such as adrenal crisis, may have been overlooked (10, 20, 21). Mineralocorticoid replacement is generally given in association with glucocorticoid replacement in primary adrenal insufficiency, but we found that 25% of our primary adrenal insufficiency patients did not have a fludrocortisone prescription, a proportion similar to that reported in the Swedish Addison Registry (25). This raises the possibility that some of the increase in mortality risk we found in our sample of primary adrenal insufficiency patients was due to inadequate mineralocorticoid replacement. In accord with this we found that among those using only glucocorticoids, the mortality risk was higher than in those using both forms of replacement therapy. Nevertheless, mortality risk relative to controls remained significantly increased in both groups, so that the lack of mineralocorticoid replacement was not the sole explanation.

Some previous studies have observed increased mortality in primary adrenal insufficiency (1, 2) and those with pituitary disorders (3-11) by comparing with unmatched national databases but in others mortality was not increased (12-17). With appropriate matching we have shown that mortality was indeed increased, more markedly in patients with primary disease. Although a previous study suggested that mortality had decreased in recent years, perhaps reflecting better clinical care (18), we confirmed this only in secondary, not primary, adrenal insufficiency.

Some previous reports have suggested that being female or young (pituitary disorders) (3, 4, 6-10, 14, 16) or young (Addison's disease) (2, 12) increased relative mortality and that risk was not increased in male (26, 27) or older (6, 8, 9) patients. We have found that mortality was increased regardless of sex or age. In addition, we explicitly showed that the higher relative mortality observed in patients of younger age or female sex reflected low mortality in the reference populations (ie, younger aged or female controls).

The leading cause of death was cardiovascular disease, as in other studies (1-5, 9-13, 16, 17, 22). Other important causes were neoplasia and respiratory disease. HRs for these conditions were also increased in our study; however, the greatest HR was for infections as had been reported in some previous studies (1, 9, 10, 16). Increased risk of death from respiratory system disease has also been reported (4, 6, 10) and in our study the main cause of respiratory death was infection. When mortality from all infectious causes was combined, this represented the third major cause of death. The risk of death from neoplasm of any kind was increased in patients with secondary but not primary adrenal insufficiency. However, when the type of neoplasm was distinguished in secondary adrenal insufficiency, death from malignant neoplasm was not increased, and this resulted from the major contribution of pituitary adenoma which is specified in the ICD neoplasm system. For patients with primary adrenal insufficiency, the HR of malignant neoplasm was increased but nonsignificantly. Some increase in risk of malignancy associated with primary adrenal insufficiency might have been expected, such an increase having previously been reported (2).

In the first year after diagnosis, peak mortality occurred in patients with adrenal insufficiency of either cause. The mortality risk relative to controls was higher in those with a follow-up period of 2 years of less, indicating the greater mortality risk among those recently diagnosed with adrenal insufficiency. Increased mortality shortly after the diagnosis of Addison's disease has been reported previously, but mortality rates were not presented (1). We noted that the incidence of adrenal crisis was higher in primary than secondary adrenal insufficiency, consistent with a previous report (20). In the first year, admissions from adrenal crisis were highest. In more than 10% of deaths, adrenal crisis was a contributing factor despite the fact that it is likely to have been underestimated (10, 20, 21). We also found that underlying cardiovascular disease increased even further the risk of adrenal crisis-related death.

In conclusion, mortality rates and relative risks were increased both in primary and secondary adrenal insufficiency, including from cardiovascular disease, and the risk was not normalized even with recent care. All-cause mortality was maximum during the first year after diagnosis and risk of death from infectious disease was considerably increased. Adrenal crisis contributed to 1 in 10 deaths, with further increased risk in patients with concomitant cardiovascular disease. Considering the peak incidences of mortality and adrenal crisis occurring soon after diagnosis, the high risk of death from infections, the significant number of adrenal crisis–related deaths, and the greater risks of mortality and adrenal crisis in primary adrenal insufficiency, adrenal crisis is likely to play an important role in the increased overall mortality, especially in primary disease.

Adrenal crisis is avoidable, as are deaths from infection and cardiovascular disease in many instances. Education of patients to avoid adrenal crisis early following diagnosis, prompt recognition and treatment of infection, and early cardiovascular risk reduction, together hold potential to reduce the excess mortality in patients with adrenal insufficiency.

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