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Research Article

Fracture risk by cortisol excess status in patients with adrenal incidentalomas: a population-based cohort study

Annette L. Adams[1,2,*], In-Lu Amy Liu[1], Iris Anne C. Reyes[1], Hina Chowdhry[1], Richard Contreras[1], Yuqian M. Gu[1], Mackenzie Crawford[3], Bennett McDonald[3], Joshua I. Barzilay[4], Tish Villanueva[5], David A. Katz[6], Frank S. Czerwiec[6], Wansu Chen[1,2]

[1]Department of Research & Evaluation, Kaiser Permanente Southern California, 100 S. Los Robles Ave, 2nd Floor, Pasadena, CA 91101, United States
[2]Department of Health Systems Science, Kaiser Bernard J. Tyson School of Medicine, 98 S. Los Robles Ave, Pasadena, CA 91101, United States
[3]Kaiser Permanente Georgia, Center for Research and Evaluation, 3495 Piedmont Center, NE, Atlanta, GA 30305, United States
[4]Kaiser Permanente Georgia, Southeastern Permanente Medical Group, 3495 Piedmont Center, NE, Atlanta, GA 30305, United States
[5]Dept of Endocrinology Southern California, Permanente Medical Group, Los Angeles Medical Center, 4950 W. Sunset Blvd, 2nd Floor, Los Angeles, CA 90027, United States
[6]Sparrow Pharmaceuticals, 1050 SW 6th Ave, Suite 1100, Portland, OR 97204, United States

*Corresponding author: Annette L. Adams, Department of Research & Evaluation, 100 S. Los Robles Ave, 2nd floor, Pasadena, CA 91101, United States (Annette.L.Adams@kp.org).

Abstract

Adrenal incidentalomas (AIs) may secrete excess cortisol, representing an elevated endogenous exposure to glucocorticoids, which could decrease bone mineral density and increase fracture risk. However, measurement of cortisol excess is not routinely done in patients with AI; thus, those with hormonally active AI at increased risk for fracture are under-identified. We sought to examine the association between excess cortisol levels and the incidence of fragility fracture in people with AI. This retrospective cohort study, conducted within two Kaiser Permanente regions (Southern California and Georgia), comprised women and men aged ≥50 yr with identified AI in the study period January 1, 2015-August 31, 2022. Patients' cortisol excess status was categorized by the type of test conducted (if any) and the test result. Fractures and relevant covariates were ascertained via International Classification of Diseases (ICD)-9/10 codes. Hazard ratios (HR) were estimated using Cox proportional hazard models with mortality as a competing risk. Among the cohort of 14 886 patients with AI, 273 (1.8%) had autonomous cortisol secretion (ACS) confirmed by dexamethasone suppression test (DST) results >1.8 μg/dL (>50 nmol/L), and another 201 (1.4%), tested with urine free or random cortisol tests, had results suggestive of excess cortisol production. Most of the cohort (n = 9353, 62.8%) were untested around AI diagnosis or during follow-up. Compared to patients with normal DST results (and adjusted for age, sex, race/ethnicity, and several other clinical characteristics), the estimated HR of fracture risk for patients with ACS (HR 1.42, CI 0.86-2.32), evidence of cortisol excess (1.41, 0.85-2.32), and untested patients (1.28, 0.88-1.87) were suggestive of elevated risk. However, none of the elevated hazard rates were statistically significant at the 95% significance level. The apparent elevated risk in the untested patients suggests that many untested patients may have hormonally active AI that puts them at risk for fracture from secondary osteoporosis.

Keywords: fractures, adrenal adenomas, cortisol, bone mineral density, screening tests

Lay summary: Adrenal incidentalomas (AIs) are small tumors found during workups for other conditions. Some AI could secrete excess cortisol, which could lead to osteoporosis and fractures. Among our patients with AI who had laboratory testing for cortisol, fractures were more common for patients with excess cortisol production compared to patients with normal levels; however, this finding was not statistically significant. Patients who were not tested for cortisol had more fractures than the group with testing who had normal cortisol levels. This suggests that the untested group may have included people with excess cortisol production. We conclude that more people with AI should be assessed for cortisol excess because they may be at risk of having fractures.

Introduction

An adrenal incidentaloma (AI) is defined as an adrenal mass of at least 1 cm detected during imaging performed for reasons other than adrenal disease.[1] The incidence of AI has increased dramatically in recent years due to the widespread use of 3D diagnostic imaging scans of the abdomen.[2–5] Most AIs are non-functioning, with no hormonal activity, though ~30% autonomously secrete cortisol.[3] Autonomous cortisol secretion (ACS) is a condition characterized by persistent release of excess cortisol without the typical signs of Cushing's syndrome.

Identification of hormonally active adrenal adenomas requires testing of cortisol levels. The most sensitive test for diagnosing ACS is a 1 mg overnight dexamethasone suppression test (DST), followed by subsequent measurement of morning cortisol levels, with a cortisol level >1.8 μg/dL (>50 nmol/L) being indicative of ACS.[1,6,7] However, DST testing is underutilized despite existing recommendations

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for its use since 2012.[3,8,9] Cortisol measurements can also be made using a 24-h urine free cortisol test, a random serum cortisol test, and cortisol tests are done first thing in the morning, typically between 8:00 AM and 9:00 AM (ie, "baseline" cortisol tests). These tests, however, are less accurate diagnostically than DST.

Hormonally active AI is associated with an increased prevalence of metabolic conditions, cardiovascular comorbidities, and all-cause mortality compared to non-functioning adrenal adenomas.[4,10–17] In addition, evidence of associations with compromised bone health—higher likelihood of osteoporosis, lower bone mineral density, poorer bone microarchitecture, and higher fracture risk—has been suggested by individual studies and a recent meta-analysis.[18–22] Long-term glucocorticoid medication use is an important risk factor for osteoporosis, and this key predictor is included in many osteoporosis and fracture risk calculators. Hormonally active adrenal adenomas represent an endogenous source of elevated glucocorticoid exposure, rather than normal circulating levels, that likely affects bone health and fracture risk, akin to exogenous exposure to glucocorticoids; thus, fracture risk is biologically plausible in patients with ACS.[23–25]

Most prior studies demonstrating an association between cortisol excess due to adrenal adenomas and bone health have been hampered by small sample sizes.[19,26] One notable exception included 20 390 subjects with AI vs 125 392 subjects with no adrenal tumors,[20] but that study focused solely on non-functional adrenal tumors. Additionally, fracture risk due to primary or secondary osteoporosis is known to vary by race/ethnicity, and prior studies had either racially homogenous study populations or were underpowered to estimate subgroup associations within a diverse patient population.

Our objectives were to (1) estimate the incidence rates (IRs) of clinical fractures in a racially/ethnically diverse population-based cohort of patients with diagnosed adrenal nodules arising from two large, integrated healthcare delivery systems in the United States; (2) estimate the associations between patient characteristics (demographic and clinical) and fracture incidence, with focus on fragility fracture outcomes (hip, spine, distal radius/ulna, and proximal humerus); and (3) to evaluate whether the risk factors for incident fragility fractures vary by ACS status, based on DST or cortisol level evaluations.

Materials and methods

Study design and setting

This retrospective cohort study was conducted using data from the electronic health record systems of Kaiser Permanente (KP) Southern California and KP Georgia, two regional integrated healthcare systems in the United States. KP Southern California has an overall membership of ~4.8 million people, which is broadly representative demographically of the underlying Southern California population.[27,28] KP Georgia serves ~320 000 members in the metropolitan Atlanta area and surrounding counties. Its membership also reflects the demographic characteristics of the city population.

KP's comprehensive electronic health records include administrative and clinical data sources, including membership details, diagnosis and procedure codes associated with every health care encounter, laboratory results, pharmacy orders and dispenses, and imaging. Since KP functions as both a healthcare provider and an insurer, healthcare services received from providers outside the KP system are associated with reimbursement claims, enabling near-complete capture of KP member care. KP members are assigned a medical record number for life, allowing longitudinal linkage across these data sources.

All study measures were extracted electronically from the two regional electronic health record systems and research data warehouses.[29,30] Both study sites employed the same data structure and programming codes,[30] ensuring consistent definitions of all variables. Statistical analyses of the data from both regions were conducted at KP Southern California.

This study was approved by the KP Southern California Institutional Review Board (IRB) and the KP Interregional IRB (for KP Georgia) and was conducted under a waiver of informed consent.

Participants

Study subjects were KP Southern California or KP Georgia members, aged ≥50 yr, who were diagnosed with an adrenal nodule from January 1, 2015 to August 31, 2022, identified using *International Classification of Diseases (ICD) codes, 9th (ICD-9: 227.0, 237.2, 255.8, 255.9) and 10th (ICD-10: D35.0, D44.1, E27.8, E27.9) Revisions*. The first adrenal nodule diagnosis during the study period was the index date. Eligible subjects were also required to be enrolled in a KP health plan in the year prior to and for 92 d after the index date. Gaps in enrollment up to 92 d were allowed since such gaps can occasionally occur for administrative reasons instead of loss of coverage. Subjects with diagnoses in the electronic health record for Cushing's disease, hyperadrenalism, or malignant adrenal cancer prior to the index date were excluded, as were subjects with procedure codes for adrenalectomy. Subjects with prevalent osteoporosis, identified by ICD-9 or ICD-10 diagnosis codes 733.00, 733.01, M80.0*, or M81.0 prior to the index date, were excluded from the primary analysis, but were included in sensitivity analyses.

Measurements

Exposure

Our primary exposure of interest was ACS status or cortisol excess among subjects with an AI. Initial ACS/cortisol excess status was determined from laboratory results from DST, urine free cortisol, random, or baseline cortisol tests conducted during the interval of ±92 d of the index date, and subjects were assigned to one of five hierarchical groups of ACS/cortisol excess status based on type of test and the associated results described in Table 1. Results of these tests of cortisol excess are typically reported in μg/dL, though we present relevant values here in SI units of nmol/L, converted as follows: 1 μg/dL = 27.6 nmol/L. More specifically, the groups were (1) confirmed ACS via DST (DST result >50 nmol/L); (2) no ACS via DST (result >50 nmol/L); (3) "inconclusive workup" (elevated urine free cortisol, random cortisol, or baseline cortisol results); (4) "no evidence of cortisol excess" (normal urine free cortisol, random cortisol, or baseline cortisol); and (5) untested. The untested group was likely comprised of subjects with and without cortisol excess, and we did not have information regarding why these patients were not tested.

During follow-up, exposure status was treated as time-varying, with updates being made if/when any subject had additional testing with results that would put them into an ACS/cortisol excess group with a higher level of certainty

Table 1. Autonomous cortisol secretion (ACS)/cortisol excess categorization based on type of test and results.

Group	Description	Test	Result
1	Confirmed ACS	DST	>50 nmol/L
2	No evidence of ACS	DST	<=50 nmol/L
3	Inconclusive or incomplete work-up	Urine free cortisol	Elevated based on the following cut-off values:
		Random cortisol	Urine free cortisol, >177 μg/24 h;
		Baseline cortisol	Random or baseline cortisol, >19.4 μg/dL
4	Tested, no evidence of cortisol excess	Urine free cortisol	At or below the following cut-off values:
		Random cortisol	Urine free cortisol, <=177 μg/24 h;
		Baseline cortisol	Random or baseline cortisol, <=19.4 μg/dL
5	Untested	None	No relevant test results

Abbreviation: DST, dexamethasone suppression test.

Table 2. International Classification of Diseases (ICD)-9/10 codes for identifying prior and incident fractures.

Fracture type	ICD-9 codes	ICD-10 codes
Any clinical[a]	805*-813*, 820*-824*	M80*, S12*, S22*, S32*, S42*, S52*, S72*, S82*
Hip	820.0*, 820.2*, 820.8, 733.14	S72.0*, S72.1*, S72.2*, M80.051*, M80.052*, M80.059*, M84.451*, M84.452*, M84.459*
Vertebral	805.0*, 805.2*, 805.4*, 805.8*, 733.13	S12.0*, S22.0*, S32.0*, M80.08X*
Distal radius/ulna	813.4*, 813.5*, 733.12	S52.5*, S52.6*, S59.0*, S59.2*, M80.031*, M80.032*, M80.039*
Proximal humerus	812.0*, 812.2*, 812.4*, 733.11	S42.2*, M80.021*, M80.022*, M80.029*
Major osteoporosis-related	Any of the codes for hip, vertebral, distal radius/ulna, or proximal humerus	

[a] Excluding fractures of skull, face, fingers, and toes.

(lower group number). For example, if a patient had an elevated random cortisol value in the window of ±92 d of the index date and an elevated DST value during follow-up, the assigned ACS/cortisol excess group for the patient changed from "inconclusive work-up" at baseline to "confirmed ACS via DST," as of the date of DST during follow-up.

Follow-up and outcome ascertainment

The follow-up period for incident fracture outcome ascertainment commenced on the 93rd day after the index date and ended at the earliest of (1) qualifying fracture outcome; (2) disenrollment from the health plan, defined as any enrollment gap ≥93 d; (3) death; or (4) December 31, 2023, the end of the study period. Fractures were identified from the electronic health record using ICD-9/10 discharge diagnosis codes and classified into four (not mutually exclusive) categories: hip fracture; clinical vertebral fracture; major osteoporotic fracture, comprised of hip, vertebral, proximal humerus, or distal radius/ulna fractures; and all clinical fractures, excluding fingers, toes, skull, and facial fractures (Table 2). Each of the four fracture categories was analyzed as an independent primary outcome. For each of the fracture categories, the earliest date during follow-up associated with a relevant ICD code was identified. These fractures were considered incident fractures if no ICD code for fracture of the same anatomic location appeared during the immediately preceding 92 d.

Covariates

Information on several demographic and clinical covariates was collected from the electronic health record and membership data sources. Demographic variables included age at time of index date (categorized as 50-59, 60-69, 70-79, and ≥80 yr), sex, and self-reported race and ethnicity.[31] Additionally, we included an index measure of neighborhood deprivation based on census-tract data derived from the American Community Survey. This index is a standardized score ranging from −3 to 3, where higher scores indicate higher neighborhood deprivation.[32–34]

Information on baseline clinical characteristics was ascertained from medical records from the 365 d prior to the index date. Body mass index (BMI) was calculated from height and weight measurements prior to and most proximal in time to the index date. Patient-reported smoking status, in response to routine questions asked at outpatient healthcare encounters, was also taken from encounters prior to and most proximal in time to the index date. The overall comorbidity burden was quantified using the Deyo adaptation[35] of the Charlson Comorbidity Index (CCI).[36] In addition to information on each of the discrete conditions comprising the Charlson, we also identified any diagnosis of a prior fracture that occurred within 1826 d (∼5 yr) prior to the index date. These prior fractures were categorized similarly to incident fractures, as described above.

Statistical analysis

Demographic and clinical characteristics were described for the overall cohort and by ACS/cortisol excess group at cohort entry. Continuous variables were summarized as medians and interquartile range (IQR) or means and SD; categorical variables were summarized as counts and proportions. For each outcome, the overall and risk factor-stratified crude IRs and the 95% CIs were calculated using Poisson regression and reported as per 100 person-years of follow-up time. For each of the four fracture outcome categories, we examined the crude and adjusted associations of time-varying ACS grouping with fracture using cause-specific Cox proportional hazards regression models while considering all-cause mortality as a competing risk. Multivariable results were quantified with hazard ratios (HR) and 95% CIs. Covariates considered for the multivariable analysis were: age, sex, race, and ethnicity (non-Hispanic White; Asian/Pacific Islander; Black; Hispanic; multiple/other/unknown), neighborhood deprivation index (quintiles 1-5), smoking status (current or prior smokers,

never smoked, or unknown), body mass index (underweight [<18.5 kg/m^2], healthy weight [18.5-24.9 kg/m^2], overweight [25-29.9 kg/m^2], obese [≥30 kg/m^2], and unknown), Charlson comorbidity index (0, 1-2, 3, 4+), history of fracture, age at prior fracture, and several discrete comorbidities, assessed as presence vs absence of the condition, including diabetes, prediabetes, chronic kidney disease, cardiovascular disease, myocardial infarction, coronary artery disease, hypertension, hyperlipidemia, deep vein thrombosis (DVT), peripheral vascular disease, stroke, transient ischemic attack, and osteopenia. An interaction term between the ACS/cortisol excess group and history of fracture was also included. A likelihood ratio test was used to test the effect of each covariate (or the interaction term) sequentially using a backward selection method. This sequential process was repeated for all covariates and the interaction term until all the obtained *p*-values were ≤.05. As a sensitivity analysis, we applied the multivariable model from the primary analysis to the overall cohort without excluding subjects with prevalent osteoporosis diagnoses. SAS version 9.4 (SAS Institute, Inc., Cary, NC, United States) was used for all statistical analyses.

Results

After applying all inclusion and exclusion criteria, we identified a cohort of 14 886 subjects during the study period who had an adrenal adenoma. Approximately 10%-12% died during follow-up; mortality varied by type of fracture outcome. Overall, the median age at time of nodule diagnosis was 61.1 yr (IQR 59.0, 72.0). The cohort was 53.2% female, 45.7% non-Hispanic White, and 50% of subjects were current or past smokers (Table 3). Comorbidities were common, with the mean Charlson score being 2.7 (SD 2.3), and only 22.1% had none of the conditions comprising the Charlson. Approximately 13% of the cohort had a history of a prior fracture, and most of those fractures (74.9%) were not fractures typically considered to be osteoporosis-related.

Within the overall cohort, 662 subjects (4.4%) had been tested with DST and 273 (41.2%) of the 662 had elevated results (DST >50 nmol/L) (Table 3). Another 4871 (32.7% of the cohort) were tested with urine free cortisol or random cortisol tests; 201 (4.1%) of these 4871 had results indicating excess cortisol secretion. A considerable proportion of the cohort members ($n = 9353$; 62.8%) were not tested for cortisol excess at the time of nodule diagnosis or during follow-up.

During follow-up, 1398 incident fractures were observed, for an overall IR of 2.8 fractures/100 person-years (Table 4). Hip fractures ($n = 172$) occurred at a rate of 0.3/100 person-years, vertebral fractures ($n = 324$) at a rate of 0.6/100 person-years, and major osteoporotic fractures ($n = 733$) at a rate of 1.4/100 person-years. Across all fracture outcome categories, IRs estimated with multivariable Poisson models increased with older age, were highest for non-Hispanic White subjects, and increased with increasing Charlson score. Hip fractures and vertebral fractures occurred at similar rates for women and men, while major osteoporotic fractures and all clinical fracture rates were higher for women. Fracture IRs were similar across the "confirmed ACS via DST," "inconclusive work-up," and "untested" groups and were consistently higher than the rates for the groups without cortisol excess ("no ACS via DST" and "no evidence of cortisol excess" groups).

Our final multivariable model quantifying the association between the ACS/cortisol excess group and any incident clinical fracture, accounting for death as a competing risk with fracture, was adjusted for age group, sex, race/ethnicity, body mass index, Charlson score, diagnosis of osteopenia or low bone mass, history of prior fracture, history of cerebrovascular disease, and history of DVT. In this model, the ACS/cortisol excess group was marginally associated with clinical fracture ($p = .055$). Compared to the "no ACS via DST" group (the referent), the adjusted HRs for the other ACS/cortisol excess groups suggested elevated fracture risk, though none of the estimates reached statistical significance (Table 5). Compared to the "no ACS via DST" group, point estimates suggested elevated fracture risk for patients with "confirmed ACS via DST" (HR 1.42, 95% CI 0.86-2.32), patients with "inconclusive work-up" (HR 1.41, 95% CI 0.85-2.32), patients with "no evidence of cortisol excess" (HR 1.11, 95% CI 0.76-1.62), and the "untested" group (HR 1.28, 95% CI 0.88-1.87), though they were not statistically significant (Table 5).

The sensitivity analysis, which included subjects with a prevalent diagnosis of osteoporosis, increased the size of the cohort to 17 380 individuals. Compared to the main analysis cohort, the sensitivity cohort was slightly older (67.5 vs 66.1 yr), included a higher proportion of women (56.7% vs 53.2%), and had a higher proportion of subjects with a history of fracture prior to baseline (16.6% vs 12.9%). The proportion of subjects in the sensitivity cohort who had a history of prior hip fracture was almost double that of the main cohort (11.8% vs 6.2%). There were smaller differences in proportions with a history of other major osteoporosis-related fractures (vertebral, radius/ulna, or proximal humerus), with the sensitivity cohort being higher for all these categories than the main cohort. The proportions of patients within each of the five ACS/cortisol excess groups were almost identical when comparing the two cohorts, aside from the sensitivity cohort having a slightly higher proportion of untested subjects (63.8% vs 62.8%). Even with these differences between the cohorts, the multivariable results were similar (Table 5), with the point estimates for the main predictor, the ACS/cortisol excess group, not being appreciably different. The results of the sensitivity analyzes did not change any of the conclusions from the main analyzes.

Discussion

Within this large, population-based study, none of the observed point estimates for fracture risk among our ACS groups (compared to the DST-tested group with no evidence of ACS) reached the level of statistical significance. For the tested group with confirmed ACS and the "inconclusive work-up" group, the point estimates are suggestive of elevated fracture risk but must be interpreted conservatively as not being supportive of our hypothesized relationship between endogenous corticosteroid exposure (as cortisol excess) and elevated risk of fracture. This finding also held true for the group of patients who had not been tested at all around the time of their AI diagnosis, nor during follow-up. The results from the sensitivity analyses, for which subjects with prior osteoporosis were not excluded and newly diagnosed osteoporosis was not censored, are aligned with our main analysis results. Prevalent osteoporosis may have

Table 3. Patient characteristics at the time of or prior to adenoma diagnosis by ACS group in patients with adrenal nodules, 2015-2022.

Characteristics	Subgroups	Confirmed ACS *n* = 273 N (%)	No ACS via DST *n* = 389 N (%)	Incomplete testing *n* = 201 N (%)	No cortisol excess *n* = 4670 N (%)	Untested *n* = 9353 N (%)	Total *n* = 14 886 N (%)
Age group	50-59 yr	58 (21.3)	134 (34.5)	71 (35.3)	1428 (30.6)	2432 (26.0)	4123 (27.7)
	60-69 yr	113 (41.4)	146 (37.5)	59 (29.4)	1815 (38.9)	3401 (36.4)	5534 (37.2)
	70-79 yr	80 (29.3)	87 (22.4)	46 (22.9)	1120 (24.0)	2517 (26.9)	3850 (25.9)
	80+ yr	22 (8.1)	22 (5.7)	25 (12.4)	307 (6.6)	1003 (10.7)	1379 (9.3)
Female sex	Female	165 (60.4)	217 (55.8)	105 (52.2)	2515 (53.9)	4916 (52.6)	7918 (53.2)
Race/ethnicity	Asian	24 (8.8)	32 (8.2)	24 (11.9)	438 (9.4)	652 (7.0)	1170 (7.9)
	Black	78 (28.6)	72 (18.5)	35 (17.4)	676 (14.5)	1739 (18.6)	2600 (17.5)
	Hispanic	59 (21.6)	125 (32.1)	47 (23.4)	1291 (27.6)	2332 (24.9)	3854 (25.9)
	Non-Hispanic White	101 (37.0)	144 (37.0)	88 (43.8)	2117 (45.3)	4356 (46.6)	6806 (45.7)
	Multiracial/Other/Unknown	–	–	–	–	–	–
NDI[a], mean (SD)	Quintile 1	−0.9 (0.3)	−1.0 (0.2)	−0.9 (0.2)	−0.9 (0.2)	−0.9 (0.2)	−0.9 (0.2)
	Quintile 2	−0.4 (0.1)	−0.4 (0.1)	−0.4 (0.1)	−0.4 (0.1)	−0.4 (0.1)	−0.4 (0.1)
	Quintile 3	0.0 (0.1)	0.0 (0.1)	0.0 (0.1)	0.0 (0.1)	0.0 (0.1)	0.0 (0.1)
	Quintile 4	0.6 (0.2)	0.5 (0.2)	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)
	Quintile 5	1.5 (0.6)	1.5 (0.6)	1.5 (0.5)	1.5 (0.5)	1.5 (0.6)	1.5 (0.6)
Smoking	Never smoked	120 (44.0)	230 (59.1)	95 (47.3)	2361 (50.6)	4252 (45.5)	7058 (47.4)
	Current or past smokers	147 (53.8)	155 (39.8)	101 (50.3)	2230 (47.7)	4804 (51.4)	7437 (50.0)
	Unknown	<20 (<10.0)	<20 (<10.0)	<20 (<10.0)	79 (1.7)	297 (3.2)	391 (2.6)
BMI[b]	Underweight	<20 (<10.0)	<20 (<10.0)	<20 (<10.0)	47 (1.0)	121 (1.3)	185 (1.2)
	Normal	58 (21.3)	60 (15.4)	47 (23.4)	741 (15.9)	1586 (17.0)	2492 (16.7)
	Overweight	73 (26.7)	119 (30.6)	63 (31.3)	1559 (33.4)	3010 (32.2)	4824 (32.4)
	Obese	70 (25.6)	107 (27.5)	35 (17.4)	1212 (25.9)	2324 (24.9)	3371 (22.6)
	Severely obese	62 (22.7)	98 (25.2)	41 (20.4)	1080 (23.1)	2090 (22.4)	3371 (22.7)
CCI[c]	0	51 (18.7)	116 (29.8)	40 (20.0)	1140 (24.4)	1942 (20.8)	3289 (22.1)
	1-2	96 (35.2)	143 (36.8)	55 (27.4)	1861 (39.8)	3215 (34.4)	5370 (36.1)
	3	31 (11.4)	52 (13.4)	29 (14.4)	481 (10.3)	1022 (10.9)	1615 (10.8)
	4+	95 (34.8)	78 (20.1)	77 (38.3)	1188 (25.4)	3174 (33.9)	4612 (31.0)
Bone health	Osteopenia (low bone mass)	45 (16.5)	57 (14.7)	38 (18.9)	729 (15.6)	1490 (15.9)	2359 (15.9)
	Prior clinical fracture	43 (15.8)	39 (10.0)	31 (15.4)	554 (11.9)	1251 (13.4)	1918 (12.9)
Comorbidities	Prediabetes	99 (36.3)	143 (36.8)	66 (32.8)	1513 (32.4)	2805 (30.0)	4626 (31.1)
	Diabetes	134 (49.1)	138 (35.5)	101 (50.3)	1887 (40.4)	4003 (42.8)	6263 (42.1)
	Cardiovascular disease	236 (86.5)	269 (69.2)	170 (84.6)	3555 (76.1)	7453 (79.7)	11 683 (78.5)
	Coronary artery disease	46 (16.9)	30 (7.7)	28 (13.9)	584 (12.5)	1592 (17.0)	2280 (15.3)
	Cerebrovascular disease	27 (9.9)	22 (5.7)	29 (14.4)	403 (8.6)	1058 (11.3)	1539 (10.3)
	DVT	<20 (<10.0)	<20 (<10.0)	<20 (<10.0)	33 (0.7)	114 (1.2)	154 (1.0)
	Hypertension	222 (81.3)	243 (62.5)	162 (80.6)	3346 (71.7)	6962 (74.4)	10 935 (73.5)
	Hyperlipidemia	206 (75.5)	260 (66.8)	139 (69.2)	3316 (71.0)	6533 (69.9)	10 454 (70.2)
	Peripheral vascular disease	79 (28.9)	97 (24.9)	54 (26.9)	1216 (26.0)	2965 (31.7)	4411 (29.6)
	Chronic kidney disease	60 (22.0)	54 (13.9)	46 (22.9)	787 (16.9)	1854 (19.8)	2801 (18.8)
	Myocardial infarction	<20 (<10.0)	<20 (<10.0)	<20 (<10.0)	286 (6.1)	795 (8.5)	1128 (7.6)
	Stroke	<20 (<10.0)	<20 (<10.0)	<20 (<10.0)	139 (3.0)	462 (4.9)	629 (4.2)
	Transient ischemic attack	<20 (<10.0)	<20 (<10.0)	<20 (<10.0)	134 (2.9)	328 (3.5)	483 (3.2)

Abbreviations: ACS, autonomous cortisol secretion; DST, dexamethasone suppression test; NDI, neighborhood deprivation index. [a]Neighborhood Deprivation Index. [b]Body mass index. [c]Charlson Comorbidity Index.

Table 4. Incidence rates of any clinical fracture, hip fracture, vertebral fracture, and major osteoporotic fracture (MOF) per 100 person-years (p-y) of follow-up, by ACS/cortisol excess group, age, sex, race/ethnicity, and Charlson comorbidity index.

	Any fracture		Hip		Vertebral		MOF	
Characteristics	N	Rate	N	Rate	N	Rate	N	Rate
All	1398	2.8	172	0.3	324	0.6	733	1.4
Age group								
50-59 yr	314	2.1	14	0.1	55	0.4	138	0.9
60-69 yr	467	2.4	50	0.2	102	0.5	238	1.2
70-79 yr	423	3.3	71	0.5	111	0.8	251	1.9
80+ yr	194	5.3	37	0.9	56	1.4	106	2.8
Sex								
Female	829	3.1	89	0.3	182	0.6	448	1.6
Male	569	2.4	83	0.3	142	0.6	285	1.2
Race/ethnicity								
Asian	62	1.5	6	0.1	16	0.4	31	0.7
Black	169	1.8	18	0.2	39	0.4	80	0.8
Hispanic	350	2.7	32	0.2	76	0.6	181	1.3
Non-Hispanic White	782	3.4	108	0.4	1887	0.8	423	1.8
ACS/cortisol excess group								
1—Confirmed ACS (elevated DST)	36	3.5	1	0.1	14	1.3	21	2.0
2—Tested by DST, no evidence of ACS	25	1.8	3	0.2	6	0.4	14	1.0
3—Inconclusive or incomplete work-up	33	3.4	3	0.3	10	1.0	20	2.0
4—Tested, no evidence of cortisol excess	508	2.4	49	0.2	120	0.5	261	1.2
5—Untested	919	3.5	126	0.4	211	0.8	486	1.8
Charlson Comorbidity Index score								
0	232	1.9	23	0.2	46	0.4	113	0.9
1-2	459	2.3	43	0.2	105	0.5	240	1.2
3	170	3.1	26	0.4	34	0.6	86	1.5
4+	537	3.9	80	0.5	139	1.0	294	2.1

Abbreviations: ACS, autonomous cortisol secretion; DST, dexamethasone suppression test.

resulted from exposure to excess endogenous cortisol from a hormonally active AI that was not diagnosed until after the onset of osteoporosis. However, the similarity of the results, excluding prevalent osteoporosis and censoring upon diagnosis of osteoporosis during follow-up, to the results from the larger cohort that included subjects with prevalent or newly diagnosed osteoporosis suggests that the risk of fracture associated with cortisol excess may be independent of the risk associated with an existing osteoporosis diagnosis.

The point estimates for fracture risk in our study, while not reaching statistical significance, are congruent with findings from prior studies. Comparing patients with ACS to patients with non-functional adrenal tumors, Moraes et al.,[26] found that while osteoporosis was common in both groups, bone mineral density was lower among the ACS group than in the group with non-functional tumors, and fractures were more common among the ACS group (73.7% vs 55.6%). Two other studies of patients with ACS demonstrated higher fracture risk than the group with non-functional tumors.[18,22] In addition, while Lindh's study[20] compared patients with non-functional tumors to patients without adrenal adenomas, the finding of greater fracture incidence among the group with adenomas is also congruent with these findings. A recent meta-analysis estimated the pooled odds ratio for the likelihood of persons with possible/mild ACS to sustain any fracture (vertebral and non-vertebral) to be 1.6 (95% CI 1.2, 2.2) compared to patients with non-functional AI.[21] Our estimates were lower than the pooled odds ratio reported in the meta-analysis and did not achieve statistical significance. The low testing rate of DST in our cohort resulted in a small number of subjects with "confirmed ACS," and thus reduced the statistical power for the hypothesis testing. The higher estimate by the meta-analysis compared to our finding could also be the result of overestimation of the risk ratio by an odds ratio.[37]

Salcuni et al.[38] observed in their study of patients with what they called "subclinical" hypercortisolism that patients subsequently treated surgically with adrenalectomy were less likely to have incident vertebral fractures than the non-surgical group, suggesting that the severity of bone disease could be proportional to cortisol concentration or duration of exposure to excess cortisol. Higher cortisol creates more bone loss over time, even if cortisol and DST do not fulfill the criteria for Cushing's disease. Our point estimates also suggest a version of increased fracture risk among subjects with higher "certainty" of ACS diagnosis. The subjects in the "confirmed ACS (elevated DST)" and "inconclusive or incomplete work-up" groups had greater point estimates for fracture risk than did the "no evidence of ACS (tested by DST)" and "tested, no evidence of cortisol excess" groups. Further, the subjects in our "untested" group also had fracture risk estimates akin to the "confirmed ACS (elevated DST)" and "inconclusive or incomplete work-up" groups and higher than the groups that were tested without evidence of ACS. This suggests that the untested group is comprised of a mixture of patients with and without cortisol excess. The observed congruence of the untested group's fracture risk with the point estimates of those with evidence of cortisol excess suggests that many among the untested group did have cortisol excess. Many of the untested patients in our cohort were too young to be screened for osteoporosis according to age-based screening guidelines, and the presence of adrenal adenomas may be an underrecognized source of secondary osteoporosis in these patients.

Professional organizations representing several medical specialties (eg, endocrinology, urology, radiology, and surgery) have issued clinical guidelines for the screening and

Table 5. Multivariable Cox proportional hazards models of the association of time-varying ACS/cortisol excess group and incident clinical fracture, with mortality as a competing risk, for the primary cohort (excluding patients with prevalent osteoporosis) and the sensitivity cohort (no exclusions for osteoporosis).

Characteristics	Primary cohort HR (95% CI)	Sensitivity cohort HR (95% CI)
ACS/cortisol excess group		
1—Confirmed ACS (elevated DST)	1.42 (0.86, 2.32)	1.38 (0.90, 2.14)
2—Tested by DST, no evidence of ACS	Referent	Referent
3—Inconclusive or incomplete work-up	1.41 (0.85, 2.32)	1.48 (0.97, 2.25)
4—Tested, no evidence of cortisol excess	1.11 (0.76, 1.62)	1.09 (0.78, 1.51)
5—Untested	1.28 (0.88, 1.87)	1.33 (0.96, 1.85)
Age group		
50-59 yr	Referent	Referent
60-69 yr	1.05 (0.91, 1.21)	1.06 (0.93, 1.22)
70-79 yr	1.26 (1.08, 1.48)	1.24 (1.07, 1.43)
80+ yr	1.83 (1.51, 2.21)	1.81 (1.52, 2.14)
Female sex	1.32 (1.19, 1.47)	1.43 (1.30, 1.57)
Race/ethnicity		
Asian	0.50 (0.39, 0.64)	0.46 (0.37, 0.57)
Black	0.56 (0.48, 0.66)	0.54 (0.47, 0.63)
Hispanic	0.89 (0.79, 1.00)	0.85 (0.77, 0.95)
Multiracial/Other/Unknown	0.77 (0.56, 1.07)	0.71 (0.54, 0.95)
Non-Hispanic White	Referent	Referent
NDI[a]		
Quintile 1		Referent
Quintile 2		0.95 (0.83, 1.07)
Quintile 3		0.94 (0.83, 1.07)
Quintile 4		0.88 (0.77, 1.01)
Quintile 5		0.93 (0.81, 1.07)
BMI[b]		
Underweight	1.05 (0.65, 1.69)	1.06 (0.81, 1.39)
Normal	Referent	Referent
Overweight	0.87 (0.75, 1.01)	0.87 (0.78, 0.98)
Obese	0.76 (0.65, 0.89)	0.80 (0.70, 0.91)
Severely obese	0.83 (0.71, 0.98)	0.83 (0.73, 0.96)
Missing	0.71 (0.43, 1.18)	0.76 (0.48, 1.22)
Smoking		
Never		Referent
Current or ever		1.08 (0.99, 1.18)
Missing		1.06 (0.72, 1.55)
CCI[c] **score**		
0	Referent	Referent
1-2	1.21 (1.04, 1.42)	1.17 (1.00, 1.35)
3	1.45 (1.19, 1.76)	1.34 (1.11, 1.62)
4+	1.63 (1.38, 1.93)	1.51 (1.26, 1.82)
History of osteopenia	1.17 (1.03, 1.33)	1.14 (1.03, 1.26)
History of osteoporosis		2.07 (1.86, 2.29)
History of any clinical fracture	3.50 (3.10, 3.96)	
History of cerebrovascular disease	1.19 (1.02, 1.38)	1.25 (1.08, 1.45)
History of deep vein thrombosis	1.61 (1.15, 2.25)	1.44 (1.10, 1.89)
History of peripheral vascular disease		1.13 (1.02, 1.26)
History of myocardial infarction		0.93 (0.78, 1.10)
History of hypertension		0.92 (0.77, 1.09)
History of prediabetes		0.93 (0.85, 1.02)
History of chronic kidney disease stages 3-5		0.98 (0.87, 1.09)
History of hyperlipidemia		1.00 (0.91, 1.11)
History of stroke		1.04 (0.85, 1.27)
History of diabetes		1.04 (0.94, 1.15)
History of coronary artery disease		1.08 (0.95, 1.23)
History of transient ischemic attack		0.93 (0.75, 1.14)
History of cardiovascular disease		1.14 (0.92, 1.40)

Abbreviations: HR, hazard ratios; ACS, autonomous cortisol secretion; DST, dexamethasone suppression test; NDI, neighborhood deprivation index. [a]Neighborhood Deprivation Index. [b]Body mass index. [c]Charlson Comorbidity Index.

management of AI, though these guidelines vary considerably in their recommendations.[7] In a comprehensive review of AI, Sherlock et al. strongly recommended that every patient with an AI should be screened for cortisol excess, while also acknowledging that there is no ideal test for diagnosing ACS and diagnosing ACS in patients with only marginally elevated cortisol excess is challenging.[39] While DST is the test with the highest sensitivity, it has low specificity with many false-positive results. Additionally, DST is often performed incorrectly. Nevertheless, none of the current clinical tests

yield an accurate diagnosis of ACS.[40] Additionally, testing rates for excess cortisol production remain low in many settings,[9] leaving many patients with AI unidentified yet potentially at risk for developing significant comorbidities associated with cortisol excess, including greater loss of bone mass and risk of fracture.

Our study is notable for several strengths. Our population-based study conducted within two KP regions, both with racial/ethnic and socioeconomic diversity representative of the underlying populations in each region, included a larger sample size than most of the prior studies on this topic. We leveraged a unique data warehouse that is harmonized throughout KP, enabling consistent variable definitions and systematic extraction of relevant exposures, outcomes, and covariables minimizing potential selection bias related to data ascertainment.

Our study does have some potential limitations. While our data extraction methods were consistent across study sites, regional differences in clinical workflow for evaluation and management of patients with adrenal adenomas may have resulted in biases related to medical care decisions for which we could not adequately adjust.

In this large population-based study of patients with AIs, we observed a trend toward higher incident fracture risk in patients with confirmed ACS or evidence of cortisol excess compared to patients with normal cortisol test results; however, these associations did not reach statistical significance. The substantial proportion of untested patients highlights the need for further investigation into optimal screening strategies for cortisol excess and its potential impact on bone health.

Author contributions

Annette Adams (Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing—original draft), In-Lu Amy Liu (Data curation, Formal analysis, Writing—review & editing), Iris Anne Reyes (Data curation, Funding acquisition, Project administration, Supervision, Writing—review & editing), Hina Chowdhry (Data curation, Validation, Writing—review & editing), Richard Contreras (Data curation, Validation, Writing—review & editing), Yuqian M. Gu (Data curation, Formal analysis, Validation, Writing—review & editing), Mackenzie Crawford (Data curation, Project administration, Supervision, Writing—review & editing), Bennett McDonald (Data curation, Validation, Writing—review & editing), Joshua Barzilay (Conceptualization, Funding acquisition, Writing—review & editing), Tish Villanueva (Conceptualization, Funding acquisition, Validation, Writing—review & editing), David A. Katz (Conceptualization, Resources, Writing—review & editing), Frank S. Czerwiec (Conceptualization, Resources, Writing—review & editing), and Wansu Chen (Conceptualization, Data curation, Formal analysis, Supervision, Writing—review & editing)

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Conflicts of interest

A.L.A, I.A.L., I.A.C.R., H.C., R.C., Y.M.G., M.C., B.M., J.I.B., T.V., and W.C. have no conflicts of interest related to this study.

D.A.K. and F.S.C. are stockholders and employees of the funding sponsor.

Data availability

The data underlying this article may be shared upon reasonable request to the site's corresponding author.

IRB Approval: Institutional Review Board approval for this study was granted by the KPSC IRB (IRB# 13485) and the KP Interregional IRB for KPGA (IRB# 2010058).

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