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"Nonfunctional" Adrenal Tumors and the Risk for Incident Diabetes and Cardiovascular Outcomes

A Cohort Study

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Background: Benign adrenal tumors are commonly discovered on abdominal imaging. Most are classified as nonfunctional and are considered to pose no health risk, but some are considered functional because they secrete hormones that increase risk for metabolic and cardiovascular diseases.

Objective: To evaluate the hypothesis that nonfunctional adrenal tumors (NFATs) increase risk for cardiometabolic outcomes compared with absence of adrenal tumors.

Design: Cohort study.

Setting: Integrated hospital system.

Participants: Participants with benign NFATs ("exposed"; *n* = 166) and those with no adrenal tumor ("unexposed"; *n* = 740), with at least 3 years of follow-up.

Measurements: Medical records were reviewed from the time of abdominal imaging for development of incident outcomes (hypertension, composite diabetes [prediabetes or type 2 diabetes], hyperlipidemia, cardiovascular events, and chronic kidney disease) (mean, 7.7 years). Primary analyses evaluated independent associations between exposure status and incident outcomes by using adjusted generalized linear models. Secondary analyses evaluated relationships between NFATs and cortisol physiology.

Results: Participants with NFATs had significantly higher risk for incident composite diabetes than those without adrenal tumors (30 of 110 [27.3%] vs. 72 of 615 [11.7%] participants; absolute risk, 15.6% [95% CI, 6.9% to 24.3%]; adjusted risk ratio, 1.87 [CI, 1.17 to 2.98]). No significant associations between NFATs and other outcomes were observed. Higher "normal" postdexamethasone cortisol levels (≤50 nmol/L) were associated with larger NFAT size and higher prevalence of type 2 diabetes.

Limitation: Potential bias in the selection of participants and ascertainment of outcomes.

Conclusion: Participants with NFATs had a significantly higher risk for diabetes than those without adrenal tumors. These results should prompt a reassessment of whether the classification of benign adrenal tumors as "nonfunctional" adequately reflects the continuum of hormone secretion and metabolic risk they may harbor.

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The use of cross-sectional abdominal imaging has increased the incidental detection of adrenal tumors (1, 2). Imaging and autopsy series estimate that the prevalence of adrenal tumors is 1% to 10% (3–5), with higher occurrences with older age (4, 5). Although nearly all of these findings represent benign adrenocortical tumors that are commonly believed to be nonfunctional (1, 2, 6), a substantial proportion may be functional in that they secrete detectable adrenocortical hormones. An estimated 10% of adrenocortical tumors may secrete excess cortisol without the classic signs or symptoms of Cushing syndrome, a phenomenon known as subclinical hypercortisolism (1, 6–9). Subclinical hypercortisolism has been associated with hypertension, insulin resistance, type 2 diabetes, hyperlipidemia, osteoporosis, and obesity (10, 11), and recent studies suggest that it may increase the risk for incident cardiovascular events and death compared with nonfunctional adrenal tumors (NFATs) (12–14). Therefore, screening for hypercortisolism is recommended for all patients with adrenal tumors (1, 2, 15, 16).

However, emerging evidence suggests a higher cross-sectional association with cardiometabolic derangements, such as insulin resistance, in patients with apparent NFATs compared with matched controls without adrenal tumors (17–19), possibly because NFATs secrete low levels of glucocorticoids (17, 20). Although these studies were small and lacked longitudinal follow-up, collectively they suggest that NFATs, as defined in current clinical practice guidelines (1, 2, 15, 16, 21), may not be nonfunctional after all; they may impart cardiometabolic risk by secreting inappropriate amounts of adrenal hormones that evade traditional clinical criteria and detection capabilities.

A better understanding of whether NFATs are an independent risk factor for cardiometabolic disease is important for public health. We hypothesized that patients with NFATs are at increased risk for incident diabetes and cardiovascular outcomes compared with similar patients without adrenal tumors.

Methods

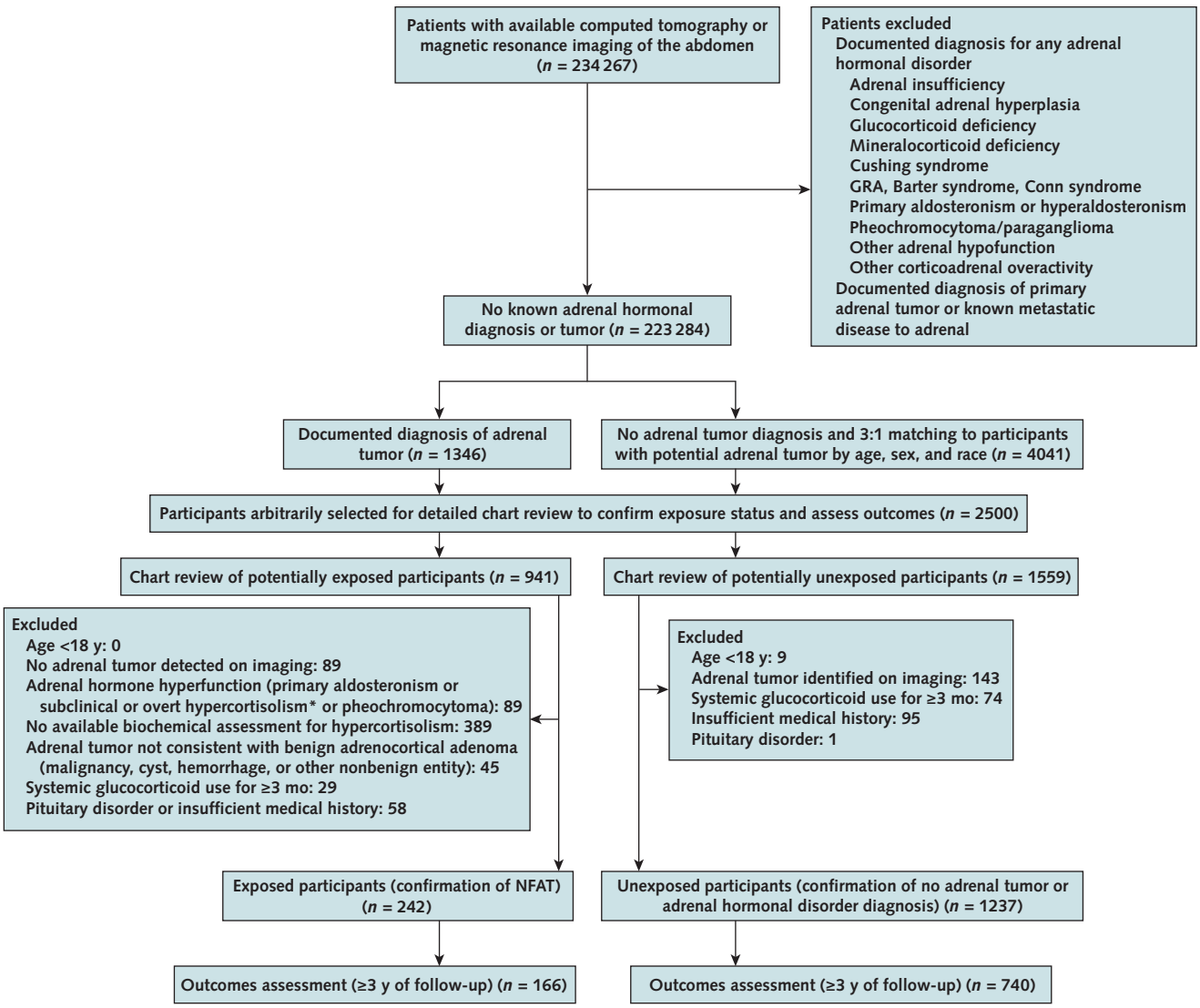
Study Population

We retrospectively assembled a cohort to examine the prospective association between NFATs and car-

See also:

Summary for Patients 1

Figure 1. Selection of study participants and identification of exposure status (NFATs vs. no adrenal tumors).



GRA = glucocorticoid-remediable aldosteronism; NFAT = nonfunctional adrenal tumor.
* Serum cortisol level >50 nmol/L on 1-mg dexamethasone suppression test or 24-h urinary free cortisol level ≥138 nmol.

diometabolic outcomes. The medical records of patients at Brigham and Women's Hospital, Massachusetts General Hospital, and their affiliated partner hospitals who had undergone computed tomography or magnetic resonance imaging of the abdomen were evaluated (Figure 1). Detailed methods for the selection of the study participants are presented in the Appendix (available at www.annals.org). After excluding participants with a documented diagnosis of any adrenal hormone disorder or tumor, we identified those who potentially had NFATs (the exposure of interest) (*n* = 941) and those who potentially did not have an adrenal tumor (*n* = 1559) (Figure 1). All study procedures were approved by the institutional research and ethics review board of Partners Inc.

Assessment of the Main Exposure (NFATs)

Individual medical record review was used to confirm exposure status (Figure 1). Detailed methods for confirming exposure status are presented in the Appendix. We excluded participants with an adrenal tumor that did not appear to be benign on imaging or who lacked biochemical evaluation to assess for subclinical hypercortisolism. From the remaining participants with adrenal tumors who were assessed for hypercortisolism, we excluded those with evidence of potential subclinical or overt hypercortisolism, defined as a serum cortisol level greater than 50 nmol/L on a 1-mg dexamethasone suppression test (DST) (21) or a 24-hour urinary free cortisol (UFC) level of at least 138 nmol (21). We also excluded participants with potential

subclinical or overt primary aldosteronism (22) (Appendix). After these exclusions, 242 participants with NFATs remained; among these, subclinical hypercortisolism was excluded by DST in 164, by 24-hour UFC level in 104, and by both in 28. We also used medical record review to confirm 1237 unexposed participants who had no adrenal tumors on imaging and no known diagnoses of adrenal hormone dysfunction (Figure 1).

Assessment of Other Relevant Exposures

Medical record review also provided details on pertinent demographic information (age, sex, race, and body mass index [BMI]), prevalent medical diagnoses (hypertension, hyperlipidemia, prediabetes, type 2 diabetes, heart failure, chronic kidney disease, myocardial infarction, ischemic stroke, atrial fibrillation, or interventional coronary procedure [coronary catheterization or coronary artery bypass graft surgery]), smoking history, and use of relevant medication classes (antihypertensive; antidiabetes [oral hypoglycemics or insulin]; and medications for coronary artery disease, hyperlipidemia, or both [aspirin, nitrates, statins, fibrates, and niacin]).

Assessment of Main Outcome Measures (Incident Diabetes and Cardiovascular Disease)

The main clinical outcomes of interest were hypertension, composite diabetes, hyperlipidemia, cardiovascular events, and chronic kidney disease. These outcomes were assessed at baseline (the time of abdominal imaging to evaluate exposure status) and again during follow-up. Follow-up assessment of outcomes was conducted only in participants who had at least 3 years of longitudinal follow-up to ensure sufficient exposure time and opportunity for the reliable detection and documentation of clinical diagnoses by health care providers (n = 166 of 242 participants with NFATs and 740 of 1237 with no adrenal tumor) (Figure 1). Participants with less than 3 years of available follow-up were not included in our data set or analysis for incident outcomes. Prospective clinical outcomes were assessed at the most recent annual or complete clinical evaluation. Examples of annual or complete evaluations included comprehensive primary care or general internal medicine visit; cardiology, nephrology, or endocrinology consultation; and preoperative anesthesia consultation. Hypertension was defined as a documented diagnosis. Prediabetes was defined as a documented diagnosis and/or a hemoglobin A_{1c} value of 5.7% to 6.4% on at least 2 occasions among patients who were not receiving any hypoglycemic agent other than metformin. Type 2 diabetes was defined as a documented diagnosis and/or a hemoglobin A_{1c} value of at least 6.5% on at least 2 occasions. Because prediabetes and type 2 diabetes are on a pathophysiologic continuum of insulin resistance, we defined "composite diabetes" as either prediabetes or type 2 diabetes. Hyperlipidemia was defined as a documented diagnosis and/or a low-density lipoprotein cholesterol level of at least 3.89 mmol/L (150 mg/dL). Cardiovascular events were a composite of any documented diagnosis of myocardial infarction, ischemic stroke, heart failure, atrial fibrillation, or interventional coronary procedure. Chronic kidney disease was defined as a documented diagnosis.

Table 1. Demographic and Clinical Characteristics of Study Participants at Baseline, by Exposure Status*

Characteristic	"Nonfunctional" Adrenal Tumor	No Adrenal Tumor	*P* Value†
Participants, *n*	242	1237	
Mean age (SD), *y*	56.8 (11.4)	59.6 (14.6)	0.005
Female	77.7	70.7	0.028
Race			0.002
White	60.7	62.3	
Black	15.7	8.9	
Hispanic	8.3	6.7	
Other	15.3	22.1	
Mean body mass index (SD), kg/m^2	30.9 (7.3)	28.1 (6.8)	<0.001
Smoking status			
Nonsmoker‡	68.6	72.4	0.24
Current smoker	31.4	27.6	
Hypertension	54.6	50.4	0.26
Prediabetes§	7.9	3.1	<0.001
Type 2 diabetes‖	20.7	14.2	0.014
Composite diabetes¶	28.5	17.3	<0.001
Hyperlipidemia	46.3	39.9	0.074
Coronary artery disease	11.2	10.2	0.64
Stroke	2.1	3.8	0.25
Atrial fibrillation	3.7	6.4	0.136
Chronic kidney disease	6.2	5.7	0.76
History of cardiovascular event**	16.9	18.1	0.71
Medication classes used			
Antihypertensive	48.8	48.3	0.94
Antidiabetes††	15.3	10.3	0.033
Agents for hyperlipidemia or coronary heart disease‡‡	35.6	27.9	0.013

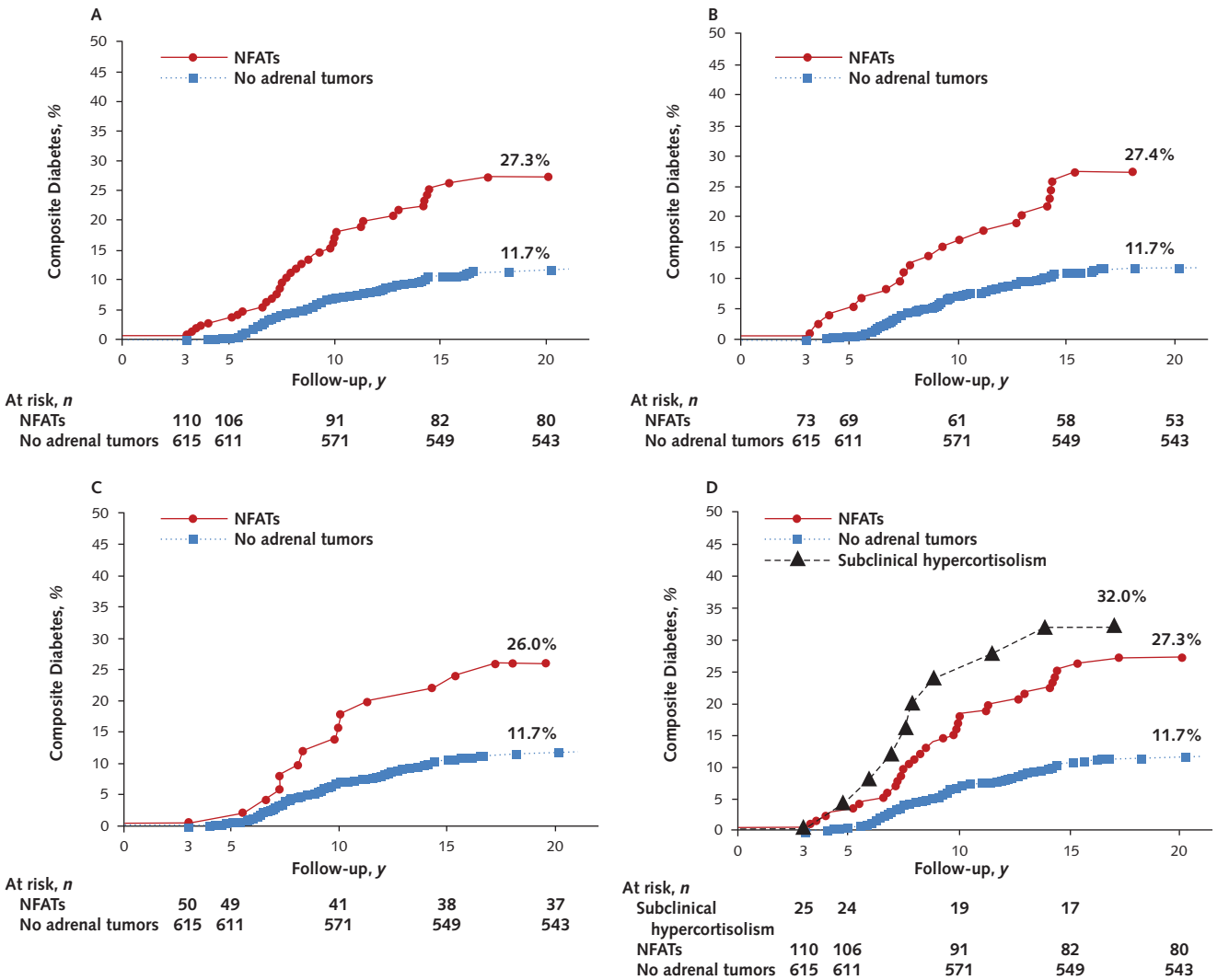
* Values are percentages unless otherwise indicated.
† Calculated with *t* test (continuous variables) or chi-square or Fisher exact test (categorical variables).
‡ Never-smoker or former smoker who quit >6 mo before.
§ Physician diagnosis and/or ≥2 separate hemoglobin A_{1c} levels of 5.7% to 6.4% without treatment with oral hypoglycemic agents (other than metformin) or injectable diabetes medications.
‖ Physician diagnosis or ≥2 separate hemoglobin A_{1c} levels ≥6.5%.
¶ Combination of prediabetes and diabetes.
** Myocardial infarction, ischemic stroke, heart failure, atrial fibrillation, or interventional coronary procedure (such as coronary catheterization or coronary artery bypass graft surgery).
†† Oral hypoglycemics or insulin.
‡‡ Aspirin, nitrates, statins, fibrates, or niacin.

Statistical Analysis

We present demographic and clinical characteristics using counts and proportions for categorical variables and means and SDs for continuous variables. Categorical variables were compared using the Fisher exact test or the chi-square test, and continuous variables were compared using the *t* test.

We fitted multivariable generalized linear regression models with binomial family and log-link functions to assess cross-sectional associations between NFATs and the prevalence of outcomes at baseline. Model 1 was adjusted for age, BMI, sex, race, and smoking

Figure 2. Cases of incident composite diabetes during longitudinal follow-up.



Eligible participants had no diabetes at baseline (the time of imaging) and had ≥3 y of follow-up. NFAT = "nonfunctional" adrenal tumor. **A.** All eligible participants (n = 110 with NFATs and 615 without adrenal tumors). Those with NFATs had subclinical hypercortisolism excluded on the basis of either 1-mg dexamethasone suppression test or 24-h urinary free cortisol level. **B.** Participants without adrenal tumors (n = 615) and those with NFATs who had subclinical hypercortisolism excluded on the basis of cortisol level ≤50 nmol/L on 1-mg dexamethasone suppression test (n = 73). **C.** Participants without adrenal tumors (n = 615) and those with NFATs who had subclinical hypercortisolism excluded on the basis of 24-h urinary free cortisol level <138 nmol (n = 50). **D.** Exploratory analysis in which participants with adrenal tumors who were initially excluded from the main analysis due to subclinical hypercortisolism were included.

status. Model 2 was adjusted for the variables in model 1 as well as other clinically relevant cardiovascular and metabolic diagnoses (hypertension, composite diabetes, hyperlipidemia, cardiovascular events, and chronic kidney disease). For these models, we derived and reported unadjusted and multivariable-adjusted prevalence ratios (PRs) and 95% CIs.

Primary analyses evaluated the independent relation between exposure status and the development of each incident outcome using adjusted generalized linear models with Poisson family and log-link functions to derive risk ratios (RRs) (incidence) and incidence rate ratios (23). Risk and rate ratios were derived for participants who had at least 3 years of follow-up and did not have the outcome in question at baseline. We used 3 multivariable models. Models 1 and 2 were described earlier; model 3 included all variables in models 1 and 2 as well as variables for the use of individual medication classes. In secondary analyses, we evaluated the association between NFAT size and cortisol levels by using linear regression.

A 2-tailed P value less than 0.05 was deemed statistically significant. All statistical analyses were performed using SAS, version 9.3 (SAS Institute).

Role of the Funding Source

The investigators were funded by the National Institutes of Health and the Doris Duke Charitable Foun-

Table 2. "Nonfunctional" Adrenal Tumors and Risk for Incident Outcomes*

Variable	Hypertension	Hyperlipidemia
Participants with incident events‡ among total eligible participants with nonfunctional adrenal tumors§, *n/N (%)*	19/74 (25.7)	15/87 (17.2)
Person-years at risk	519	617
Participants with incident events‡ among total eligible participants with no adrenal tumors§, *n/N (%)*	125/400 (31.3)	66/461 (14.3)
Person-years at risk	3318	3687
Unadjusted risk ratio (95% CI)	0.82 (0.51–1.33)	1.20 (0.69–2.11)
Unadjusted rate ratio (95% CI)	0.97 (0.56–1.58)	1.35 (0.72–2.40)
Multivariable model 1‖		
Risk ratio (95% CI)	0.83 (0.51–1.35)	1.06 (0.58–1.92)
Rate ratio (95% CI)	0.95 (0.58–1.55)	1.17 (0.64–2.13)
Multivariable model 2¶		
Risk ratio (95% CI)	0.76 (0.46–1.26)	1.03 (0.55–1.91)
Rate ratio (95% CI)	0.85 (0.51–1.41)	1.10 (0.59–2.05)
Multivariable model 3**		
Risk ratio (95% CI)	0.93 (0.55–1.57)	0.95 (0.51–1.78)
Rate ratio (95% CI)	1.03 (0.61–1.72)	1.04 (0.55–1.95)

* Results of adjusted regression models to evaluate the risk for incident outcomes in participants with nonfunctional adrenal tumors versus those without adrenal tumors are shown.
† Incident events of composite diabetes do not sum to the total number of incident events of type 2 diabetes and prediabetes because 15 participants who developed incident type 2 diabetes had a diagnosis of prediabetes at baseline.
‡ Outcome that was not present at baseline assessment but developed during follow-up.
§ Includes those who did not have the outcome of interest at baseline and who had ≥3 y of follow-up data to assess the incident development of this outcome over time.
‖ Includes adjustment for age, body mass index, sex, race, and smoking status.
¶ Includes adjustment for model 1 variables plus other clinically relevant baseline cardiovascular and metabolic diagnoses (hypertension, composite diabetes, hyperlipidemia, cardiovascular events, and chronic kidney disease).
** Includes adjustment for model 2 variables plus use of antihypertensive medications, antidiabetes medications (oral hypoglycemics and insulin), and medications to treat coronary artery disease or hyperlipidemia (antiplatelet agents, nitrates, statins, fibrates, and niacin).

dation. Neither funding source played a role in the study's design, conduct, or reporting.

RESULTS

Study Population and Baseline Metabolic and Cardiovascular Outcomes

Baseline characteristics of the study population are shown in Table 1. Participants with NFATs were slightly younger, had higher BMI, and had higher prevalence of prediabetes and diabetes than those without adrenal tumors. In adjusted regression models, NFATs were independently associated with a higher prevalence of baseline composite diabetes (Appendix Table, available at www.annals.org). This association was present whether subclinical hypercortisolism was excluded using the DST (adjusted PR, 1.62 [95% CI, 1.16 to 2.27]; n = 164 with NFATs and 1237 without adrenal tumors) or the 24-hour UFC level (adjusted PR, 1.81 [CI, 1.13 to 3.91]; n = 104 with NFATs and 1237 without adrenal tumors).

NFATs and Incident Outcomes

Among participants with at least 3 years of follow-up, the mean duration of follow-up was 7.2 years (range, 3.0 to 23.1 years) for those with NFATs and 7.8 years (range, 3.0 to 22.1 years) for those without adrenal tumors. Incident composite diabetes was detected in 27.3% of participants with NFATs and 11.7% of those without adrenal tumors (Figure 2, *A*). Participants with NFATs had a significantly higher risk for composite diabetes than those without adrenal tumors (absolute risk, 15.6% [CI, 6.9% to 24.3%]; adjusted RR, 1.87 [CI, 1.17 to 2.98]) (Table 2). There were no other significant associations between NFATs and other incident outcomes; however, wide CIs preclude firm conclusions (Table 2). Of note, among eligible participants in these analyses for incident composite diabetes, there were no major differences in demographic profiles, comorbidities, medication use, duration of follow-up, or assessment of pertinent laboratory values (Table 3).

Sensitivity Analyses for Incident Composite Diabetes

The relationship between NFATs and incident composite diabetes remained stable regardless of whether subclinical hypercortisolism was excluded using the 1-mg DST (unadjusted RR, 2.34 [CI, 1.43 to 3.84]; adjusted RR, 1.78 [CI, 1.03 to 3.08]) or the 24-hour UFC level (unadjusted RR, 2.22 [CI, 1.23 to 4.01]; adjusted RR, 2.10 [CI, 1.13 to 3.91]) (Figure 2, *B* and *C*). Because 24-hour UFC level can be less sensitive than the DST at excluding subclinical hypercortisolism (21), we also used a stricter criterion of a 24-hour UFC level less than 96.6 nmol and observed no material difference in the result (adjusted RR, 2.40 [CI, 1.26 to 4.58]).

Table 2–Continued

Composite Diabetes†	Prediabetes	Type 2 Diabetes	Chronic Kidney Disease	Cardiovascular Events
30/110 (27.3)	23/110 (20.9)	14/126 (11.1)	15/152 (9.9)	13/138 (9.4)
807	807	902	1104	1019
72/615 (11.7)	36/615 (5.8)	44/646 (6.8)	62/715 (8.7)	55/629 (8.7)
4946	4946	5161	5651	5031
2.33 (1.52–3.57)	3.57 (2.12–6.03)	1.63 (0.89–2.98)	1.14 (0.65–2.00)	1.08 (0.59–1.97)
2.55 (1.61–3.96)	3.91 (2.21–6.79)	1.82 (0.92–3.38)	1.23 (0.65–2.20)	1.16 (0.59–2.16)
2.09 (1.33–3.27)	3.34 (1.93–5.80)	1.54 (0.81–2.92)	1.10 (0.59–2.05)	0.94 (0.49–1.78)
2.26 (1.44–3.54)	3.64 (2.10–6.31)	1.71 (0.90–3.25)	1.19 (0.64–2.24)	0.97 (0.50–1.85)
2.03 (1.29–3.19)	3.26 (1.87–5.69)	1.50 (0.79–2.87)	0.99 (0.52–1.86)	0.78 (0.41–1.50)
2.17 (1.37–3.42)	3.59 (2.05–6.28)	1.63 (0.85–3.14)	1.15 (0.60–2.16)	0.76 (0.39–1.49)
1.87 (1.17–2.98)	3.19 (1.83–5.59)	0.99 (0.49–1.98)	1.00 (0.53–1.89)	0.72 (0.37–1.39)
1.98 (1.23–3.17)	3.56 (2.02–6.25)	1.10 (0.54–2.24)	1.12 (0.59–2.14)	0.69 (0.34–1.37)

Higher adiposity may confound the association between NFATs and incident composite diabetes; however, it may also be a consequence of NFATs that secrete low-grade glucocorticoids and may therefore be in the causal pathway between NFATs and incident diabetes. Considering the potential for confounding by higher adiposity, we repeated our analysis for incident composite diabetes after adjusting for the change in BMI over time because weight gain may be an important risk factor for diabetes. We observed a stable adjusted RR of 2.05 (CI, 1.29 to 3.27). Further, we repeated our analysis for incident composite diabetes after restricting the eligible participants to only those with a BMI less than 30 kg/m^2 such that the mean BMI was 25.0 kg/m^2 for participants with NFATs and 24.5 kg/m^2 for those without adrenal tumors. There were no other notable differences in demographic or comorbid factors between exposure groups, and the adjusted RR for incident composite diabetes remained significant at 2.44 (CI, 1.17 to 5.08).

Exploratory Analyses Including Subclinical Hypercortisolism

We explored whether there was a continuum of risk for incident composite diabetes when participants with subclinical hypercortisolism were included. Of the 89 participants with adrenal tumors who we had excluded because of adrenal hormone excess, 35 were excluded for subclinical hypercortisolism, and of these, only 25 were eligible for analyses of incident composite diabetes (≥3 years of follow-up and no diabetes at baseline). Subclinical hypercortisolism was defined by the DST in 21 of 25 (mean postdexamethasone cortisol level, 77 nmol/L) and by 24-hour UFC level in 4 of 25 (mean UFC level, 201 nmol). During a mean follow-up of 7.9 years, 32.0% of participants with subclinical hypercortisolism developed incident composite diabetes (Figure 2, *D*).

NFAT Size, Cortisol Levels, and Outcomes

In secondary analyses, larger NFAT size was associated with higher "normal" serum cortisol levels after a DST ($\beta = 0.42$; $P < 0.001$) and higher "normal" 24-hour UFC levels ($\beta = 1.33$; $P < 0.001$) (Figure 3, *A* and *B*). Both relationships remained significant after adjustment for age; sex; race; BMI; smoking status; and prevalent hypertension, diabetes, hyperlipidemia, cardiovascular events, and chronic kidney disease. The prevalence of type 2 diabetes was higher with higher postdexamethasone cortisol values (Figure 3, *C*).

There was no significant association between NFAT size or the degree of postdexamethasone cortisol suppression and the incidence of composite diabetes or other outcomes; however, the number of incident cases in these analyses was small, which limited robust analysis.

DISCUSSION

Adrenal tumors are discovered on 1% to 10% of abdominal imaging studies (1–5). More than 200 million computed tomography and magnetic resonance imaging studies were done worldwide in 2013, suggesting that the global prevalence of incidentally discovered adrenal tumors could be very high (24). Despite this, adrenal tumors often are not recognized or are lost to clinical follow-up (25), either because many health care providers do not understand the importance of screening for adrenal hormone excess or because the tumors are considered unimportant when another nonadrenal issue is the focus. Biochemical assessment of adrenal tumors is relevant because they may be functional in that they autonomously secrete hormones that cause overt or subclinical hormone excess and increase the risk for cardiovascular or meta-

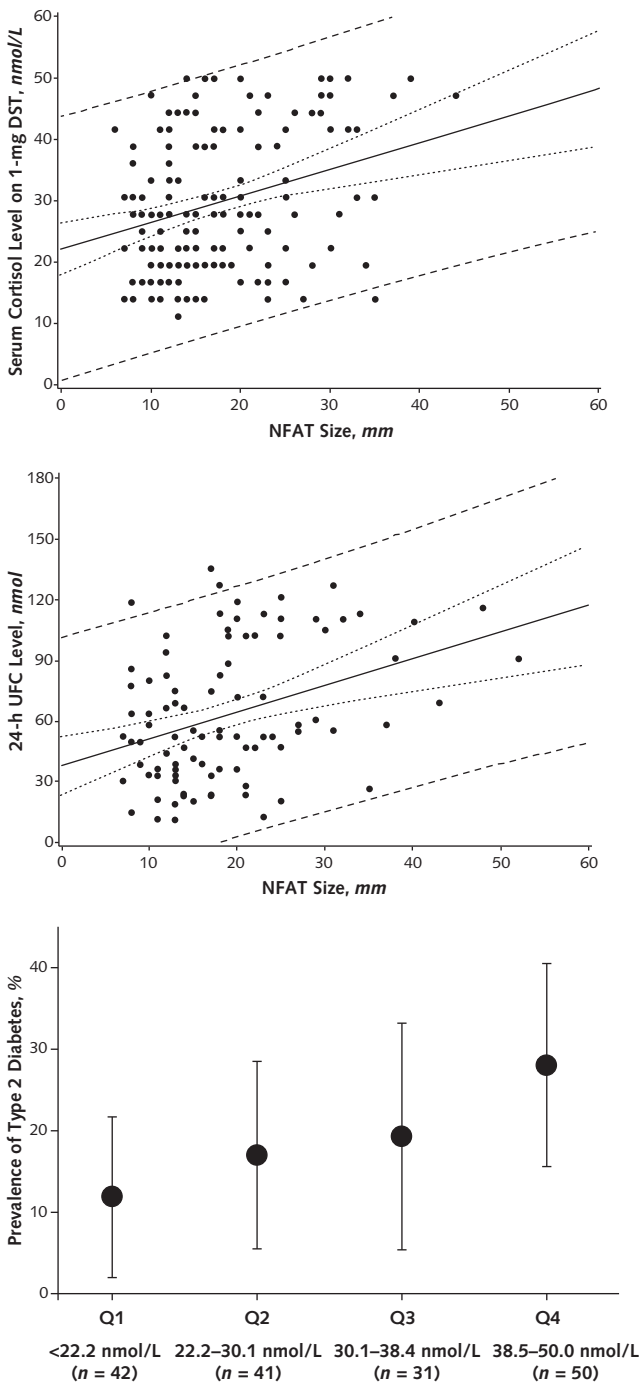
Table 3. Demographic and Clinical Characteristics of Eligible Participants for Analyses of Incident Composite Diabetes*

Characteristic	"Nonfunctional" Adrenal Tumor	No Adrenal Tumor	*P* Value†
Participants, *n*	110	615	
Mean age (SD), *y*	56.1 (12.1)	56.3 (14.5)	0.92
Female	84.6	80.5	0.37
Race			
White	65.5	67.3	0.97
Black	9.1	9.3	
Hispanic	7.3	6.2	
Other	18.2	17.3	
Mean body mass index (SD), kg/m^2	29.5 (6.9)	27.7 (6.4)	0.012
Mean follow-up (SD), *y*	7.3 (3.3)	8.0 (3.7)	0.060
Smoking status			
Nonsmoker‡	66.4	75.0	0.077
Current smoker	33.6	25.0	
Hypertension	45.5	38.9	0.21
Hyperlipidemia	40.0	31.7	0.099
Coronary artery disease	8.2	5.5	0.27
Stroke	0.9	3.4	0.23
Atrial fibrillation	1.8	4.2	0.29
Chronic kidney disease	7.3	2.4	0.015
History of cardiovascular event§	10.9	11.5	1.00
Medication classes used			
Antihypertensive	40.5	37.4	0.60
Agents for hyperlipidemia or coronary heart disease‖	22.7	17.6	0.23
Assessments within 1 y of final follow-up			
Basic metabolic panel¶	100.0	100.0	1.00
Lipid profile**	75.5	67.6	0.27
Hemoglobin A_{1c} level††	43.8	35.7	0.170
In-office blood pressure measurement	100.0	100.0	1.00

* Participants who had no baseline prediabetes or type 2 diabetes and ≥3 y of follow-up. Values are percentages unless otherwise indicated. Percentages may not sum to 100 due to rounding.
† Calculated with *t* test (continuous variables) or chi-square or Fisher exact test (categorical variables).
‡ Never-smoker or former smoker who quit >6 mo before.
§ Myocardial infarction, ischemic stroke, heart failure, atrial fibrillation, or interventional coronary procedure (such as coronary catheterization or coronary artery bypass graft surgery).
‖ Aspirin, nitrates, statins, fibrates, or niacin.
¶ Laboratory assessment that included electrolyte, creatinine, and glucose measurement.
** Laboratory assessment that included total cholesterol, triglyceride, and low- and high-density lipoprotein cholesterol measurement among participants not receiving lipid-lowering medications.
†† Laboratory assessment among participants not receiving medications for diabetes.

bolic outcomes (or both). However, most adrenal tumors are ultimately determined to be nonfunctional and are therefore considered to pose no health risk (12, 14). Our findings substantially extend and potentially redefine the current paradigm of NFATs: We observed that participants with apparent NFATs, as defined by current clinical guidelines, had approximately a 2-fold higher risk for incident diabetes than participants without adrenal tumors. Further, our results indicate that a potential mechanism underlying this increased risk for diabetes may be glucocorticoid excess within a range that is considered normal by accepted standards. In this regard, our findings suggest that NFATs may not be nonfunctional after all; rather, they

Figure 3. "Nonfunctional" adrenal tumor size, cortisol levels, and prevalence of type 2 diabetes.



DST = dexamethasone suppression test; NFAT = nonfunctional adrenal tumor; Q = quartile; UFC = urinary free cortisol. **Top.** Relationship between NFAT size and degree of serum cortisol suppression after 1-mg DST, where all values are ≤50 nmol/L. **Middle.** Relationship between NFAT size and 24-h UFC level, where all values are <138 nmol. Solid lines are mean regression lines, dotted lines indicate 95% CIs for mean regressions, and dashed lines indicate 95% CIs for observed values. **Bottom.** Prevalence of type 2 diabetes in participants with NFATs, by quartile of "normal" serum cortisol levels after 1-mg DST, where all values are ≤50 nmol/L. Circles indicate prevalence, and error bars represent 95% CIs.

may secrete small and inappropriate amounts of glucocorticoids that increase the risk for metabolic disease over time.

Prior longitudinal studies by Di Dalmazi (13), Debono (12), and Morelli (14) and their respective colleagues have described associations between adrenal tumors with subclinical hypercortisolism and incident cardiovascular events (14) and mortality (12, 13). These 3 studies used the NFAT group as the control and did not include comparisons with participants without adrenal tumors. Whether the higher risk for cardiovascular events and death associated with hypercortisolism in these studies was mediated by the development of incident insulin resistance or diabetes–a major risk factor for death (26)–was not directly evaluated. In contrast, our study was designed to focus only on NFATs versus no adrenal tumors; however, we also conducted an exploratory analysis that included a small population of participants with subclinical hypercortisolism that suggested a continuum of risk across these classifications. Collectively, our studies (12–14) suggest a continuum of metabolic and cardiovascular risk: Persons with NFATs may have an increased risk for insulin resistance and diabetes compared with those without adrenal tumors, and the addition of subclinical hypercortisolism may further increase the risk for cardiovascular events and death, which are dramatically increased in the rare instance of overt Cushing syndrome (27, 28) (**Appendix Figure**, available at www.annals.org). In contrast to the studies by Di Dalmazi and Morelli and their respective colleagues, we did not have measures of adrenocorticotropic hormone (ACTH) because our study was observational and ACTH is rarely measured in patients with NFATs and those without adrenal tumors. These prior studies reported that ACTH levels were detectable and slightly higher in persons with NFATs than in those with subclinical hypercortisolism (13, 14); therefore, the demonstration that ACTH levels are slightly higher in participants with no adrenal tumors than in those with NFATs could have further supported a continuum of glucocorticoid excess to parallel the risk for incident diabetes we observed.

Some small cross-sectional studies have suggested a potential link between NFATs and cardiometabolic diseases (10, 17–19). Androulakis and associates showed that persons with NFATs had greater insulin resistance indices and endothelial dysfunction than healthy control participants without adrenal tumors (17). Further, they observed associations between higher carotid intima–media thickness and higher cortisol levels within the nonfunctional range, suggesting that even normal cortisol concentrations may confer a spectrum of risk. The findings of our secondary analyses showed that higher cortisol secretion within the presumed normal range was associated with larger NFAT size and higher prevalence of type 2 diabetes. Although we did not observe a significant relationship between NFAT size and incident outcomes, we presume that this effect was negated by the fact that larger NFATs (>4 cm) may have been preferentially surgically resected in accordance with current recommendations (1, 2, 4, 15, 16).

Cortisol is a potent glucocorticoid receptor (GR) and mineralocorticoid receptor (MR) agonist. As shown by Arlt and coworkers in their studies of adrenal steroid profiling using mass spectrometry (20), compared with the absence of adrenal tumors in healthy control participants, NFATs secrete higher levels of glucocorticoids that are not typically measured or captured by standard clinical assays of cortisol. Thus, our reliance on assessing cortisol as a surrogate for the functionality of adrenal tumors may be inadequate in that the spectrum of GR and MR agonists that are secreted may be much greater. Our findings provide general support for the speculation that adrenal tumors may continue to secrete low concentrations of GR or MR agonists (or both) that can contribute to diabetes and cardiovascular disease risk; therefore, future studies of NFATs should incorporate methods such as broad adrenal steroid profiling to better evaluate the spectrum of GR and MR agonists that might account for our findings of incident diabetes (20).

Our findings must be interpreted in the context of the limitations of our study design. First, observational studies can have confounding and selection bias. Second, because the root cause of adrenal neoplasia is undetermined, an alternative interpretation of our findings could be that an unknown factor that induces adrenal neoplasia may also increase the risk for diabetes. Regardless of the interpretation, the ultimate clinical applicability of our findings remains: Patients with NFATs have a higher risk for diabetes and, therefore, risk stratification should be considered.

Third, we recognize that selection bias may have played a role in how we classified NFATs and that bias in the ascertainment of outcomes could have influenced the result. We used documentation of diagnoses to screen for adrenal tumors and detected only 1346 participants among the more than 220 000 eligible participants without an adrenal hormonal diagnosis who underwent abdominal imaging. This prevalence of adrenal tumors on imaging (<1%) is much lower than in previous reports (3–5) and may reflect the fact that most incidentally discovered adrenal tumors were not officially included as diagnoses in the patient record or were lost to follow-up during clinical care of the primary indication for imaging. Therefore, our selection of participants with NFATs may have represented those who had more visits to their health care providers, more conscientious health care providers, or more abdominal imaging due to a greater burden of medical problems. However, we observed no major demographic or comorbidity differences in the eligible participants included in our analyses of incident composite diabetes, and both groups were followed for similar durations with comparable screening and assessments of outcomes at comprehensive health encounters.

Fourth, our findings may not be generalizable to men, given that our study population was predominantly female. This was unexpected and may be due to

the fact that women are more likely to visit and maintain longitudinal follow-up with their physicians (29, 30) and more likely to undergo abdominal imaging (of the >234 000 abdominal scans available, 65% were in women).

Fifth, we cannot exclude meaningful associations between NFATs and other outcomes where CIs suggest a potential relationship. It should be noted that our classification of diabetes outcomes was the most refined because it incorporated both documented diagnoses and supportive hemoglobin A_{1c} levels. In contrast, the classification of some other clinical outcomes (such as hypertension) relied on documentation of diagnoses alone, and the baseline prevalence of some of these outcomes was already high.

Sixth, we did not have repeated and longitudinal measurements of adrenal hormone levels or NFAT size to assess whether new or worsening adrenal hormone excess could account for our findings (12–14). It is possible that NFATs are related to risk for diabetes due to the development of incident subclinical hypercortisolism that we did not assess; however, the underlying message of our study–that NFATs should be recognized and monitored as potential risk factors for diabetes–would be unlikely to change even if we had repeated measures of hormone levels or NFAT size. Finally, we did not have ACTH levels to analyze, as discussed earlier.

In summary, our findings show a significantly higher risk for incident diabetes in persons with NFATs than in those without adrenal tumors. Given the high prevalence of incidentally discovered adrenal tumors that predominantly comprise benign NFATs, our findings have several important implications for general clinical practice and future research investigations. First, "nonfunctional" may be an inadequate and misleading term to ascribe to benign adrenal tumors because it minimizes the potential continuum of adrenal hormone secretion that can contribute to cardiometabolic risk; therefore, the currently accepted criteria by which adrenal tumors are classified as nonfunctional may need reevaluation. Second, these findings underscore the importance of recognizing incidentally discovered adrenal tumors as independent risk factors for diabetes that may warrant more frequent surveillance for glucose intolerance. Finally, future studies that include broad adrenal steroid metabolite profiling are needed to investigate whether NFATs secrete inappropriate amounts of glucocorticoid that evade current clinical practice and contribute to adverse outcomes.

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Reproducible Research Statement: *Study protocol:* Described in the text. *Statistical code and data set:* Available from Dr. Vaidya (e-mail, anandvaidya@bwh.harvard.edu).

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Appendix: Detailed Methods

Study Population

The study population was selected from the Research Patient Data Registry at Partners Inc., a centralized clinical data registry that includes patients from Brigham and Women's Hospital, Massachusetts General Hospital, and their affiliated partner hospitals. All study procedures were approved by the Partners institutional research and ethics review board. Our study protocol permitted use of the data registry to build a cohort of patients with adrenal disorders and control participants without adrenal disorders to evaluate exposures and outcomes. The cohort was deidentified once relevant data were extracted from medical records; personal identifiers were not saved in the database. We followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement of reporting.

We performed queries within the Research Patient Data Registry to identify all patients who had undergone computed tomography or magnetic resonance imaging of the abdomen for any indication between 1991 and 2014 (n = 234 267) (Figure 1). Adrenal tumors can also occasionally be detected on some chest computed tomography or magnetic resonance imaging studies that extend into the abdominal cavity; however, we did not include chest imaging in our selection process. From this population, we excluded participants who had a documented diagnosis (health care provider registration of the diagnosis in the medical record problem list or use of a diagnostic code from the International Classification of Diseases, Ninth Revision) for any adrenal hormonal disorder or tumor (Figure 1).

Potentially "exposed" persons were identified by a documented diagnosis of an "adrenal tumor," "adrenal mass," "adrenal nodule," or "adrenal incidentaloma" (n = 1346). Although it is likely that more than 1346 participants had evidence of an adrenal tumor on imaging, this method to screen for potentially exposed participants captured only those whose health care providers officially documented the diagnosis. We identified potentially "unexposed" persons by performing a blinded computer-based match in a 3:1 ratio (matched by age, sex, and race) to identify participants who did not have a documented diagnosis for any adrenal tumor (n = 4041). From these 5387 potentially exposed and unexposed study participants, we arbitrarily selected 2500 participants (in an approximate 2:1 ratio of potentially exposed to potentially unexposed participants) to undergo individual and detailed medical record review to confirm exposure status and to assess cardiometabolic outcomes and other potential confounders (Figure 1).

Assessment of Main Exposure

To confirm exposure status, we analyzed individual medical records. The exposure of interest was NFATs. Participants with no adrenal tumor were considered to be unexposed. To confirm benign NFATs, we excluded participants who did not have an adrenal mass detected on their official abdominal imaging report, had imaging characteristics to suggest a malignant or nonadenomatous adrenal mass, did not have biochemical assessments for subclinical hypercortisolism, had any biochemical evidence of adrenal hormone hyperfunction (see the next paragraph), had a documented diagnosis of any adrenal hormone disorder, used any systemic glucocorticoid for at least 3 months, were not adults (aged <18 years), and had insufficient medical history to confirm the presence of an adrenal mass (Figure 1). Radiographic reports were reviewed to confirm the size and location of adrenal masses on their first detection. In instances where multiple or bilateral adrenal masses occurred, we recorded the size of the largest mass or nodule.

We used biochemical test results to exclude participants with adrenal tumors who might have subclinical or overt adrenal hormone excess. Participants with potential subclinical hypercortisolism were excluded if they had a serum cortisol level greater than 50 nmol/L on a 1-mg DST, a 24-hour UFC level of at least 138 nmol, or both. Of the remaining 244 participants, 70% had serum aldosterone and plasma renin activity measurements to assess for primary aldosteronism, and we therefore further excluded participants (n = 2) with po-

tential subclinical or overt primary aldosteronism if they had an aldosterone–renin ratio greater than 30 ng/dL per ng/mL per hour or a combination of a serum aldosterone level greater than 15 ng/dL and plasma renin activity less than 1.0 ng/mL per hour (22). After these exclusions, we confirmed 242 participants with NFATs (Figure 1), among whom subclinical hypercortisolism was excluded using the 1-mg DST (n = 164), 24-hour UFC level (n = 104), or both (n = 28).

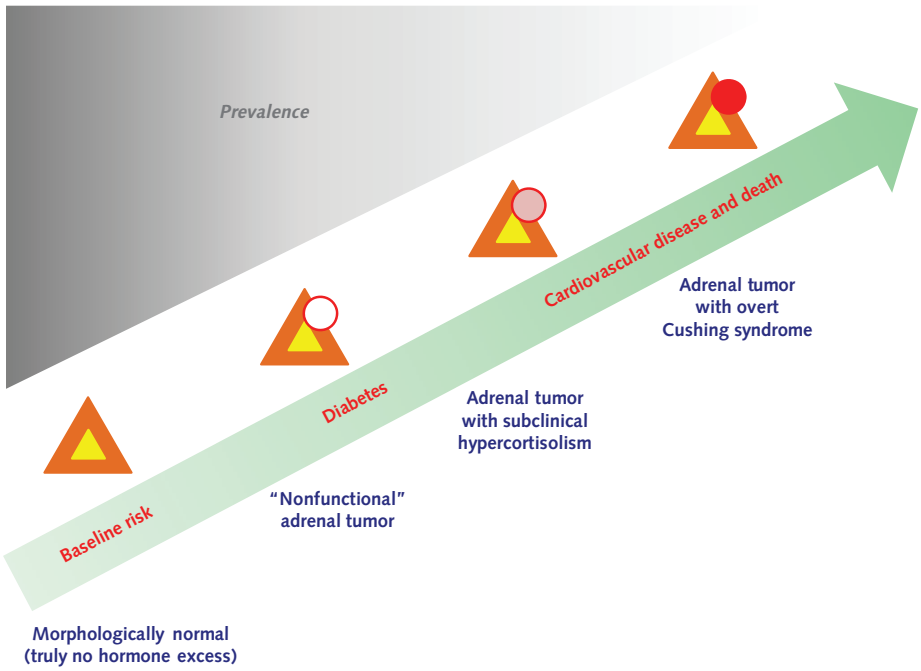
We conducted similar detailed chart reviews on potentially unexposed participants to confirm that they had no adrenal mass or nodules on abdominal imaging reports and no evidence or documentation of adrenal hormonal disorders or diagnoses, resulting in a population of 1237 participants with confirmation of no adrenal tumors or known adrenal hormonal disorders (Figure 1).

Appendix Table. Prevalence Ratios (95% CIs) for Association Between "Nonfunctional" Adrenal Tumors and Individual Diagnoses at Baseline Versus Absence of Adrenal Tumors*

Variable	Hypertension	Hyperlipidemia	Composite Diabetes	Prediabetes	Type 2 Diabetes	Chronic Kidney Disease	Cardiovascular Events
Participants with diagnosis at baseline among participants with nonfunctional adrenal tumors, *n/N (%)*	132/242 (54.6)	112/242 (46.3)	69/242 (28.5)	19/242 (7.9)	50/242 (20.7)	15/242 (6.2)	41/242 (16.9)
Participants with diagnosis at baseline among participants with no adrenal tumor, *n/N (%)*	624/1237 (50.4)	494/1237 (39.9)	214/1237 (17.3)	38/1237 (3.1)	176/1237 (14.2)	70/1237 (5.7)	224/1237 (18.1)
Unadjusted	1.08 (0.89–1.30)	1.16 (0.94–1.42)	1.64 (1.25–2.16)	2.56 (1.47–4.43)	1.45 (1.06–1.99)	1.10 (0.63–1.91)	0.94 (0.67–1.31)
Multivariable model 1†	1.16 (0.95–1.41)	1.19 (0.96–1.48)	1.63 (1.22–2.19)	2.37 (1.32–4.23)	1.45 (1.03–2.04)	1.44 (0.79–2.61)	1.29 (0.89–1.88)
Multivariable model 2‡	1.11 (0.91–1.35)	1.12 (0.90–1.39)	1.42 (1.05–1.91)	2.16 (1.20–3.88)	1.23 (0.88–1.75)	1.26 (0.69–2.31)	1.17 (0.80–1.70)

* A total of 242 participants had nonfunctional adrenal tumors, and 1237 had no adrenal tumors.
† Includes adjustment for age, body mass index, sex, race, and smoking status.
‡ Includes adjustment for model 1 variables plus other clinically relevant cardiovascular and metabolic diagnoses (hypertension, composite diabetes, hyperlipidemia, chronic kidney disease, and cardiovascular events).

Appendix Figure. Schematic representation of the continuum of metabolic and cardiovascular risk associated with adrenal tumors.



Compared with morphologically normal adrenal glands that secrete no excess adrenocortical hormones, what we currently define as "nonfunctional" adrenal tumors (according to current criteria) are associated with a higher risk for diabetes. This risk may be attributed to low-grade secretion of adrenal glucocorticoid within ranges currently considered normal. The development of subclinical hypercortisolism, compared with nonfunctional adrenal tumors, increases the risk for cardiovascular events and death, whereas overt hypercortisolism (Cushing syndrome) carries a high risk for severe metabolic and cardiovascular complications. The importance of this continuum is underscored by the fact that nonfunctional adrenal tumors are highly prevalent, whereas subclinical hypercortisolism is less common and overt Cushing syndrome is rare.