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**Age-dependent and sex-dependent disparity in mortality in patients with adrenal incidentalomas and autonomous cortisol secretion: an international, retrospective, cohort study**

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(Article begins on next page)

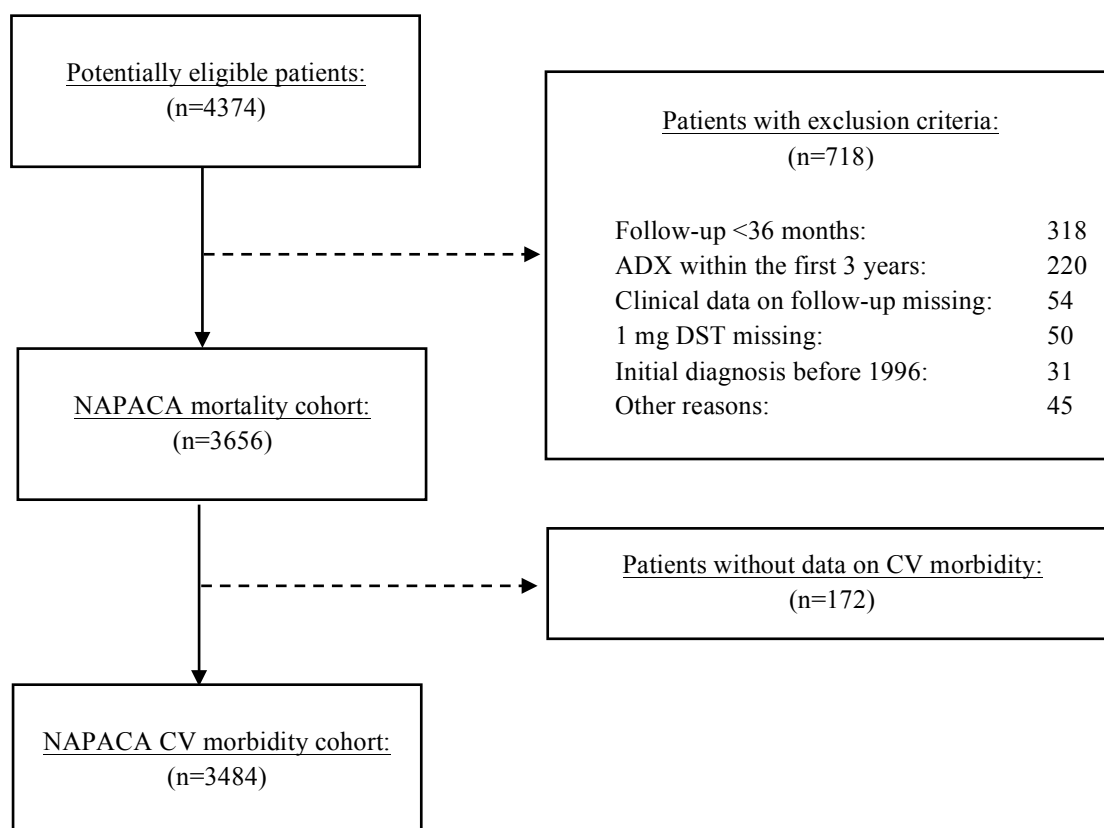
**Supplementary Table 6.** Cardiovascular events after initial diagnosis of the adrenal incidentaloma.

|                              | <b>All patients<br/>(n=3325)</b> | <b>NFA<br/>(n=1892)</b> | <b>PACS<br/>(n=1208)</b> | <b>ACS<br/>(n=225)</b> |
|------------------------------|----------------------------------|-------------------------|--------------------------|------------------------|
| Coronary intervention (n, %) | 146 (4.4%)                       | 69 (3.6%)               | 66 (5.5%)                | 11 (4.9%)              |
| Myocardial infarction (n, %) | 132 (4.0%)                       | 64 (3.4%)               | 60 (5.0%)                | 8 (3.6%)               |
| Stroke (n, %)                | 110 (3.3%)                       | 53 (2.8%)               | 44 (3.6%)                | 13 (5.8%)              |
| Venous thrombosis (n, %)     | 65 (2.0%)                        | 35 (1.8%)               | 24 (2.0%)                | 6 (2.7%)               |
| Pulmonary embolism (n, %)    | 43 (1.3%)                        | 19 (1.0%)               | 20 (1.7%)                | 4 (1.8%)               |
| MACE *                       | 297 (8.9%)                       | 145 (7.7%)              | 130 (10.8%)              | 22 (9.8%)              |

% refers to the number of patients per group for whom data were available for the given variable. \* at least one of the following events: acute myocardial infarction, coronary intervention, stroke, or cardiovascular death.

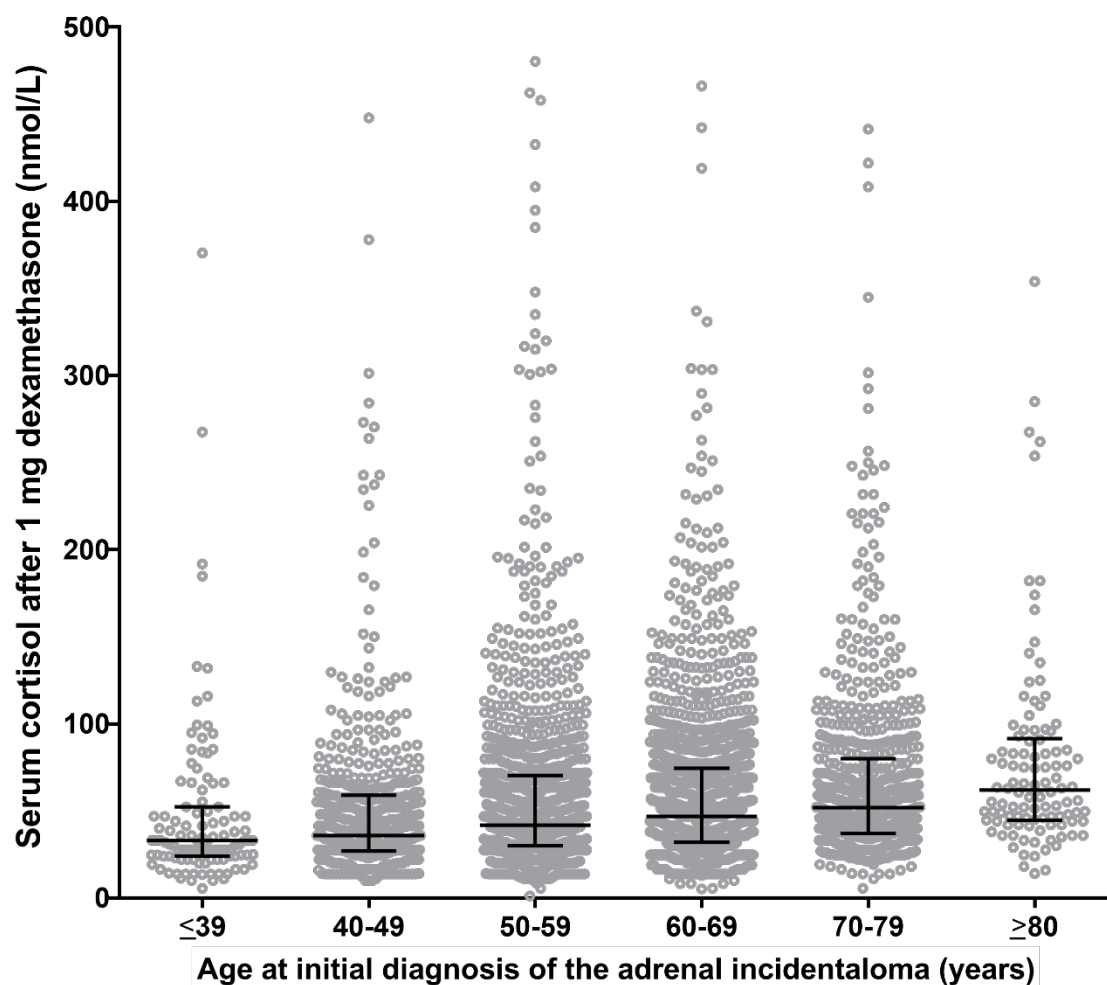
Abbreviations: ACS, autonomous cortisol secretion; HR, hazard ratio; MACE, major adverse cardiovascular event; NFA, non-functioning adenoma; PACS, possible autonomous cortisol secretion.

**Supplementary Figure 1.** Flow chart of patient selection.



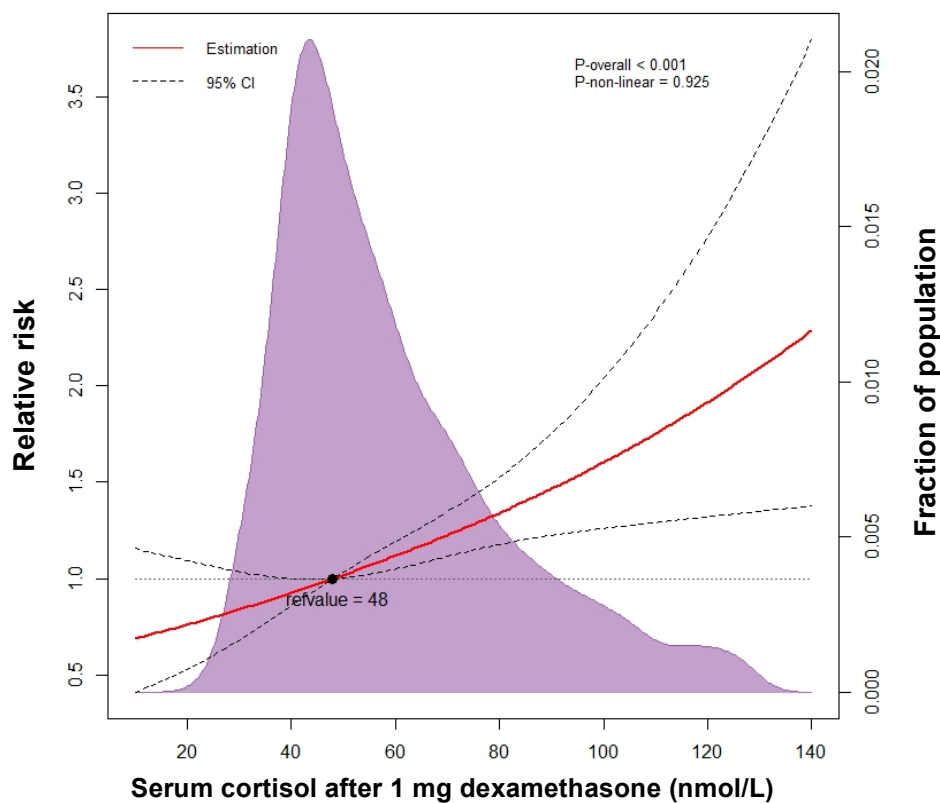
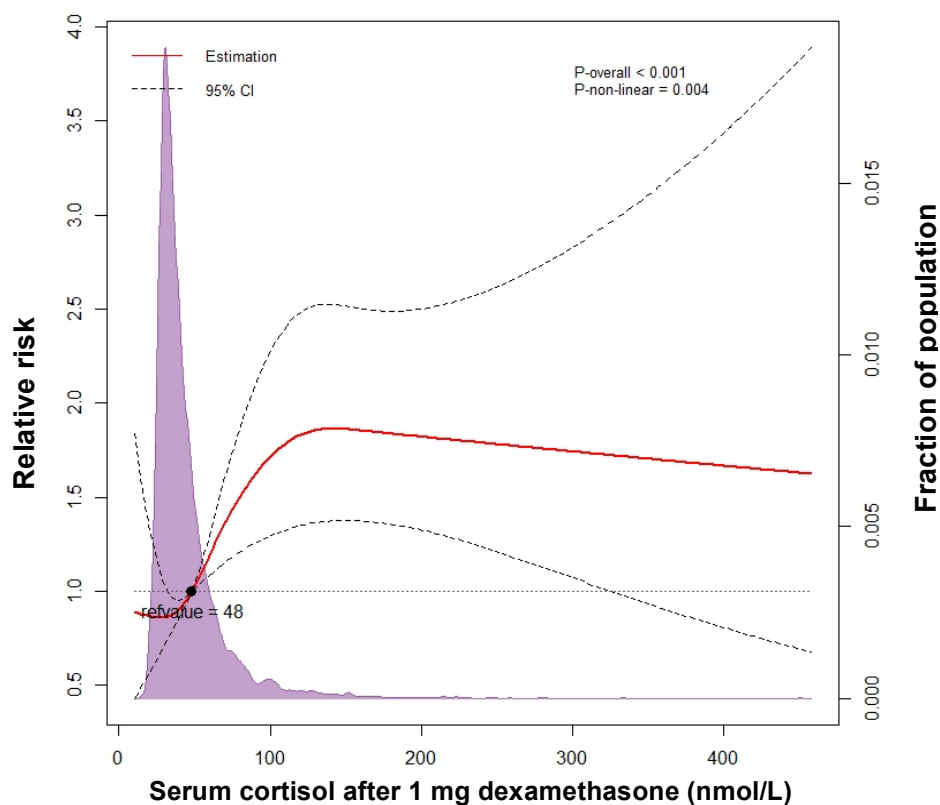
Abbreviations: ADX, adrenalectomy; CV, cardiovascular; DST, dexamethasone suppression test; NAPACA, non-aldosterone-producing adrenocortical adenoma.

**Supplementary Figure 2.** Serum cortisol after the 1 mg dexamethasone-suppression test according to age.



Each patient is represented by a single circle. Patients are sorted by age in decades. For each subgroup, the horizontal bars indicate the median serum cortisol levels after 1 mg dexamethasone along with the 95% confidence intervals.

**Supplementary Figure 3.** The functional form of the risk for death associated with different serum cortisol values after the 1 mg dexamethasone-suppression test (adjusted for age and sex).



The upper figure shows the entire cohort. The lower figure focuses only on patients with a serum cortisol after the 1 mg dexamethasone-suppression test of  $\leq 138$  nmol/L.

## Study protocol.

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| Project outline and justification for data request |
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### 1. Investigators

#### 1.1. Recipient Scientists, coordinators of the proposed project

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#### 1.3. Associated Investigators

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### 2. Project

#### 2.1. Name of Project

CLINICAL OUTCOMES OF AUTONOMOUS CORTISOL SECRETION IN ADRENAL INCIDENTALOMAS.

#### 2.2. Scientific context

The natural history of adrenal incidentalomas is largely unknown. A number of recent studies have provided evidence for an increased rate of cardiovascular (CV) events and mortality in patients with adrenal incidentalomas and autonomous cortisol secretion. However, evidence comes from limited patient cohorts with rather short follow-up. Furthermore, a heterogeneous definition of autonomous cortisol secretion hampered to recognize which levels of functional autonomy are associated to increased morbidity and/or mortality.

#### 2.3. Aim

The primary aim of the study is to assess mortality, CV events and the rate of vascular and metabolic comorbidities potentially linked to cortisol excess (hypertension, diabetes, dyslipidemia, obesity) in patients with adrenal incidentalomas and calculate HRs for patient groups stratified by cortisol values following the 1-mg overnight dexamethasone test.

Two types of CV events are differentiated:

- ‘major CV events’: clinically symptomatic myocardial infarction or stroke followed by hospitalization, or CV-related death.

- ‘minor CV events’: any other type of myocardial infarction and therapeutic procedures for coronary heart disease (PTCA, surgical bypass), any stroke, transient ischemic attack, heart failure, deep vein thrombosis, pulmonary embolism.

CV events are optimally registered by hospital medical records reporting one (or more) of the followings: acute myocardial infarction and related therapeutic procedures (PTCA, surgical bypass), stroke, TIA, heart failure, deep vein thrombosis, pulmonary embolism, sudden death, or death from cardiovascular cause.

However, it will be allowed to obtain data with telephonic interview using a structured questionnaire aimed to recognize the presence of the above-mentioned comorbidities and the occurrence of major CV events (clinically symptomatic myocardial infarction, stroke, death).

We will assess:

- Overall Survival (OS) as primary endpoint, defined as the time interval between the date of discovery of adrenal incidentaloma and the date of death from any cause, in patients stratified by different cortisol cut-offs.
- Event-free Survival (ES), defined as the time interval between the date of discovery of adrenal incidentaloma and the date of occurrence of a ‘major’ and/or ‘minor’ CV event, in patients stratified by different cortisol cut-offs.
- CV mortality, defined as death from any CV cause, in patients stratified by different cortisol cut-offs. Other causes of death will be specified, as well.

## 2.4. Methods

Retrospective, multi-center study

CV events are optimally registered by hospital medical records or can be obtained with telephonic interview using a structured questionnaire aimed to recognize the presence of the above-mentioned comorbidities and the occurrence of CV events.

Statistical analysis:

CV event rates will be expressed as the number of events per 1000 person-years.

Kaplan-Meier analysis will be used to construct survival curves and compute risks. Cox regression will be used for time-to-event analysis, and hazard ratios (HRs) computed with accompanying 95% confidence intervals (95% CI). Analysis will be stratified according to post-dexamethasone cortisol levels with three pre-specified cutoffs:  $\leq 50$  nmol/L (1.8  $\mu\text{g/dL}$ ), 51-138 nmol/L (1.9-5.0  $\mu\text{g/dl}$ ) and  $>138$  nmol/L ( $>5$   $\mu\text{g/dL}$ ), However, additional cutoffs might be analysed as well.

Depending on the level of comprehensive documentation of the patients’ characteristics two cohorts will be separately analysed:

- Cohort A: all requested data are available
- Cohort B: patients with missing data, but the following data are available: date of diagnosis the adrenal incidentaloma, result of 1mg DST, and survival status (or date of death).

## 2.5. Requested clinical annotations (type, justification)

Inclusion criteria:

- Age  $\geq 18$  years
- Adrenal mass detected by sensitive imaging tests (CT or MRI) not done for suspected adrenal disease since 1-1-2000 (modified in Oct 2018 to 1-1-1996 to allow longer follow-up time)

- Imaging characteristics typical of adrenal adenoma: unenhanced or delayed enhanced CT, MRI with chemical shift and FDG-PET are all acceptable to secure this diagnosis. In the absence of appropriate imaging study, results of 12-month follow-up showing unchanged mass characteristics can be considered as surrogate criterion.
- Availability of 1-mg overnight dexamethasone test results done at diagnosis or during follow-up
- Follow-up duration of at least 36 months (from the date of diagnosing the adrenal mass the first time)
- Availability of follow-up data on living status and occurrence of CV events (telephone interview allowed to capture data)

Exclusion criteria:

- Presence of clinical features of overt Cushing's syndrome
- $\text{UFC} \geq 2 \times \text{ULN}$
- ACTH-dependent Cushing syndrome
- Any active malignancy

Minimum clinical annotations:

- Date of birth, date of diagnosis
- Imaging characteristics (mass size, density on unenhanced CT (HU units), absolute or relative wash-out on delayed enhanced CT, results of MRI with chemical shift, results of FDG-PET, or imaging during follow-up > 12 months after initial imaging demonstrating unchanged tumor size)
- Serum cortisol following 1-mg DST, UFC, plasma ACTH (only serum cortisol after dexamethasone will be entered into the statistical model)
- Presence of obesity, hypertension, diabetes, dyslipidemia at initial diagnosis
- Information on prevalent CV events
- Date of last follow-up (date of death)
- Presence of obesity, hypertension, diabetes, dyslipidemia at last follow-up
- Information on incident CV events and date of first event

Minimum expected patient cohort per center: 50

Data acquisition via ENS@T registry

**2.6. Requested samples (type, justification of sample size)**

None

**2.7. Expected results**

To assess the existence of a relationship between risk of death and CV events with different levels of cortisol following an overnight 1-mg dexamethasone suppression test.

**2.8. Projected time frame**

Deadline for affirmation of participation in the study (e-mail to Fassnacht\_m@ukw.de): 31-10-2018

Deadline for data acquisition: 31-11-2018

Deadline for data analysis: 31-03-2019

Expected manuscript submission: 31-12-2019

Targeted Journals: depending on outcome



### **3. Publication policy**

1. Recipient scientist formally agrees with the provider(s) - at the time of the request or soon after the provider(s) have accepted the collaboration - the(ir) presence (if any) as co-authors in the publications originating from the collaboration.
2. Number of authors per center and order of authorships are specified as a general rule as follows: 51-100: 1 author; 101-150: 2; 151-200: 3; 201-250: 4; 251-350: 5; 351-450: 6; 450-600: 7. A minimum of 50 patients per center to qualify for authorship.
3. The order of authors depends on the number of recruited patients per center. However, due to the work already done and their role in analysing the data, the following authorship positions are already predefined: Massimo Terzolo as first author, Martin Fassnacht as last author. The next 5 most attractive positions will be given to the 5 best recruiting centers and these centers can choose in downward order on the respective position.
4. Depending on the contribution of each centre, or if number of authors has to be limited on the basis of a specific journal style, co-authors will be represented as “on behalf of ENS@T” and placed in an appropriate list depending on the Journal format (acknowledgment or collaborators list). In this case the recipient scientist will contact all provider(s) and obtain agreement.
5. The authors agree to acknowledge ENS@T contribution: “This project has been supported by the European Network for the Study of Adrenal Tumors (ENS@T).”

### **4. Conditions of data usage**

1. The Recipient scientist will use the data for research purposes only.
2. The data will be used by the Recipient scientist solely in connection with the Research Project as outlined above.
3. The Recipient scientist shall use the data in compliance with all applicable laws and government regulations of the Recipient's country.
4. The Recipient Scientist shall not release the data to any person other than the personnel under the Recipient Scientist's direct supervision.
5. When the Research Project is completed, a detailed description of the use of the data will be made available to the appropriate ENS@T Working Group
6. In the event that a journal publication or scientific article is published based on use of the data, the Recipient Scientist will send a copy of such publication, or the publication cite, promptly after it becomes available to the Recipient, to the appropriate ENS@T Working Group

Date                      1 December 2014 (updated 29 December 2016, and 4 October 2018)

Massimo Terzolo, Martin Fassnacht