5-6-2022

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

Timo Deutschbein

Giuseppe Reimondo

Guido Di Dalmazi

Irina Bancos

Jekaterina Patrova

See next page for additional authors

Recommended Citation
Deutschbein T, Reimondo G, Di Dalmazi G, Bancos I, Patrova J, Vassiliadi DA, Nekić AB, Debono M, Lardo P, Ceccato F, Petramala L, Prete A, Chiodini I, Ivović M, Pazaitou-Panayiotou K, Alexandraki KI, Hanzu FA, Loli P, Yener S, Langton K, Spyroglou A, Kocjan T, Zacharieva S, Valdés N, Ambroziak U, Suzuki M, Detomas M, Puglisi S, Tucci L, Delivanis DA, Margaritopoulos D, Dusek T, Maggio R, Scaroni C, Concistrè A, Ronchi CL, Altieri B, Mosconi C, Diamantopoulos A, Iñiguez-Ariza NM, Vicennati V, Pia A, Kroiss M, Kaltsas G, Chrisoulidou A, Marina LV, Morelli V, Arlt W, Letizia C, Boscaro M, Stigliano A, Kastelan D, Tsagarakis S, Athimulam S, Pagotto U, Maeder U, Falhammar H, Newell-Price J, Terzolo M, and Fassnacht M. Age-dependent and sex-dependent disparity in mortality in patients with adrenal incidentalomas and autonomous cortisol secretion: an international, retrospective, cohort study. Lancet Diabetes Endocrinol 2022.

Authors

Timo Deutschbein, Giuseppe Reimondo, Guido Di Dalmazi, Irina Bancos, Jekaterina Patrova, Dimitra Argyro Vassiliadi, Anja Barač Nekić, Miguel Debono, Pina Lardo, Filippo Ceccato, Luigi Petramala, Alessandro Prete, Iacopo Chiodini, Miomira Ivović, Kalliopi Pazaitou-Panayiotou, Krystallenia I Alexandraki, Felicia Alexandra Hanzu, Paola Loli, Serkan Yener, Katharina Langton, Ariadni Spyroglou, Tomaz Kocjan, Sabina Zacharieva, Nuria Valdés, Urszula Ambroziak, Mari Suzuki, Mario Detomas, Soraya Puglisi, Lorenzo Tucci, Danae Anastasia Delivanis, Dimitris Margaritopoulos, Tina Dusek, Roberta Maggio, Carla Scaroni, Antonio Concistrè, Cristina Lucia Ronchi, Barbara Altieri, Cristina Mosconi, Aristidis Diamantopoulos, Nicole Marie Iñiguez-Ariza, Valentina Vicennati, Anna Pia, Matthias Kroiss, Gregory Kaltsas, Alexandra Chrisoulidou, Ljiljana V. Marina, Valentina Morelli, Wiebke Arlt, Claudio Letizia, Marco Boscaro, Antonio Stigliano, Darko Kastelan, Stylianos Tsagarakis, Shobana Athimulam, Uberto Pagotto, Uwe Maeder, Henrik Falhammar, John Newell-Price, Massimo Terzolo, and Martin Fassnacht

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

Timo Deutschbein, Giuseppe Reimondo*, Guido Di Dalmazi, Irina Bancos, Jekaterina Patrova, Dimitra Argyro Vassiliadi, Anja Barač Nekić, Miguel Debono, Pina Lardo, Filippo Ceccato, Luigi Petramala, Alessandro Prete, Iacopo Chiodini, Miomira Ivović, Kalliopi Pazaitou-Panayiotou, Krystallenia I Alexandraki, Felicia Alexandra Hanzu, Paola Loli, Serkan Yener, Katharina Langton, Ariadni Spyroglou, Tomaz Kocjan, Sabina Zacharieva, Nuria Valdés, Urszula Ambroziak, Mari Suzuki, Mario Detomas, Soraya Puglisi, Lorenzo Tucci, Danae Anastasia Delivanis, Dimitris Margaritopoulos, Tina Dusek, Roberta Maggio, Carla Scaroni, Antonio Concistrè, Cristina Lucia Ronchi, Barbara Altieri, Cristina Mosconi, Aristidis Diamantopoulos, Nicole Marie Iñiguez-Ariza, Valentina Vicennati, Anna Pia, Matthias Kroiss, Gregory Kaltsas, Alexandra Chrisoulidou, Ljiljana V Marina, Valentina Morelli, Wiebke Arlt, Claudio Letizia, Marco Boscaro, Antonio Stigliano, Darko Kastelan, Stylianos Tsagarakis, Shobana Athimulam, Uberto Pagotto, Uwe Maeder, Henrik Falhammar, John Newell-Price, Massimo Terzolo†, Martin Fassnacht†*

Summary

Background The association between cortisol secretion and mortality in patients with adrenal incidentalomas is controversial. We aimed to assess all-cause mortality, prevalence of comorbidities, and occurrence of cardiovascular events in uniformly stratified patients with adrenal incidentalomas and cortisol autonomy (defined as non-suppressible serum cortisol on dexamethasone suppression testing).

Methods We conducted an international, retrospective, cohort study (NAPACA Outcome) at 30 centres in 16 countries. Eligible patients were aged 18 years or older with an adrenal incidentaloma (diameter ≥1 cm) detected between Jan 1, 1996, and Dec 31, 2015, and availability of a 1 mg dexamethasone suppression test result from the time of the initial diagnosis. Patients with clinically apparent hormone excess, active malignancy, or follow-up of less than 36 months were excluded. Patients were stratified according to the 0800–0900 h serum cortisol values after an overnight 1 mg dexamethasone suppression test; less than 50 nmol/L was classed as non-functioning adenoma, 50–138 nmol/L as possible autonomous cortisol secretion, and greater than 138 nmol/L as autonomous cortisol secretion. The primary endpoint was all-cause mortality. Secondary endpoints were the prevalence of cardiometabolic comorbidities, cardiovascular events, and cause-specific mortality. The primary and secondary endpoints were assessed in all study participants.

Findings Of 4374 potentially eligible patients, 3656 (2089 [57·1%] with non-functioning adenoma, 1320 [36·1%] with possible autonomous cortisol secretion, and 247 [6·8%] with autonomous cortisol secretion) were included in the study cohort for mortality analysis (2350 [64·3%] women and 1306 [35·7%] men; median age 61 years [IQR 53–68]; median follow-up 7·0 years [IQR 4·7–10·2]). During follow-up, 352 (9·6%) patients died. All-cause mortality (adjusted for age, sex, comorbidities, and previous cardiovascular events) was significantly increased in patients with possible autonomous cortisol secretion (HR 1·52, 95% CI 1·19–1·94) and autonomous cortisol secretion (1·77, 1·20–2·62) compared with patients with non-functioning adenoma. In women younger than 65 years, autonomous cortisol secretion was associated with higher all-cause mortality than non-functioning adenoma (HR 4·39, 95% CI 1·93–9·96), although this was not observed in men. Cardiometabolic comorbidities were significantly less frequent with non-functioning adenoma than with possible autonomous cortisol secretion and autonomous cortisol secretion (hypertension occurred in 1186 [58·6%] of 2024 patients with non-functioning adenoma, 944 [74·0%] of 1275 with possible autonomous cortisol secretion, and 179 [75·2%] of 238 with autonomous cortisol secretion; dyslipidaemia occurred in 724 [36·2%] of 1999 patients, 547 [43·8%] of 1250, and 123 [51·9%] of 237; and any diabetes occurred in 365 [18·2%] of 2002, 288 [23·0%] of 1250, and 62 [26·7%] of 232; all p values <0·001).

Interpretation Cortisol autonomy is associated with increased all-cause mortality, particularly in women younger than 65 years. However, until results from randomised interventional trials are available, a conservative therapeutic approach seems to be justified in most patients with adrenal incidentaloma.

Funding Deutsche Forschungsgemeinschaft, Associazione Italiana per la Ricerca sul Cancro, Università di Torino.

Lancet Diabetes Endocrinol 2022

Published **Online** May 6, 2022 https://doi.org/10.1016/S2213-8587(22)00100-0

See **Online/Comment** https://doi.org/10.1016/S2213-8587(22)00110-3

*Joint first authors

†Joint last authors

Department of Internal Medicine I, Division of Endocrinology and Diabetes, University Hospital, University of Würzburg, Würzburg, Germany (T Deutschbein MD, M Detomas MD, C L Ronchi MD, B Altieri MD, Prof M Kroiss MD, Prof M Fassnacht MD); **Medicover Oldenburg MVZ, Oldenburg, Germany** (T Deutschbein); **Department of Clinical and Biological Sciences, San Luigi Hospital, University of Turin, Turin, Italy** (G Reimondo MD, S Puglisi MD, A Pia MD, Prof M Terzolo MD); **Endocrinology and Prevention and Care of Diabetes Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy** (G Di Dalmazi MD, L Tucci MD, C Mosconi MD, V Vicennati MD, Prof U Pagotto MD); **Department of Medical and Surgical Sciences, Alma Mater University of Bologna, Bologna, Italy** (G Di Dalmazi, L Tucci, V Vicennati, Prof U Pagotto); **Division of Endocrinology, Diabetes and Metabolism, Mayo Clinic, Rochester, MN, USA** (I Bancos MD, D A Delivanis MD, N M Iñiguez-Ariza MD, S Athimulam MD);

Department of Clinical Science and Education, Södersjukhuset AB, Karolinska Institutet, Stockholm, Sweden (J Patrova MD); **Department of Endocrinology, Diabetes, and Metabolism, National Expertise Centre for Rare Endocrine Diseases, Evangelismos Hospital, Athens, Greece** (D A Vassiliadi MD, D Margaritopoulos MD, A Diamantopoulos MD, S Tsagarakis MD); **Department of Endocrinology, University Hospital Centre Zagreb, Zagreb, Croatia** (A B Nekić MD, T Dusek MD, Prof D Kastelan MD); **Department of Oncology and Metabolism, University of Sheffield, Sheffield, UK** (M Debono MD, Prof J Newell-Price FRCP); **Endocrinology, Department of Clinical and Molecular Medicine, Sant'Andrea Hospital, Sapienza University of Rome, Rome, Italy** (P Lardo MD, R Maggio MD, A Stigliano MD); **Endocrinology Unit, Department of Medicine DIMED, University-Hospital of Padova, Padova, Italy** (F Ceccato MD, C Scaroni MD, Prof M Boscaro MD); **Second Hypertension Unit, Department of Translational and Precision Medicine, University Sapienza, Rome, Italy** (L Petramala MD, A Concistrè MD, C Letizia MD); **Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, UK** (A Prete MD, C L Ronchi, Prof W Arlt MD); **Centre for Endocrinology, Diabetes, and Metabolism, Birmingham Health Partners, Birmingham, UK** (A Prete, C L Ronchi, Prof W Arlt); **NIHR Birmingham Biomedical Research Centre, University Hospitals Birmingham NHS Foundation Trust and University of Birmingham, Birmingham, UK** (A Prete, C L Ronchi, Prof W Arlt); **Istituto Auxologico Italiano, IRCCS, University of Milan, Milan, Italy** (Prof I Chiodini MD, V Morelli MD); **Clinic for Endocrinology, Diabetes, and Metabolic Diseases, University Clinical Centre of Serbia, Faculty of Medicine, University of Belgrade, Belgrade, Serbia** (M Ivović MD, L V Marina MD); **Department of Endocrinology, Theagenio Cancer Hospital, Thessaloniki, Greece**

Research in context

Evidence before this study

Adrenal incidentalomas are found in at least 3% of adults. In up to 50% of these people, endocrine investigations identify evidence of biochemical hypercortisolism without clinically overt glucocorticoid excess, a condition historically described as subclinical Cushing's syndrome. During preparation of the European Society of Endocrinology and European Network for the Study of Adrenal Tumours (ENSAT) 2016 Clinical Guidelines on Management of Adrenal Incidentalomas, a comprehensive literature search of PubMed, the NHS Economic Evaluation Database, and the Cochrane Database of Systematic Reviews and Database of Abstracts of Reviews of Effects was performed, from Jan 1, 2000, to Nov 30, 2014, for all systematic reviews and studies that had assessed any association between cortisol autonomy (defined as non-suppressible serum cortisol on dexamethasone suppression testing) with morbidity and mortality. This search revealed only two small studies, that together summarised 404 patients (including only 39 deaths), showing an increased mortality in patients with unsuppressed cortisol after dexamethasone. To confirm or refute this association, we initiated the present study under the auspices of ENSAT. Due to the paucity of available multicentre data for a sound power calculation, we aimed initially to collect data from at least 2000 patients. In 2021, we updated our initial literature search (to include literature from Dec 1, 2014, to July 31, 2021), and identified a systematic review from 2020 and a Swedish cohort study published in 2021. The systematic review, which included 1356 patients from nine studies, could not confirm the claimed association between cortisol autonomy and mortality, whereas the more recent cohort study, which included 1048 patients, found increased mortality in patients in whom serum cortisol was greater than 83 nmol/L after dexamethasone suppression testing.

Added value of this study

Our large, retrospective, international, cohort study, which included more than 3600 patients with adrenal adenomas and a follow-up of at least 3 years (median 7 years), provides additional strong evidence for an overall association of possible autonomous cortisol secretion (defined as 0800–0900 h serum cortisol of 50–138 nmol/L after an overnight 1 mg dexamethasone suppression test) and autonomous cortisol secretion (defined as >138 nmol/L) with all-cause mortality. To our knowledge, this is the first study to indicate that this risk varies by age and sex. Women younger than 65 years with autonomous cortisol secretion had the highest relative risk of death, with an adjusted hazard ratio (HR) of 4·39 (95% CI 1·93–9·96), whereas men older than 65 years did not appear to be at increased risk (HR 1·09, 95% CI 0·55–2·16) compared with patients with non-functioning adenoma. We also confirmed that the prevalence of cardiometabolic morbidity increases progressively with the degree of cortisol autonomy, which was more frequently detected in women and in the presence of bilateral tumours.

Implications of all the available evidence

Although our study confirms the association between cortisol autonomy, all-cause mortality and cardiometabolic morbidity, we highlight a need for caution with regard to therapeutic interventions. Our findings suggest that women younger than 65 years could benefit most from normalising cortisol secretion. However, only randomised interventional trials will be able to determine whether any intervention (either medical or surgical) is able to mitigate both cardiometabolic morbidity and mortality in patients with adrenal adenomas. Our study clearly provides the rationale and the statistical basis for such a randomised trial. Until these data are available, however, a conservative approach seems reasonable, especially in men aged 65 years or older.

Introduction

Over the past several decades, wider availability and use of cross-sectional imaging has resulted in an increased incidental detection of clinically inapparent adrenal masses. Such adrenal incidentalomas have an increasing age-dependent prevalence, ranging from 3% in adults aged 50 years to 10% in adults older than 70 years.[1–3]

Most of these tumours are benign non-functioning adrenal adenomas.[3,4] However, endocrine investigations find biochemical evidence of hypercortisolism in 30–50% of patients without clinically overt glucocorticoid excess, which has historically been described as subclinical Cushing's syndrome. As only very few of these patients progress to having overt Cushing's syndrome,[5,6] it is currently recommended that patients be categorised by the 0800–0900 h serum cortisol value after an overnight 1 mg dexamethasone suppression test; non-functioning adenoma was defined as less than 50 nmol/L, possible autonomous cortisol secretion as 50–138 nmol/L, and autonomous cortisol secretion as greater than 138 nmol/L.[7]

In 2019, a cohort study reported a slightly increased mortality in 969 patients with adrenal incidentalomas compared with 2907 patients without adrenal incidentalomas, as outlined by a multivariable-adjusted hazard ratio (HR) for mortality of 1·14 (95% CI 1·00–1·29).[8] Furthermore, several studies have focused on the association between adrenocorticotropic hormone (ACTH)-independent cortisol autonomy (defined as non-suppressible serum cortisol on dexamethasone suppression testing) and mortality in these patients, but the results are conflicting. Three single-centre studies that included 198–365 patients[9–11] and one population-based study from Sweden (that included 1048 patients)[12] reported an increased mortality in people who had elevated cortisol after the 1 mg dexamethasone suppression test. By contrast, a systematic review (including 32 studies and 4121 patients) found

cardiovascular and metabolic risk factors (ie, hypertension, any diabetes, dyslipidaemia, and obesity) to be more prevalent in the presence of what the authors termed mild autonomous cortisol excess.[6] However, mortality was only studied in a subgroup of 1356 patients from nine studies and was similar to that in patients with non-functioning adrenal adenomas. In line with this finding, a population-based study from Minnesota, USA, compared 1004 patients with adrenal incidentalomas to sex-matched and age-matched participants without adrenal tumours and found no difference in mortality.[13] These discrepancies might be explained in part by the heterogeneity of the criteria used for the definition of cortisol autonomy in these studies.

Taken together, although it is plausible that there is an association between low-grade cortisol excess (as shown by dexamethasone suppression test), comorbidities (including cardiovascular events), and mortality, previously studies were limited by small sample sizes and potential single-centre bias. We aimed to assess all-cause mortality, prevalence of comorbidities, and occurrence of cardiovascular events in patients with adrenal incidentalomas, applying unified diagnostic criteria to define cortisol autonomy.

Methods

Study design

We conducted an international, retrospective, cohort study at 30 centres in 16 countries (NAPACA Outcome). The study was approved by the European Network for the Study of Adrenal Tumours (ENSAT) in December, 2014. Each centre had local ethical approval for pseudonymised, standardised, phenotype recording. All patients provided written informed consent to participate (except for at nine centres where the ethics committees waived this requirement). Centres were asked to report patients in a consecutive manner to minimise selection bias. Retrospective data acquisition was done over a 56-month period (from January, 2015, to August, 2019).

Participants

Patients were eligible for inclusion if they were aged 18 years or older and had an adrenal incidentaloma (unilateral or bilateral with a diameter ≥1 cm) detected by cross-sectional imaging between Jan 1, 1996, and Dec 31, 2015, diagnosis of an adrenal adenoma based on typical imaging characteristics[7] or follow-up imaging excluding malignancy, availability of a 1 mg dexamethasone suppression test result from the time of the initial diagnosis, and follow-up data on survival status and occurrence of cardiovascular events with a follow-up duration of at least 36 months. Exclusion criteria were a confirmed diagnosis of clinically overt Cushing's syndrome (defined according to an established clinical practice guideline[14] as presence of hypercortisolism with specific clinical signs of cortisol excess, such as easy bruising, facial plethora, and proximal myopathy), ACTH-dependent hypercortisolism, urinary free cortisol greater than or equal to two times the upper limit of normal, phaeochromocytoma, primary aldosteronism, surgery within 36 months after initial diagnosis, or any active malignancy (including adrenocortical carcinoma) at the time of primary diagnosis of the adrenal mass. The considerable variation in use of other diagnostic tests at different centres, including plasma ACTH and urinary free cortisol, precluded formal analysis of other tests.

Procedures

Following the European Society of Endocrinology and ENSAT 2016 Clinical Guidelines on Management of Adrenal Incidentalomas,[7] patients were categorised according to their first 0800–0900 h serum cortisol result on an overnight 1 mg dexamethasone suppression test after initial diagnosis of the adrenal incidentaloma; less than 50 nmol/L was classed as non-functioning adenoma, 50–138 nmol/L as possible autonomous cortisol secretion, and greater than 138 nmol/L as autonomous cortisol secretion. The conversion factor for serum cortisol in µg/dL is nmol/L divided by 27·59 (hence, important cutoffs for the 1 mg dexamethasone suppression test are 50 nmol/L or 1·8 µg/dL, and 138 nmol/L or 5·0 µg/dL).

We collected data on age, sex, and BMI from the time of the initial diagnosis of adrenal incidentaloma; tumour characteristics (ie, size and laterality); and medical history (eg, cardiometabolic risk factors and cardiovascular events) both at primary diagnosis and during follow-up. Diagnosis of comorbidities was done according to the existing guidelines available at the time of adrenal tumour diagnosis.

Outcomes

The primary endpoint was all-cause mortality. Prespecified secondary endpoints were prevalence of cardiometabolic comorbidities (hypertension, any diabetes, and dyslipidaemia), occurrence of cardiovascular events, and cause-specific mortality. The primary and secondary endpoints were assessed in all study participants. For cardiovascular morbidity, we defined a composite endpoint of the following major adverse cardiovascular events (MACE): myocardial infarction or coronary revascularisation (either bypass surgery or percutaneous intervention), stroke, or cardiovascular-related death. In addition, we collected data on venous thrombosis and pulmonary embolism.

Statistical analysis

Patients who had surgery after at least 36 months of follow-up were censored, setting the date of surgery as the date of last follow-up. For subgroup analyses, patients were categorised according to their age at diagnosis (<65 years *vs* ≥65 years, based on age-dependent thresholds established to assess cardiovascular risk in patients with diabetes or hypertension[15,16]), with separate analyses by sex.

(K Pazaitou-Panayiotou MD, A Chrisoulidou MD); **1st Department of Propaedeutic and Internal Medicine, Laiko Hospital, National and Kapodistrian University of Athens, Athens, Greece** (K I Alexandraki MD, Prof G Kaltsas MD); **Endocrinology and Nutrition, Hospital Clinic de Barcelona, Barcelona, Spain** (F A Hanzu MD); **Department of Endocrinology, Ospedale Niguarda Cà Granda, Milan, Italy** (P Loli MD); **Department of Endocrinology, Dokuz Eylul University School of Medicine, Izmir, Turkey** (Prof S Yener MD); **Institute of Clinical Chemistry and Laboratory Medicine, University Hospital Dresden, Dresden, Germany** (K Langton MD); **Klinik für Endokrinologie, Diabetologie und Klinische Ernährung, Universitäts-Spital Zürich, Zürich, Switzerland** (A Spyroglou MD); **University Hospital Munich, Ludwig-Maximilians-Universität München, Munich, Germany** (A Spyroglou, Prof M Kroiss); **Department of Endocrinology, Diabetes, and Metabolic Diseases, University Medical Centre Ljubljana, Ljubljana, Slovenia** (T Kocjan MD); **Department of Internal Medicine, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia** (T Kocjan); **Department of Endocrinology, University Hospital of Endocrinology, Medical University, Sofia, Bulgaria** (Prof S Zacharieva MD); **Hospital Universitario Central de Asturias, Oviedo, Spain** (N Valdés MD); **Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Oviedo, Spain** (N Valdés); **Hospital Universitario de Cabueñes, Gijón, Spain** (N Valdés); **Department of Internal Medicine and Endocrinology, Medical University of Warsaw, Warsaw, Poland** (U Ambroziak MD); **Eunice Kennedy Shriver National Institute of Child Health & Human Development (NICHD), National Institutes of Health, Bethesda, MD, USA** (M Suzuki MD); **Diagnostic and Interventional Radiology Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy** (C Mosconi); **Department of Endocrinology**

and Metabolism, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico (N M Iñiguez-Ariza); NIHR Birmingham Biomedical Research Centre, University of Birmingham and University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK (Prof W Arlt); Division of Endocrinology, Diabetes, Bone and Mineral Disorders, Henry Ford Health System, Detroit, MI, USA (S Athimulam); Comprehensive Cancer Center Mainfranken, University of Würzburg, Würzburg, Germany (U Maeder PhD, Prof M Fassnacht); Department of Endocrinology, Karolinska University Hospital, Stockholm, Sweden (H Falhammar MD); Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden (H Falhammar)

Correspondence to: Prof Martin Fassnacht, Department of Internal Medicine I, Division of Endocrinology and Diabetes, University Hospital, University of Würzburg, Würzburg 97080, Germany
fassnacht_m@ukw.de

Absolute numbers and percentages were calculated for categorical data. Missing values were discounted when calculating proportions. The results for continuous variables are expressed as medians with IQR. The intergroup differences between the different dexamethasone suppression test categories were analysed via χ^2 test. All-cause mortality was calculated as the time between the initial diagnosis of the adrenal incidentaloma and death or last follow-up.

A power analysis was performed on the basis of the assumption of a clinically meaningful HR of at least 1·5 for a two-group comparison and a mortality rate of about 10%. Using a type I error α of 0·05 and a power of 80%, about 2000 patients with 191 deaths would need to be included. Survival curves were constructed using the Kaplan-Meier method, and the log-rank test was used for subgroup analysis. Patients were censored either at the date of last follow-up, adrenalectomy, or death. Relevant prognostic variables were identified by univariable and multivariable analyses, using the Cox proportional hazards model. HRs are provided with 95% CIs. Multivariable Cox analyses included the three dexamethasone suppression test categories (non-functioning adenoma, possible autonomous cortisol secretion, and autonomous cortisol secretion) and known prognostic factors for all-cause mortality and cardiovascular events (age, sex, any diabetes, hypertension, dyslipidaemia, and any previous cardiovascular event) as covariables. To study the functional forms of a relationship between cortisol after the 1 mg dexamethasone suppression test as a continuous variable and all-cause mortality, we applied restricted cubic splines. For the subgroup analyses by age and sex, we used a formal three-way interaction test, using Cox regression for age (<65 years or ≥65 years), sex (male or female), and dexamethasone suppression test category (non-functioning adenoma, possible autonomous cortisol secretion, or autonomous cortisol secretion). Time to first MACE was defined as the time between the initial diagnosis of the adrenal incidentaloma and first documentation of any MACE thereafter. As a quality check for data integrity, a completeness index was calculated for each centre: patients with available follow-up data within the previous 12 months on Dec 31, 2018 were counted as complete (ie, centres with an index of ≥90% qualified for a subgroup analysis), and the results were then compared with those derived from the whole study group. Two-tailed p values of less than 0·05 were deemed significant.

Following the cutoff criteria of a study published in 2021,[12] we performed a post-hoc analysis where we divided our study cohort into four groups on the basis of

	All patients (n=3656)	Non-functioning adenoma (n=2089)	Possible autonomous cortisol secretion (n=1320)	Autonomous cortisol secretion (n=247)
Sex				
Women	2350 (64·3%)	1321 (63·2%)	860 (65·2%)	169 (68·4%)
Men	1306 (35·7%)	768 (36·8%)	460 (34·8%)	78 (31·6%)
Age, years	61 (53–68)	60 (52–67)	63 (56–70)	63 (55–70)
Age <65 years	2264 (61·9%)	1404 (67·2%)	726 (55·0%)	134 (54·3%)
Follow-up, years	7·0 (4·7–10·2)	7·2 (4·8–10·5)	6·9 (4·7–10·0)	6·9 (4·5–10·0)
BMI, kg/m²*	28·1 (25·0–32·3)	28·6 (25·4–32·6)	27·8 (24·6–31·9)	27·7 (24·3–31·9)
Tumour characteristics†				
Left side	1497 (44·6%)	946 (49·8%)	468 (38·1%)	83 (36·2%)
Right side	1093 (32·6%)	646 (34·0%)	385 (31·4%)	62 (27·1%)
Bilateral	764 (22·8%)	306 (16·1%)	374 (30·5%)	84 (36·7%)
Maximum tumour diameter, mm	22 (15–30)	20 (15–25)	26 (19–33)	29 (20–37)
1 mg dexamethasone suppression test serum cortisol result, nmol/L	47 (30–72)	33 (28–50)	72 (61–94)	190 (157–253)
Comorbidities				
Hypertension‡	2309 (65·3%)	1186 (58·6%)	944 (74·0%)	179 (75·2%)
Dyslipidaemia§	1394 (40·0%)	724 (36·2%)	547 (43·8%)	123 (51·9%)
Any diabetes¶	715 (20·5%)	365 (18·2%)	288 (23·0%)	62 (26·7%)
Previous cardiovascular events				
Myocardial infarction or coronary intervention, or both‖	199 (6·0%)	87 (4·6%)	96 (8·0%)	16 (7·1%)
Stroke**	70 (2·1%)	31 (1·6%)	27 (2·3%)	12 (5·3%)
Deep vein thrombosis or pulmonary embolism, or both††	62 (1·9%)	31 (1·7%)	26 (2·2%)	5 (2·2%)
At least one cardiovascular event‡‡	319 (9·3%)	150 (7·6%)	139 (11·4%)	30 (13·2%)

Data are n (%) or median (IQR). Centre-specific data on ethnicity are shown in the appendix (p 2). *n=3216. †n=3354. ‡n=3537. §n=3486. ¶n=3484. ‖n=3306. **n=3299. ††n=3293. ‡‡n=3415.

Table 1: **Patient characteristics at initial diagnosis of the adrenal incidentaloma**

dexamethasone suppression test result (ie, serum cortisol <50 nmol/L, 50–80 nmol/L, 81–138 nmol/L, and >138 nmol/L).

Statistical analyses were performed using SPSS (version 28.0), and R (version 4.0.2) using the survival (version 3.2-13) and smoothHR (version 1.0.3) packages.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Of 4374 potentially eligible patients, 3656 from 28 centres in 15 countries were included in the study cohort for mortality analysis (appendix pp 2, 8). In 131 (3·6%) patients, adrenalectomy was performed later than 36 months after initial diagnosis (appendix p 3); these patients were censored at the time of surgery. Median age at initial diagnosis was 61 years (IQR 53–68), and 2350 (64·3%) patients were women and 1306 (35·7%) were men. According to the result of the first dexamethasone suppression test, 2089 (57·1%) of 3656 patients had non-functioning adenoma, 1320 (36·1%) had possible autonomous cortisol secretion, and 247 (6·8%) had autonomous cortisol secretion. Bilateral tumours were most frequent in patients with autonomous cortisol secretion, and this group also had the largest median tumour diameter (table 1). Serum cortisol after the 1 mg dexamethasone suppression test increased with age (appendix p 9). None of the patients developed overt Cushing's syndrome during follow-up.

During a median follow-up of 7·0 years (IQR 4·7–10·2), 352 (9·6%) of 3656 patients died. Figure 1A shows the crude overall survival of the three dexamethasone suppression test groups. Compared with patients with non-functioning adenoma, the proportion of patients who died was higher in those with possible autonomous cortisol secretion and autonomous cortisol secretion (143 [6·8%] of 2089 patients *vs* 168 [12·7%] of 1320 and 41 [16·6%] of 247, respectively). After multivariable Cox analysis adjusting for age, sex, hypertension, any diabetes, dyslipidaemia, and previous cardiovascular events, all-cause mortality was significantly higher in patients with possible autonomous cortisol secretion (HR 1·52, 95% CI 1·19–1·94; p=0·001) and autonomous cortisol secretion (1·77, 1·20–2·62; p=0·004) than in patients with non-functioning adenoma (figure 1B). Bilateral adenomas had a greater association with possible autonomous cortisol secretion and autonomous cortisol secretion (table 1), but presence of bilateral adenomas was itself not an independent risk factor for death (data not shown).

Information on the individual causes of death was available in 306 (86·9%) of 352 patients who died (figure 2). The two most frequent causes of death were cancer (98 patients) and cardiovascular-related events (95 patients; appendix p 6).

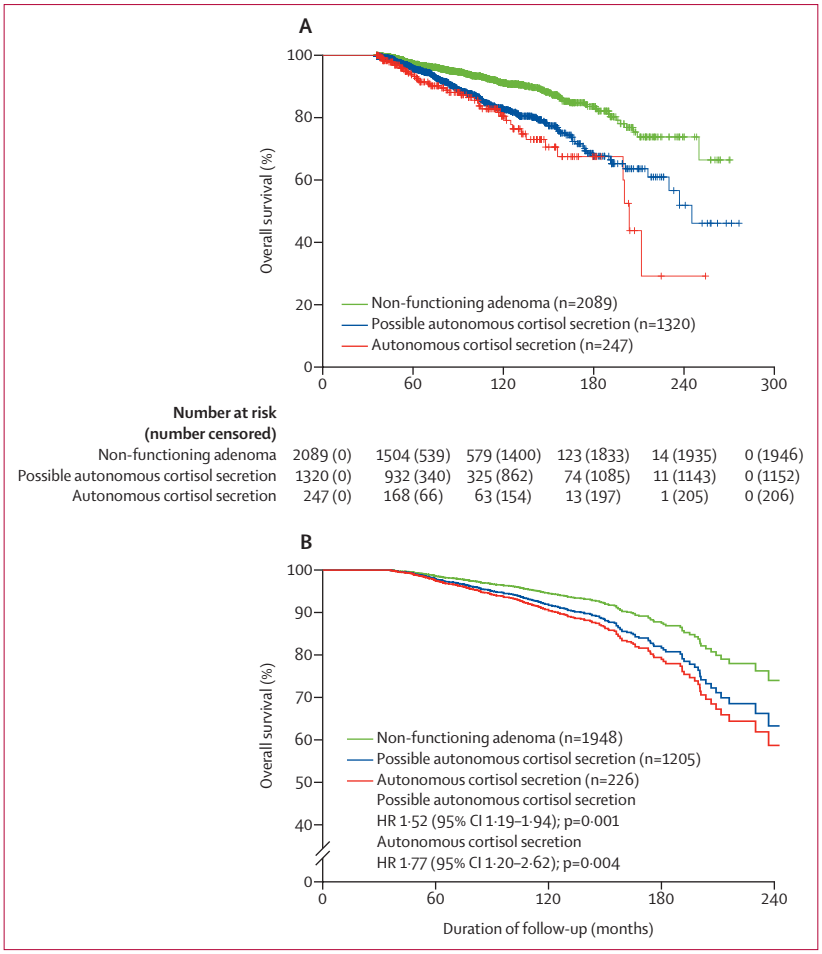

Figure 1: **Overall survival in the entire cohort**
(A) Kaplan-Meier curves (n=3656); ticks indicate censored patients; median overall survival was not reached in the non-functioning adenoma group, 246 months in the possible autonomous cortisol secretion group, and 206 months (95% CI 187–209) in the autonomous cortisol secretion group; overall log-rank p<0·001 (non-functioning adenoma group *vs* possible autonomous cortisol secretion group, p<0·001; non-functioning adenoma group *vs* autonomous cortisol secretion group, p<0·001; possible autonomous cortisol secretion group *vs* autonomous cortisol secretion group, p=0·10). (B) Multivariable Cox regression analysis (n=3379; adjusted for sex, age, hypertension, dyslipidaemia, any diabetes, and previous cardiovascular events); patients with missing data for these variables were excluded from the analysis. HR=hazard ratio.

In the post-hoc analysis when we divided the study cohort into four groups, we found that all-cause mortality in the 766 patients with a serum cortisol of 50–80 nmol/L was not significantly higher than in the less than 50 nmol/L non-functioning adenoma group (HR 1·29, 95% CI 0·97–1·71; p=0·085; appendix p 4). Furthermore, when we studied serum cortisol after the dexamethasone suppression test as a continuous variable in relation to all-cause mortality, although there was no significant linear relationship in the entire cohort, we found a linear increase in the HR for death in patients with serum cortisol of 138 nmol/L or less (appendix p 10).

In sensitivity analyses, 10-year overall survival was heterogeneous among centres (ranging from 69% to 100%). In the analysis restricted to the 21 centres with more reliable follow-up (completeness index score ≥90%),

See Online for appendix

overall survival of the 2730 patients was not changed in a relevant manner compared with the entire study cohort (appendix p 5). Accordingly, we decided not to exclude any centre from the analysis. The association between mortality and the degree of cortisol autonomy was age-dependent; in patients younger than 65 years, all-cause mortality was significantly higher in the autonomous cortisol secretion group than in the non-functioning adenoma group (adjusted HR 3·16, 95% CI 1·65–6·05), whereas there was no significant difference in patients aged 65 years or older (1·43, 0·87–2·33). The association between mortality and serum cortisol after the dexamethasone suppression test was much stronger in women than in men (autonomous cortisol secretion *vs* non-functioning adenoma; adjusted HR 2·50 [95% CI 1·45–4·31] in women *vs* 1·19 [0·67–2·10] in men). The combined analysis of age-specific and sex-specific mortality is presented in table 2 and figure 3. This analysis revealed a significant interaction of age, sex, and dexamethasone suppression test category (p<0·01). It is important to note, however, that the number of patients in each of these groups meant that a separate formal analysis group by group was underpowered.

Data on cardiometabolic morbidity and cardiovascular events were available in 3484 (95·3%) of 3656 patients (2002 with non-functioning adenoma, 1250 with possible autonomous cortisol secretion, and 232 with autonomous cortisol secretion). Overall, hypertension was the most frequent comorbidity at initial diagnosis (2309 [65·3%] of 3537 patients), followed by dyslipidaemia (1394 [40·0%] of 3486), and any diabetes (715 [20·5%] of 3484). The prevalence of each of these comorbid conditions by group increased sequentially from lowest in the non-functioning adenoma group to highest in the autonomous cortisol secretion group (table 1).

With regard to cardiovascular endpoints, 319 (9·3%) of 3415 patients had experienced at least one cardiovascular event by the time of the initial diagnosis of the adrenal incidentaloma (table 1). During follow-up, a total of 476 non-fatal cardiovascular events occurred in 375 patients, with more cardiovascular events occurring in patients with possible autonomous cortisol secretion and autonomous cortisol secretion than in patients with non-functioning adenoma. Overall, 297 (8·9%) of 3325 patients with available data experienced a MACE (145 [7·3%] patients in the non-functioning adenoma group, 130 [10·3%] in the possible autonomous cortisol secretion group, and 22 [9·4%] in the autonomous cortisol secretion group; appendix p 7). However, after adjusting for cardiometabolic comorbidities, compared with patients with non-functioning adenoma, time to the first MACE was only significantly shorter in women aged 65 years or older with autonomous cortisol secretion (table 3).

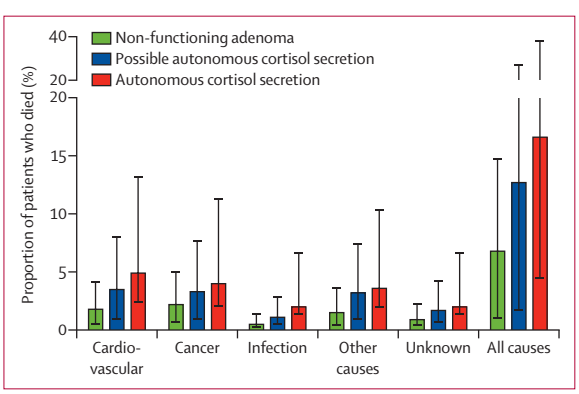

Figure 2: **Mortality and causes of death**
Error bars are 95% CI.

Discussion

To our knowledge, this study is the largest retrospective analysis on mortality and cardiovascular morbidity in patients with adrenal incidentalomas performed to date. By contrast with a meta-analysis from 2019,[6] but similar to a study from Sweden published in 2021,[12] we found that all-cause mortality was increased in patients with possible autonomous cortisol secretion and autonomous cortisol secretion compared with patients with non-functioning adenoma. Because of our large sample size (>3600 patients), we were able to reliably analyse effects of age and sex on mortality. Our findings show that, compared with patients with non-functioning adenoma, autonomous cortisol secretion in women younger than 65 years was associated with a four-times increase in adjusted all-cause mortality, whereas all-cause mortality in the autonomous cortisol secretion group was only moderately increased in women aged 65 years or older

	Age, years	All patients, n	All events, n	Possible autonomous cortisol secretion				Autonomous cortisol secretion			
				Patients, n	HR	95% CI	p value	Patients, n	HR	95% CI	p value
Women	<65	1424	51	472	1·82	0·99–3·31	0·052	96	4·39	1·93–9·96	<0·001
	≥65	723	108	302	1·99	1·31–3·01	0·001	57	1·80	0·86–3·76	0·12
Men	<65	734	43	222	1·35	0·70–2·59	0·37	34	1·77	0·59–5·33	0·31
	≥65	479	94	200	1·26	0·81–1·97	0·31	36	1·09	0·55–2·16	0·81

The analysis was adjusted for hypertension, any diabetes, dyslipidaemia, and previous cardiovascular events. Patients with missing data for these variables were excluded from the analysis. Patients with non-functioning adenoma were the reference cohort. HR=hazard ratio.

Table 2: **Multivariable Cox regression analysis of all-cause mortality by sex and age**

and men younger than 65 years, and was not affected in men aged 65 years or older.

We found that possible autonomous cortisol secretion and autonomous cortisol secretion were associated with an increased frequency of cardiometabolic comorbidities. In particular, hypertension had a higher prevalence in both the possible autonomous cortisol secretion and autonomous cortisol secretion groups than in the non-functioning adenoma group, and any diabetes and dyslipidaemia showed progressively increased frequencies in the non-functioning adenoma, possible autonomous cortisol secretion, and autonomous cortisol secretion groups, reflecting a continuum in metabolic disturbance, as shown previously.[17,18] Furthermore, cardiovascular events occurring either before or after the initial diagnosis of the adrenal tumour were more frequently observed in patients with possible autonomous cortisol secretion and autonomous cortisol secretion than in patients with non-functioning adenoma. However, after adjusting for cardiometabolic comorbidities, a significant increase in MACE was only observed in women aged 65 years or older with autonomous cortisol secretion, suggesting that glucocorticoid-related cardiovascular events might not be the main drivers of overall mortality in this cohort, as has been suggested previously.[9,10,12] This finding is in line with the reported causes of death, which indicated there were few cardiovascular-related deaths in women younger than 65 years with cortisol autonomy. In our study, we found a relative increase in cardiovascular-related mortality, which paralleled that for other causes of death in patients with autonomous cortisol secretion. Another study pointed to cancer as the leading cause of death in the presence of autonomous cortisol secretion;[11] we could only partly confirm this observation in our large cohort in which cardiovascular-related and cancer-related deaths were almost equal in patients with cortisol autonomy (appendix p 6). In line with other studies, however, our findings suggest that cortisol autonomy might have systemic detrimental effects.[18–20] Nevertheless, we are aware that a retrospective study can by definition never confirm any causal relationship.

The finding that the association between autonomous cortisol secretion and mortality appeared to be clinically relevant mostly in younger women has not yet been described by other studies and might suggest that autonomous cortisol secretion is a prognostic factor that has greater influence at younger ages, when other age-related comorbidities are less prominent. Although a different clinical presentation was observed for men and women with overt Cushing's disease,[21] less is known about sex-specific organ effects by hypercortisolism. Studies on stress associated with the COVID-19 pandemic have shown that younger and middle-aged women were more susceptible to stress than men, and displayed an increased vascular reactivity to glucocorticoids.[22] Besides, it has been shown that women with any diabetes or coronary heart disease were likely to receive less aggressive medical management of their cardiovascular risk factors, which might have contributed to sex differences in cardiovascular mortality.[23,24] In the present study, however, we adjusted our survival analysis for comorbidities to mitigate the risk of such a confounder. Interestingly, a large, prospective, multicentre study in 1305 patients with adrenal adenomas showed an increased risk and severity of hypertension and type 2 diabetes in patients with cortisol autonomy and, similar to our findings, showed an increasing proportion of affected women with increasing cortisol after a 1 mg dexamethasone suppression test.[25] Although it would be important to screen for (and treat) autonomous cortisol secretion in young (and presumably otherwise more healthy) patients, it is probably less relevant to do so in frail older patients. However, only a large, randomised, intervention trial would provide a definitive answer, and such a trial is not yet available. Thus, for the time being, our study suggests that any decision on initiating cortisol-lowering treatment or surgery should be made with care, and on an individual basis.

We also observed that serum cortisol after the dexamethasone suppression test increased with age. A retrospective study, however, cannot establish whether

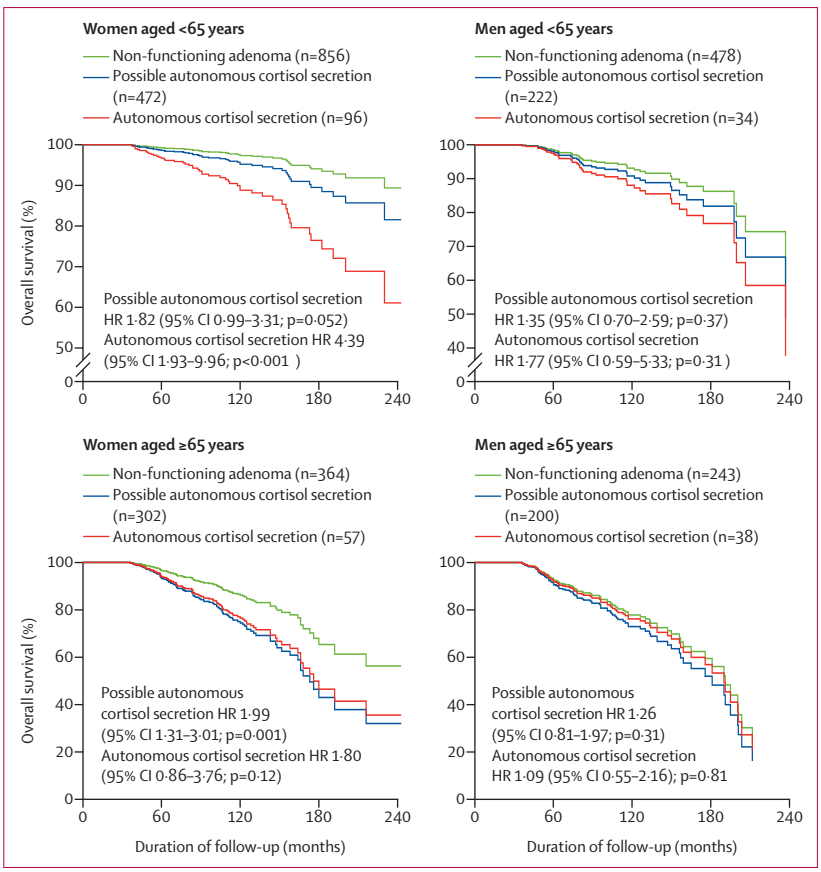

Figure 3: **Overall survival by sex and age**
Multivariable Cox regression analysis adjusted for hypertension, dyslipidaemia, any diabetes, and previous cardiovascular events. Patients with missing data for these variables were excluded from the analysis. HR=hazard ratio.

	Age, years	All patients, n	All events, n	Possible autonomous cortisol secretion				Autonomous cortisol secretion			
				Patients, n	HR	95% CI	p value	Patients, n	HR	95% CI	p value
Women	<65	1377	75	466	1·20	0·74–1·95	0·46	94	1·61	0·71–3·61	0·25
	≥65	705	92	296	1·33	0·84–2·06	0·22	56	2·09	1·08–4·05	0·028
Men	<65	694	91	218	1·05	0·67–1·63	0·83	33	0·73	0·29–1·85	0·51
	≥65	466	89	193	1·10	0·70–1·72	0·69	36	1·04	0·48–2·24	0·92

The analysis was adjusted for hypertension, any diabetes, dyslipidaemia, and previous cardiovascular events. Patients with missing data for these variables were excluded from the analysis. Patients with non-functioning adenoma were the reference cohort. HR=hazard ratio. MACE=major adverse cardiovascular event.

Table 3: **Multivariate Cox regression analysis of MACE by sex and age**

this association might also reflect chronic stress associated with age-related illnesses. Future studies will have to confirm this finding and clarify if this is a hallmark of the brain aging process affecting the hypothalamic–pituitary–adrenal axis,[26] reduced cortisol inactivation due to a reduced activity of 11b-hydroxysteroid dehydrogenase type 2 as a consequence of a lower nephron mass in ageing,[27] increasing adrenal tumour mass with age,[18] or potentially accelerated metabolism of dexamethasone (eg, CYP3A4 induction due to polypharmacy in older patients).[28] Overall, these data raise questions as to the clinical importance of elevated serum cortisol after the 1 mg dexamethasone suppression test in older patients. Besides, as has been reported previously,[12] we could not find any clear relationship between cortisol after the dexamethasone suppression test as a continuous variable and all-cause mortality in the entire cohort. However, there was a nearly linear relationship when serum cortisol was 138 nmol/L or less. For higher values, the accuracy of the results was likely to be limited by the low number of patients.

This study has several limitations. First, a retrospective design is prone to bias, including heterogeneous or possibly inaccurate capture of relevant clinical information. Nevertheless, we tried to minimise such an impact by requesting consecutively recruited patients, a minimum number of included patients per centre, and did a sensitivity analysis focusing on centres with a follow-up rate of more than 90%. Second, the number of patients with the highest serum cortisol after the 1 mg dexamethasone suppression test (ie, the autonomous cortisol secretion group) was small compared with the number in the possible autonomous cortisol secretion and non-functioning adenoma groups, which might have weakened the statistical power of some of our analyses. However, the 247 patients in the autonomous cortisol secretion group exceeded the total number of patients included in all previous studies on this topic (n=154).[9–12] Third, we relied on a single 1 mg dexamethasone suppression test only, with variability in the performance of the cortisol assays used between centres over time, and without availability of dexamethasone serum concentrations.[29] However, the biochemical tests used to assess for cortisol autonomy have not been changed over the last 25 years. Fourth, it is possible that the inclusion criterion of a 1 mg dexamethasone suppression test result in itself leads to some bias, because some patients with adrenal incidentaloma might not have undergone testing. However, this bias is not resolvable, as shown by a population-based study in which only few patients with adrenal incidentalomas had some type of endocrine screening.[13] In addition, we acknowledge that all participating institutions are tertiary care centres and our sample might not be representative of patients seen in the community. Finally, the diagnostic criteria of the comorbidities were not uniform across centres and have changed over the study period of 23 years.

In conclusion, this large, retrospective, international, cohort study provides additional strong evidence for an overall association between possible autonomous cortisol secretion and autonomous cortisol secretion and increased all-cause mortality (although causality cannot be confirmed due to the retrospective study design). However, this risk was not equally distributed. Women younger than 65 years with autonomous cortisol secretion had the highest relative risk, whereas men aged 65 years or older did not appear to be at increased risk (irrespective of the degree of cortisol autonomy). Although several studies have claimed benefits of adrenalectomy in patients with autonomous cortisol secretion, all of these studies were prone to bias and had small sample sizes.[30] Randomised interventional trials are needed to determine whether intervention (either medical or surgical) is able to mitigate the cardiometabolic morbidity and mortality in patients with adrenal adenomas. On the basis of our findings, and until results from such trials are available, we suggest that a conservative approach might be prudent, in particular in men aged 65 years or older with cortisol autonomy.

Contributors

TDe, GR, MT, and MF designed the study. Except for UM, all authors collected samples and clinical data from patients. UM, TDe, GR, MT, and MF had full access to all the data in the study and performed the statistical analyses. TDe, GR, MT, and MF wrote the first draft of the manuscript and JN-P conducted extensive content and language editing. All authors contributed to writing the manuscript and approved the final version to be published. All authors had full access to all the data in the

study and had final responsibility for the decision to submit for publication.

Declaration of interests

IB has served as a consultant for Corcept Therapeutics, Sparrow Pharmaceutics, and Spruce Biosciences; was as a member of advisory or data safety monitoring boards for Adrenas Therapeutics, Recordati, and Strongbridge Biopharma (in all cases, institution fees were provided); and reports personal honoraria from Elsevier ClinicalKey. IC reports consulting fees and honoraria from HRA Pharma Rare Diseases and Recordati; was a member of advisory or data safety monitoring boards for HRA Pharma Rare Diseases and Recordati; and has participated in clinical studies from Corcept Therapeutics. ACh reports personal support for attending meetings or travel from Sanofi; personal honoraria from Ipsen; and was a member of advisory or data safety monitoring boards for Ipsen. TDe reports personal consulting fees for being a member of advisory or data safety monitoring boards for HRA Pharma Rare Diseases and Recordati; personal honoraria from Novartis; and has participated in clinical studies from Corcept Therapeutics and HRA Pharma Rare Diseases (for these, institution fees were provided). MF has participated in clinical studies from Corcept Therapeutics and HRA Pharma Rare Diseases (for these, institution fees were provided). LM was a member of the expert panel "Focus Area Adrenal and Cardiovascular Endocrinology" from the European Society of Endocrinology, and led the working group 5 of the project "CA20122—Harmonizing clinical care and research on adrenal tumours in European countries" from the European Cooperation in Science in Technology. JN-P reports grants from Diurnal Group; and has served as a consultant for and received honoraria from HRA Pharma Rare Diseases, Crinetics Pharmaceuticals, and Recordati (in all cases, institution fees were provided). CS reports consulting fees and honoraria from HRA Pharma Rare Diseases and Recordati; was a member of advisory or data safety monitoring boards for HRA Pharma Rare Diseases and Recordati; and has served as coordinator of the Pituitary Club of the Italian Society of Endocrinology. MT reports personal consulting fees (for being a member of advisory or data safety monitoring boards for Corcept Therapeutics and HRA Pharma Rare Diseases); and has participated in clinical studies from HRA Pharma Rare Diseases (for which institution fees were provided). ST reports personal support for attending meetings or travel from Ipsen, Pfizer, and Recordati; personal honoraria from Recordati; and has participated in clinical studies from Crinetics Pharmaceuticals, Novartis, and Strongbridge Biopharma. All other authors declare no competing interests.

Data sharing

We will consider sharing deidentified, individual participant-level data that underlie the results reported in this Article on receipt of a request detailing the study hypothesis and statistical analysis plan. All requests should be sent to the corresponding author. The corresponding author and lead investigators of this study will discuss all requests and make decisions about whether data sharing is appropriate based on the scientific rigour of the proposal. All applicants will be asked to sign a data access agreement.

Acknowledgments

This project was supported by the European Network for the Study of Adrenal Tumours, Deutsche Forschungsgemeinschaft (project number 314061271; CRC/Transregio 205/1 "The Adrenal: Central relay of health and disease" grant to MF), Associazione Italiana per la Ricerca sul Cancro (grant number IG2019-23069 to MT), and Ricerca Locale Università di Torino 2020 (grant to GR). IB is the recipient of a National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health K23 Award (grant number K23DK121888). AP is the recipient of a Diabetes UK Sir George Alberti Research Training Fellowship (grant number 18/0005782). We are grateful to Yvonne Möhres (University Hospital Würzburg, Würzburg, Germany) for her help in data management and and to Prof Maura Arosio (Fondazione IRCCS Cà Granda-Ospedale Maggiore Policlinico, Milan, Italy) for contributing patient data. We also thank the staff of the participating centres for their commitment to this study. MS works for the US Federal Government; however, the presented views do not necessarily represent those of the US Federal Government.

References

1 Reimondo G, Castellano E, Grosso M, et al. Adrenal incidentalomas are tied to increased risk of diabetes: findings from a prospective study. *J Clin Endocrinol Metab* 2020; **105:** dgz284.

2 Ebbehoj A, Li D, Kaur RJ, et al. Epidemiology of adrenal tumours in Olmsted County, Minnesota, USA: a population-based cohort study. *Lancet Diabetes Endocrinol* 2020; **8:** 894–902.

3 Sherlock M, Scarsbrook A, Abbas A, et al. Adrenal incidentaloma. *Endocr Rev* 2020; **41:** 775–820.

4 Mantero F, Terzolo M, Arnaldi G, et al. A survey on adrenal incidentaloma in Italy. *J Clin Endocrinol Metab* 2000; **85:** 637–44.

5 Cawood TJ, Hunt PJ, O'Shea D, Cole D, Soule S. Recommended evaluation of adrenal incidentalomas is costly, has high false-positive rates and confers a risk of fatal cancer that is similar to the risk of the adrenal lesion becoming malignant—time for a rethink? *Eur J Endocrinol* 2009; **161:** 513–27.

6 Elhassan YS, Alahdab F, Prete A, et al. Natural history of adrenal incidentalomas with and without mild autonomous cortisol excess: a systematic review and meta-analysis. *Ann Intern Med* 2019; **171:** 107–16.

7 Fassnacht M, Arlt W, Bancos I, et al. Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. *Eur J Endocrinol* 2016; **175:** G1–34.

8 Taya M, Paroder V, Bellin E, Haramati LB. The relationship between adrenal incidentalomas and mortality risk. *Eur Radiol* 2019; **29:** 6245–55.

9 Debono M, Bradburn M, Bull M, Harrison B, Ross RJ, Newell-Price J. Cortisol as a marker for increased mortality in patients with incidental adrenocortical adenomas. *J Clin Endocrinol Metab* 2014; **99:** 4462–70.

10 Di Dalmazi G, Vicennati V, Garelli S, et al. Cardiovascular events and mortality in patients with adrenal incidentalomas that are either non-secreting or associated with intermediate phenotype or subclinical Cushing's syndrome: a 15-year retrospective study. *Lancet Diabetes Endocrinol* 2014; **2:** 396–405.

11 Patrova J, Kjellman M, Wahrenberg H, Falhammar H. Increased mortality in patients with adrenal incidentalomas and autonomous cortisol secretion: a 13-year retrospective study from one center. *Endocrine* 2017; **58:** 267–75.

12 Kjellbom A, Lindgren O, Puvaneswaralingam S, Löndahl M, Olsen H. Association between mortality and levels of autonomous cortisol secretion by adrenal incidentalomas: a cohort study. *Ann Intern Med* 2021; **174:** 1041–49.

13 Zhang CD, Li D, Kaur RJ, et al. Cardiometabolic outcomes and mortality in patients with adrenal adenomas in a population-based setting. *J Clin Endocrinol Metab* 2021; **106:** 3320–30.

14 Nieman LK, Biller BM, Findling JW, et al. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2008; **93:** 1526–40.

15 Selvin E, Coresh J, Brancati FL. The burden and treatment of diabetes in elderly individuals in the U.S. *Diabetes Care* 2006; **29:** 2415–19.

16 Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* 2018; **39:** 3021–104.

17 Lopez D, Luque-Fernandez MA, Steele A, Adler GK, Turchin A, Vaidya A. "Nonfunctional" adrenal tumors and the risk for incident diabetes and cardiovascular outcomes: a cohort study. *Ann Intern Med* 2016; **165:** 533–42.

18 Prete A, Subramanian A, Bancos I, et al. Cardiometabolic disease burden and steroid excretion in benign adrenal tumors: a cross-sectional multicenter study. *Ann Intern Med* 2022; **175:** 325–34.

19 Whitworth JA, Williamson PM, Mangos G, Kelly JJ. Cardiovascular consequences of cortisol excess. *Vasc Health Risk Manag* 2005; **1:** 291–99.

20 Mohd Azmi NAS, Juliana N, Azmani S, et al. Cortisol on circadian rhythm and its effect on cardiovascular system. *Int J Environ Res Public Health* 2021; **18:** e676.

21 Pecori Giraldi F, Moro M, Cavagnini F. Gender-related differences in the presentation and course of Cushing's disease. *J Clin Endocrinol Metab* 2003; **88:** 1554–58.

22 Dhaibar HA, Cruz-Topete D. Predisposition of women to cardiovascular diseases: a side-effect of increased glucocorticoid signaling during the COVID-19 pandemic? *Front Glob Womens Health* 2021; **2:** 606833.

23 Wang H, Ba Y, Cai RC, Xing Q. Association between diabetes mellitus and the risk for major cardiovascular outcomes and all-cause mortality in women compared with men: a meta-analysis of prospective cohort studies. *BMJ Open* 2019; **9:** e024935.

24 Mansour O, Golden SH, Yeh HC. Disparities in mortality among adults with and without diabetes by sex and race. *J Diabetes Complications* 2020; **34:** 107496.

25 Pivonello R, Isidori AM, De Martino MC, Newell-Price J, Biller BM, Colao A. Complications of Cushing's syndrome: state of the art. *Lancet Diabetes Endocrinol* 2016; **4:** 611–29.

26 Yiallouris A, Tsioutis C, Agapidaki E, et al. Adrenal aging and its implications on stress responsiveness in humans. *Front Endocrinol (Lausanne)* 2019; **10:** 54.

27 Quinkler M, Zehnder D, Lepenies J, et al. Expression of renal 11beta-hydroxysteroid dehydrogenase type 2 is decreased in patients with impaired renal function. *Eur J Endocrinol* 2005; **153:** 291–99.

28 Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. *Pharmacol Ther* 2013; **138:** 103–41.

29 Vogg N, Kurlbaum M, Deutschbein T, Gräsl B, Fassnacht M, Kroiss M. Method-specific cortisol and dexamethasone thresholds increase clinical specificity of the dexamethasone suppression test for Cushing syndrome. *Clin Chem* 2021; **67:** 998–1007.

30 Terzolo M, Reimondo G. Insights on the natural history of adrenal incidentalomas. *Ann Intern Med* 2019; **171:** 135–36.