Dynamic testing for differential diagnosis of ACTH-dependent Cushing Syndrome: a systematic review and meta-analysis

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SUPPLEMENTARY FILES

Structured according to the PRISMA-DTA checklist

PRISMA-DTA Checklist Item downloaded from http://www.prisma-statement.org/Extensions/DTA

Section/topic	#	PRISMA-DTA Checklist Item	Reported on page #
TITLE / ABSTRACT			
Title	1	Identify the report as a systematic review (+/- meta-analysis) of diagnostic test accuracy (DTA) studies.	1
Abstract	2	Abstract: See PRISMA-DTA for abstracts.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Clinical role of index test	D1	State the scientific and clinical background, including the intended use and clinical role of the index test, and if applicable, the rationale for minimally acceptable test accuracy (or minimum difference in accuracy for comparative design).	5-6
Objectives	4	Provide an explicit statement of question(s) being addressed in terms of participants, index test(s), and target condition(s).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (participants, setting, index test(s), reference standard(s), target condition(s), and study design) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7-8
Search	8	Present full search strategies for all electronic databases and other sources searched, including any limits used, such that they could be repeated.	7-8
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-8
Definitions for data extraction	11	Provide definitions used in data extraction and classifications of target condition(s), index test(s), reference standard(s) and other characteristics (e.g. study design, clinical setting).	7-8
Risk of bias and applicability	12	Describe methods used for assessing risk of bias in individual studies and concerns regarding the applicability to the review question.	8
Diagnostic accuracy measures	13	State the principal diagnostic accuracy measure(s) reported (e.g. sensitivity, specificity) and state the unit of assessment (e.g. per-patient, per-lesion).	9

Synthesis of results	14	Describe methods of handling data, combining results of studies and describing variability between studies. This could include, but is not limited to: a) handling of multiple definitions of target condition. b) handling of multiple thresholds of test positivity, c) handling multiple index test readers, d) handling of indeterminate test results, e) grouping and comparing tests, f) handling of different reference standards	9
Meta-analysis	D2	Report the statistical methods used for meta-analyses, if performed.	9-10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9-10
RESULTS			
Study selection	17	Provide numbers of studies screened, assessed for eligibility, included in the review (and included in meta-analysis, if applicable) with reasons for exclusions at each stage, ideally with a flow diagram.	11
Study characteristics	18	For each included study provide citations and present key characteristics including: a) participant characteristics (presentation, prior testing), b) clinical setting, c) study design, d) target condition definition, e) index test, f) reference standard, g) sample size, h) funding sources	11-12
Risk of bias and applicability	19	Present evaluation of risk of bias and concerns regarding applicability for each study.	12-13
Results of individual studies	20	For each analysis in each study (e.g. unique combination of index test, reference standard, and positivity threshold) report 2x2 data (TP, FP, FN, TN) with estimates of diagnostic accuracy and confidence intervals, ideally with a forest or receiver operator characteristic (ROC) plot.	11-12
Synthesis of results	21	Describe test accuracy, including variability; if meta-analysis was done, include results and confidence intervals.	11-12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression; analysis of index test: failure rates, proportion of inconclusive results, adverse events).	11-12
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence.	14
Limitations	25	Discuss limitations from included studies (e.g. risk of bias and concerns regarding applicability) and from the review process (e.g. incomplete retrieval of identified research).	14-15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence. Discuss implications for future research and clinical practice (e.g. the intended use and clinical role of the index test).	15-16
FUNDING			
Funding	27	For the systematic review, describe the sources of funding and other support and the role of the funders.	1

Database search strategies

1. OVID (limit to humans)
   - ✓ cushing*.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw, tn, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, an, ui, sy]
   - ✓ cushing syndrome.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw, tn, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, an, ui, sy]
   - ✓ cushing disease.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw, tn, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, an, ui, sy]
   - ✓ ectopic ACTH secretion.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw, tn, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, an, ui, sy]
   - ✓ CRH test.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw, tn, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, an, ui, sy]
   - ✓ desmopressin test.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw, tn, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, an, ui, sy]
   - ✓ high dose dexamethasone suppression test.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw, tn, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, an, ui, sy]

2. Medline (limit to humans)
   - ✓ "cushing syndrome"[MeSH Terms] OR ("cushing"[All Fields] AND "syndrome"[All Fields]) OR "cushing syndrome"[All Fields] OR ("cushing s"[All Fields] AND "syndrome"[All Fields]) OR "cushing s syndrome"[All Fields] AND 1990/01/01:2021/12/31[Date - Publication]
   - ✓ "pituitary acth hypersecretion"[MeSH Terms] OR ("pituitary"[All Fields] AND "acth"[All Fields] AND "hypersecretion"[All Fields]) OR "pituitary acth hypersecretion"[All Fields] OR ("cushing s"[All Fields] AND "disease"[All Fields]) OR "cushing s disease"[All Fields] AND 1990/01/01:2021/12/31[Date - Publication]
   - ✓ "acth syndrome, ectopic"[MeSH Terms] OR ("acth"[All Fields] AND "syndrome"[All Fields] AND "ectopic"[All Fields]) OR "ectopic acth syndrome"[All Fields] OR ("ectopic"[All Fields] AND "acth"[All Fields] AND "secretion"[All Fields]) OR "ectopic acth secretion"[All Fields] AND 1990/01/01:2021/12/31[Date - Publication]
   - ✓ "CRH"[All Fields] AND ("research design"[MeSH Terms] OR ("research"[All Fields] AND "design"[All Fields]) OR "research design"[All Fields] OR "test"[All Fields]) AND 1990/01/01:2021/12/31[Date - Publication]
   - ✓ ("deamino arginine vasopressin"[MeSH Terms] OR ("deamino"[All Fields] AND "arginine"[All Fields] AND "vasopressin"[All Fields]) OR "deamino arginine vasopressin"[All Fields] OR "desmopressin"[All Fields] OR "desmopressine"[All Fields]) AND ("research design"[MeSH Terms] OR ("research"[All Fields] AND "design"[All Fields]) OR "research design"[All Fields] OR "test"[All Fields]) AND 1990/01/01:2021/12/31[Date - Publication]
   - ✓ "high"[All Fields] AND "dose"[All Fields] AND ("dexamethason"[All Fields] OR "dexamethasone"[MeSH Terms] OR "dexamethasone"[All Fields] OR "dexamethasone s"[All Fields] OR "dexamethasones"[All Fields]) AND ("suppress"[All Fields] OR "suppressed"[All Fields] OR "suppresser"[All Fields] OR "suppresses"[All Fields] OR "suppressibility"[All Fields] OR "suppressible"[All Fields] OR "suppressing"[All Fields] OR "suppression"[All Fields] OR "suppressions"[All Fields] OR "suppressive"[All Fields] OR "suppressives"[All Fields]) AND ("research design"[MeSH Terms] OR ("research"[All Fields] AND "design"[All Fields]) OR "research design"[All Fields] OR "test"[All Fields]) AND 1990/01/01:2021/12/31[Date - Publication]

- ✓ ("bilateral"[All Fields] OR "bilaterally"[All Fields] OR "bilaterals"[All Fields]) AND ("petrosal sinus sampling"[MeSH Terms] OR ("petrosal"[All Fields] AND "sinus"[All Fields] AND "sampling"[All Fields]) OR "petrosal sinus sampling"[All Fields] OR ("inferior"[All Fields] AND "petrosal"[All Fields] AND "sinus"[All Fields] AND "sampling"[All Fields]) OR "inferior petrosal sinus sampling"[All Fields]) AND 1990/01/01:202/12/31[Date - Publication]

3. Web of Science
   - ✓ 1. TS=(cushing* OR hypercortisol*)
   - ✓ 2. TS=(dexamethasone)
   - ✓ 3. TS=(crh OR corticotrophin* OR corticotropin* OR corticorelin)
   - ✓ 4. TS=(ddavp OR desmopressin)
   - ✓ 5. TS=(cortiso* OR ACTH OR corticotropin)
   - ✓ 6. #5 AND #4
   - ✓ 7. #5 AND #3
   - ✓ 8. #5 AND #2
   - ✓ 9. TS=(diagnos* OR accura* OR establish* OR sensitiv* OR specific* OR assess* OR detect* OR predict* OR reliab* OR valid* OR evaluat* OR ROC OR receiver operating characteristic curve OR AUC OR area under the curve OR reproducib*)
   - ✓ 10. #9 AND #1 AND #1
   - ✓ 11. Exclude: DOCUMENT TYPES: (CASE REPORT OR REVIEW)

QUADAS-2 protocol for methodological assessment

The following protocol was established prior to bias assessment

Patient selection:

- • High risk of bias: a study that considered only CD or only EAS

- • High concern about applicability: incomplete description of patients

Index tests:

- • High risk of bias: incomplete description of the tests or the number of subjects studied

- • High concern about applicability: incomplete description of the cut-off

For the reference standard:

- Low risk of bias and low concern about applicability: use of histopathology, post-surgical adrenal insufficiency, BIPSS or detailed combination imaging and dynamic tests

For flow and timing:

- low risk of bias: dynamic tests before the established final diagnosis of CD or EAS
- High risk of bias: excluding patients from the analysis

Supplementary Table 1. Characteristics of the included studies reporting CRH test (continued 1/3).

First Author	Year	male	female	setting	recruitment	cases per year	total ACTH-dependent CS	CD	EAS	reference standard
Tabarin	1990	na	na	referral center	na	na	28	21	7	surgical remission / pathology/ BIPSS
Colao	1993	4	16	university hospital	na	na	20	18	2	BIPSS/imaging
Malerbi (only CD)	1993	na	na	university hospital	na	na	10	10	0	pathology/imaging/BIPSS/ surgical remission
Nieman	1993			referral center	1986-1989	38.67	116	100	16	surgical remission/pathology
Suda	1993	10	10	university hospital	na	na	20	10	10	pathology
Freda	1995	na	na	university hospital	1989-1993	4.5	18	17	1	pathology/surgical remission
Dickstein (only CD vs pseudo-CS)	1996	8	43	referral center	na	na	51	51	0	surgical remission
Colombo	1997	na	na	university hospital	na	na	18	17	1	surgical remission / imaging/ BIPSS / dynamic tests
Al-Saadi	1998	7	21	university hospital	na	na	25	24	1	surgical remission
Teramoto	1998	9	29	university hospital	last 6 years	6.33	38	34	4	pathology/BIPSS/surgical remission
Invitti #	1999	na	na	multicentric referral (Italy)	1979-1999	8.55	171	158	13	surgical remission/dynamic tests/BIPS
Wiggam	2000	na	na	referral center	na	na	24	23	1	pathology/surgical remission
Newell-Price *,£	2002	30	85	referral center	1987-2000	8.85	115	101	14	pathology/surgical remission
Tsagarakis §	2002	20	11	university hospital	na	na	31	26	5	pathology/surgical remission/BIPSS
Reimondo	2003	na	na	university hospital	1987-2001	4.21	59	49	10	pathology/surgical remission

Supplementary Table 1. Characteristics of the included studies reporting CRH test (continued 2/3).

First Author	Year	male	female	setting	recruitment	cases per year	total ACTH-dependent CS	CD	EAS	reference standard
Isidori (only EAS) %	2006	na	na	university hospital	1969-2001	0.56	18	0	18	pathology/imaging/follow-up
Salgado (only EAS)	2006	na	na	university hospital	1975-2005	0.06	2	0	2	pathology/imaging
Gasinska (only CD)	2007	7	8	university hospital	na	na	15	15	0	pathology/surgical remission
Lin (only CD)	2007	15	2	university hospital	1992-2006	1.21	17	17	0	BIPSS/pathology
Tsagarakis	2007	17	37	university hospital	na	na	54	47	7	pathology/surgical remission/BIPSS
Vilar	2008	na	na	university hospital	2000-2007	2.71	19	16	3	BIPSS / dynamic tests/imaging
Arnaldi $	2009	11	47	university hospital	na	na	58	51	7	pathology/surgical remission
Suda	2009	23	65	university hospital	1978-2008	2.93	88	73	15	pathology/surgical remission
Wang (only CD)	2012	25	4	university hospital	1998-2011	2.23	29	29	0	pathology
Ritzel	2015	na	na	university hospital	1994-2014	4,8	96	78	18	pathology/surgical remission
Barbot ^	2016	37	133	multicentric referral (Italy, Padova - Ancona)	2003-2013	17	170	149	21	BIPSS/surgical remission /dynamic tests
Davì (only EAS)	2017	na	na	multicentric referral (Italy)	1986-2014	2.07	58	0	58	BIPSS / dynamic tests
Polat Korkmaz (only CD)	2019	2	7	university hospital	2004-2016	0,75	9	9	0	pathology
Ceccato §	2020	13	40	university hospital	2014-2019	10.6	53	42	11	pathology/surgical remission/BIPSS
Frete	2020	40	154	multicentric referral (France, Bordeaux - Paris)	2001-2016	12.93	194	167	27	BIPSS/surgical remission / dynamic tests/imaging

Supplementary Table 1. Characteristics of the included studies reporting CRH test (continued 3/3).

First Author	Year	male	female	setting	recruitment	cases per year	total ACTH-dependent CS	CD	EAS	reference standard
Ferrante ¥	2021	17	51	university hospital	2000-2017	3.78	68	57	11	pathology/surgical remission / dynamic tests
Gonzalez Fernandez	2021	8	15	university hospital	2004-2019	1.48	23	19	4	pathology/surgical remission / BIPSS / dynamic tests
total							*1715*	*1428*	*287*	

#: Pecori Giraldi Clin Endo 2001 reported 160 patients (148 CD, 12 EAS) included in Invitti JCEM 1999
§: Ceccato JCEM 2020 only the 53 patients (42 CD 11 EAS) not included in Barbot Pituitary 2016
*: Newell-Price JCEM 2002 described patients included in Newell-Price JCEM 1997
^: Barbot Pituitary 2016 included patients (31 CD) reported in Testa Eur J Endocrinol 2007
$: Tirabassi Clin Endo 2011 (30 CD) were included in Arnaldi Eur J Endocrinol 2009 (51 CD, 7 EAS)
£: Isidori JCEM 2003 (CRH performed in 123 CD and 20 EAS) reported in Newell-Price JCEM 2002
%: reported only ACTH response to CRH, cortisol response is reported in Newell-Price JCEM 2002
": series reported in Tabarin JCEM 1991
¥: Ferrante JENI 2021: considered only patients from Milan (those from Padova previously reported in Barbot Pituitary 2016 or Ceccato JCEM 2020)

Supplementary Table 2. Characteristics of the included studies reporting HDDST (continued 1/3).

First Author	Year	male	female	setting	recruitment years	cases per year	total ACTH-dependent CS	CD	EAS	reference standard
Blunt	1990	7	23	referral center	1967-1987	1	30	23	7	pathology/surgical remission/imaging
Findling	1991	10	19	referral center	na	na	29	20	9	BIPSS/follow-up
Flack	1992	na	na	referral center	1981-1988	14.86	104	94	10	pathology/surgical remission
Colao	1993	4	23	university hospital	na	na	27	25	2	BIPSS/imaging
Suda	1993	10	10	university hospital	na	na	20	10	10	pathology
Freda	1995	na	na	university hospital	1989-1993	6.25	25	24	1	pathology/surgical remission
Avgerinos	1994	na	na	referral center	1982-1992	18.5	185	170	15	pathology/surgical remission
Dichek	1994	14	27	referral center	1986-1990	10.25	41	34	7	pathology/ surgical remission
Aron	1997	27	46	university hospital	1982-1995	5.62	73	58	15	BIPSS
Teramoto	1998	9	31	university hospital	last 6 years	6.67	40	35	5	pathology/BIPSS/ surgical remission
Al-Saadi	1998	7	21	university hospital	na	na	28	26	2	Surgical remission
Van Den Bogaert §	1999	na	na	university hospital	1973-1997	3.58	86	78	8	imaging/BIPSS/pathology/surgical remission
Puig	1999	na	na	university hospital	1982-1997	3.2	48	45	3	pathology/follow-up
Invitti	1999	na	na	multicentric referral (Italy)	1979-1999	7.95	159	143	16	surgical remission/dynamic tests/BIPSS
Wiggam	2000	na	na	referral center	na	na	45	44	1	pathology/ surgical remission
Isidori	2003	na	na	university hospital	1964-2001	5.92	219	187	32	pathology/surgical remission/follow-up

Supplementary Table 2. Characteristics of the included studies reporting HDDST (continued 2/3).

First Author	Year	male	female	setting	recruitment years	cases per year	total ACTH-dependent CS	CD	EAS	reference standard
Reimondo	2003	na	na	university hospital	1987-2001	4.21	59	49	10	pathology/ surgical remission
Isidori (only EAS)	2006	na	na	university hospital	1969-2001	1	32	0	32	pathology/imaging/follow-up
Salgado (only EAS)	2006	na	na	university hospital	1975-2005	0.67	20	0	20	pathology/imaging
Hernandez (only EAS)	2006	4	4	referral center	1994-2004	0,8	8	0	8	BIPSS
Shah	2006		na	university hospital	16 years	4.62	74	66	8	BIPSS/follow-up / dynamic tests
Castinetti	2007	9	34	university hospital	1995-2005	4.3	43	36	7	pathology / surgical remission/
Tsagarakis	2007	na	na	university hospital	na	na	52	45	7	pathology/surgical remission/BIPSS
Gasinska (only CD)	2007	7	8	university hospital	na	na	15	15	0	pathology/ surgical remission
Lin (only CD)	2007	14	2	university hospital	1992-2006	1.14	16	16	0	BIPSS/pathology
Vilar	2008	na	na	university hospital	2000-2007	6.57	46	39	7	BIPSS / dynamic tests/imaging
Esfahanian	2009	na	na	university hospital	2002-2005	11.67	35	32	3	surgical remission /pathology/imaging
Suda	2009	23	65	university hospital	1978-2008	2.93	88	73	15	pathology/surgical remission
Shi	2011	18	51	university hospital	2003-2011	8.63	69	64	5	pathology/surgical remission
Aytug (only CD)	2012	31	110	university hospital	na	na	141	141	0	BIPSS/pathology/surgical or RT remission/imaging

Supplementary Table 2. Characteristics of the included studies reporting HDDST (continued 3/3).

First Author	Year	male	female	setting	recruitment years	cases per year	total ACTH-dependent CS	CD	EAS	reference standard
Wang (only CD)	2012	25	4	university hospital	1998-2011	2.15	28	28	0	pathology
Ammini	2014	na	na	referral center	1985-2012	6.93	187	165	22	BIPSS/dynamic tests / imaging
Barbot ^	2016	na	na	multicentric referral (Italy, Padova - Ancona)	2003-2013	14.3	147	126	21	BIPSS/surgical remission / dinamic tests
Chen (only EAS)	2016	8	8	university hospital	1984-2014	0.8	16	0	16	pathology
Davì (only EAS)	2017	na	na	multicentric referral (Italy)	1986-2014	2.5	70	0	70	BIPSS / dynamic tests
Polat Korkmaz (only CD)	2019	2	7	university hospital	2004-2016	0.75	9	9	0	pathology
Liu	2020	32	86	university hospital	2015-2018	39.33	118	102	16	pathology/surgical remission
Chen	2020	na	na	university hospital	2011-2018	33.43	227	206	21	pathology/surgical remission
Ferrante ¥	2021	14	45	university hospital	2000-2017	3.28	59	48	11	pathology/surgical remission / dynamic tests
Ding	2021	25	87	university hospital	2004-2020	6.88	112	88	24	pathology/surgical remission
Qiao	2021	21	87	referral center	2013-2020	13.5	108	92	16	pathology/surgical remission / BIPSS / dynamic tests
Shi	2021	27	92	university hospital	2008-2020	9.15	119	101	18	pathology/surgical remission
total							*3057*	*2557*	*500*	

#: Pecori Giraldi Clin Endo 2001 reported 160 patients (148 CD, 12 EAS) included in Invitti JCEM 1999

§: Van Den Bogaert Clin Endo 1999 reported 121 patients included in their previous study Biemond Ann Intern Med 1990

^: Barbot Pituitary 2016 included patients (31 CD) reported in Testa Eur J Endocrinol 2007

$: Chen JCEM 2020 reported 227 cases (206 CD, 21 EAS, time span 2011-2013) Included in Feng 2017 World Neurosurgery (315 CD and no EAS, studied 2013-2015)

¥: Ferrante JENI 2021: considered only patients from Milan (those from Padova previously reported in Barbot Pituitary 2016 or Ceccato JCEM 2020)

Supplementary Table 3. Characteristics of the included studies reporting desmopressin test (continued 1/2).

First Author	Year	male	female	setting	recruitment years	cases per year	total ACTH-dependent CS	CD	EAS	reference standard
Malerbi	1993	13	3	university hospital	na	na	16	15	1	pathology/imaging/BIPSS/surgical remission
Colombo	1997	na	na	university hospital	na	na	18	17	1	surgical remission/ BIPSS / dynamic tests/ imaging
Newell-Price	1997	5	17	referral center	na	na	22	17	5	pathology/BIPSS
Sakai	1997	na	na	university hospital	na	na	13	10	3	pathology
Moro (only CD)	2000			university hospital			76	76	0	pathology/surgical remission
Terzolo #	2001	na	na	university hospital	1987-1999	2	24	19	5	pathology/surgical remission
Tsagarakis §	2002	20	11	university hospital	na	na	31	26	5	pathology/surgical remission/BIPSS
Salgado (only EAS)	2006	na	na	university hospital	1975-2005	0.43	13	0	13	pathology/imaging
Gasinska (only CD)	2007	7	8	university hospital	na	na	15	15	0	pathology/surgical remission
Pecori (only CD)	2007	na	na	referral center	6 years	4.5	27	27		pathology/imaging
Marova	2008	na	na	referral center	na	na	32	21	11	Pathology / imaging
Vilar	2008	na	na	university hospital	2000-2007	3.57	25	21	4	BIPSS / dynamic tests/imaging
Suda	2009	na	na	university hospital	1978-2008	1.03	31	22	9	pathology/surgical remission
Tirabassi (only CD vs pseudo-CS) $	2010	8	44	university hospital	1999-2008	5.78	52	52	0	pathology/surgical remission
Wang (only CD)	2012	25	4	university hospital	1998-2011	2.23	29	29	0	pathology
Rollin (only CD vs pseudo-CS)	2014	12	56	university hospital	na	na	68	68	0	pathology/surgical remission/BIPSS
Barbot ^	2016	na	na	multicentric referral (Italy, Padova - Ancona)	2003-2013	16.3	163	142	21	BIPSS/surgical remission / dinamic tests

Supplementary Table 3. Characteristics of the included studies reporting desmopressin test (continued 2/2).

First Author	Year	male	female	setting	recruitment years	cases per year	total ACTH-dependent CS	CD	EAS	reference standard
Davì (only EAS)	2017	na	na	multicentric referral (Italy)	1986-2014	0.93	26	0	26	BIPSS / dynamic tests
Frete	2020	40	154	multicentric referral (France, Bordeaux - Paris)	2001-2016	12.93	194	167	27	BIPSS/surgical remission / dynamic tests/imaging/
Ferrante ¥	2021	11	44	university hospital	2000-2017	3.06	55	48	7	pathology/surgical remission / dynamic tests
Qiao	2021	21	87	referral center	2013-2020	13.5	108	92	16	pathology/surgical remission / BIPSS / dynamic tests
	total						*1038*	*884*	*154*	

Terzolo Clin Endo 2001: the reported data regarding HDDST and CRH test are included in Reimondo Clin Endo 2003

§: Tsagarakis JCEM 2002 reported patients included in Tsagarakis Clin Endo 1999 (25 CD 3 EAS)

*: Malerbi Clin Endo 1993 included 14 women with CD reported in Malerbi JCEM 1996

^: Barbot Pituitary 2016 included patients (31 CD) reported in Testa Eur J Endocrinol 2007

$: Tirabassi Clin Endo 2011 (30 CD) were included in Tirabassi JCEM 2010 (52 CD)

¥: Ferrante JENI 2021: considered only patients from Milan (those from Padova previously reported in Barbot Pituitary 2016 or Ceccato JCEM 2020)

Supplementary Table 4. CRH test results from individual studies (continued 1/3).

First Author	Year	type of test	cutoff	type of cutoff	TP	FP	FN	TN
Tabarin	1990	100 µg ovine	CD: Δcortisol +60.6%	ROC-based	18	0	3	7
Colao	1993	100 µg human	CD: ΔACTH +50%	predefined	18	1	0	1
			CD: Δcortisol +20%	predefined	18	1	0	1
Malerbi (only CD)	1993	1 µg/kg BW ovine	CD: Δcortisol +40%	predefined	9		1	
Nieman	1993	1 µg/kg BW ovine	CD: ΔACTH +30%	ROC-based	93	0	7	16
			CD: Δcortisol +20%	ROC-based	88	2	9	14
Suda	1993	100 µg	CD: ΔACTH +50%	predefined	10	3	0	7
Freda	1995	100 µg ovine	CD: ΔACTH +50% / Δcortisol +20%	predefined	17	0	0	1
Dickstein (only CD vs pseudo-CS)	1996	1 µg/kg BW ovine	CD: ΔACTH +35%	predefined	45		6	
			CD: Δcortisol +20%	predefined	43		8	
Colombo	1997	1 µg/kg BW ovine	CD: ΔACTH +35%	predefined	15	0	2	1
			CD: Δcortisol +20%	predefined	16	0	1	1
Al-Saadi	1998	100 µg human	CD: ΔACTH +50%	predefined	21	0	3	1
			CD: Δcortisol +20%	predefined	24	0	0	1
Teramoto	1998	100 µg human	CD: yes / no	predefined	31	0	3	4
Invitti #	1999	100 µg human (36%) ovine (64%)	CD: ΔACTH +50%	predefined	134	0	24	13
			CD: Δcortisol +20%	predefined	123	6	35	7
			CD: Δcortisol +50%	predefined	93	1	65	12
Wiggam	2000	100 µg ovine	CD: Δcortisol +50%	predefined	16	0	7	1
Newell-Price *,£	2002	100 µg human	CD: ΔACTH +35% (22 cases JCEM 1997)	predefined	14	2	3	3
			CD: ΔACTH +105% (115 cases JCEM 2002)	ROC-based	65	0	28	14
			CD: Δcortisol +20% (22 cases JCEM 1997)	predefined	15	0	2	5
			CD: Δcortisol +14% (115 cases JCEM 2002)	ROC-based	85	0	15	14
			CD: Δcortisol +20% (143 cases JCEM 2003)	predefined	99	1	24	19
Tsagarakis §	2002	100 µg human	CD: ΔACTH +35%	ROC-based	19	0	7	5
			CD: Δcortisol +20%	ROC-based	19	0	7	5
Reimondo	2003	100 µg ovine	CD: ΔACTH +50%	ROC-based	42	1	7	9
			CD: Δcortisol +30%	ROC-based	30	3	19	7

Supplementary Table 4. CRH test results from individual studies (continued 2/3).

First Author	Year	type of test	cutoff	type of cutoff	TP	FP	FN	TN
Isidori (only EAS) %	2006	100 µg human (89%) ovine (11%)	CD: ACTH response yes/no	predefined		0		18
Salgado (only EAS)	2006	not specified	CD: ACTH response yes/no	predefined		0		2
			CD: cortisol response yes/no	predefined		0		2
Gasinska (only CD)	2007	100 µg	CD: ΔACTH +35%	predefined	12		2	
			CD: Δcortisol +20%	predefined	14		1	
Lin (only CD)	2007	100 µg ovine	CD: ΔACTH +50% or Δcortisol +20%	predefined	12		5	
Tsagarakis	2007	100 µg human	CD: ΔACTH +50% and/or Δcortisol +20%	predefined	39	0	8	7
Vilar	2008	100 µg ovine	CD: ΔACTH +35%	predefined	15	0	1	3
			CD: ΔACTH +50%	predefined	13	0	3	3
			CD: Δcortisol +20%	predefined	13	1	3	2
			CD: Δcortisol +50%	predefined	10	1	6	2
Arnaldi $	2009	100 µg human	CD: ΔACTH +9%	ROC-based	44	0	7	7
			CD: Δcortisol +14%	ROC-based	51	0	0	7
Suda	2009	100 µg human	CD: ΔACTH +50%	predefined	70	4	3	11
Wang (only CD)	2012	100 µg	CD: ΔACTH +50%	predefined	14		15	
			CD: Δcortisol +20%	predefined	16		13	
Ritzel	2015	100 µg human	CD: ΔACTH +43% at 15 minutes	ROC-based	65	1	13	17
			CD: ΔACTH +50%	predefined	65	2	13	16
			CD: Δcortisol +32% at 30 minutes	ROC-based	46	1	32	17
			CD: Δcortisol +30%	predefined	61	4	17	14
Barbot ^	2016	100 µg human (70%) ovine (30%)	CD: ΔACTH +72.4%	ROC-based	113	0	36	21
Davì (only EAS)	2017	not specified	EAS: no response	predefined		3		55
Polat Korkmaz (only CD)	2019	100 µg ovine	CD: ΔACTH +115%	ROC-based	6		3	
			CD: ΔACTH +50%	predefined	9		0	
			CD: Δcortisol +86%	ROC-based	7		2	
			CD: ΔACTH +20%	predefined	9		0	

Supplementary Table 4. CRH test results from individual studies (continued 3/3).

First Author	Year	type of test	cutoff	type of cutoff	TP	FP	FN	TN
Ceccato §	2020	100 µg human	CD: ΔACTH +31%	ROC-based	40	2	2	9
			CD: Δcortisol +20%	ROC-based	36	2	6	9
Frete	2020	100 µg human	CD: ΔACTH +37%	ROC-based	147	5	20	22
			CD: Δcortisol +17%	ROC-based	151	4	16	23
Ferrante ¥	2021	100 µg human	CD: ΔACTH +50%	predefined	47	1	10	10
			CD: Δcortisol +20%	predefined	50	1	7	10
Gonzalez Fernandez	2021	100 µg human	CD: ΔACTH +50%	predefined	18	1	1	3
			CD: ΔACTH +45.3%	ROC-based	19	1	0	3
			CD: Δcortisol +20%	predefined	13	0	0	2

#: Pecori Giraldi Clin Endo 2001 reported 160 patients (148 CD, 12 EAS) included in Invitti JCEM 1999

§: Ceccato JCEM 2020 53 patients (42 CD 11 EAS) not included in Barbot Pituitary 2016

*: Newell-Price JCEM 2002 described patients included in Newell-Price JCEM 1997

^: Barbot Pituitary 2016 included patients (31 CD) reported in Testa Eur J Endocrinol 2007

$: Tirabassi Clin Endo 2011 (30 CD) were included in Arnaldi Eur J Endocrinol 2009 (51 CD, 7 EAS)

£: Isidori JCEM 2003 (CRH performed in 123 CD and 20 EAS) reported in Newell-Price JCEM 2002

%: reported only ACTH response to CRH, cortisol response is reported in Newell-Price JCEM 2002

¥: Ferrante JENI 2021: considered only patients from Milan (those from Padova previously reported in Barbot Pituitary 2016 or Ceccato JCEM 2020)

Supplementary Table 5. HDDST results from individual studies (continued 1/3).

First Author	Year	type of test	cutoff	type of cutoff	TP	FP	FN	TN
Blunt	1990	2mg/6h for 2 days - urinary cortisol	CD: 50% serum cortisol suppression	predefined	11	2	8	5
			CD: 50% urinary cortisol suppression	predefined	16	1	5	4
Findling	1991	not specified (8mg overnight or 2mg/6h, urinary or serum)	CD: 50% cortisol suppression	predefined	16	3	4	6
Flack	1992	6-day (2mg/6h for 2 days) - urinary cortisol	CD: 50% cortisol suppression	predefined	85	4	9	6
			CD: 80% cortisol suppression	predefined	76	2	18	8
			CD: 90% cortisol suppression	predefined	65	0	29	10
Colao	1993	not specified - urinary and serum cortisol	CD: 50% serum cortisol suppression	predefined	22	0	3	2
			CD: 50% urinary cortisol suppression	predefined	20	0	5	2
Suda	1993	8mg overnight - serum cortisol	CD: 50% cortisol suppression	predefined	10	1	0	9
Freda	1995	not specified (92% urinary, 8% serum cortisol)	CD: 50% cortisol suppression	predefined	20	0	4	1
Avgerinos	1994	6-day (2mg/6h for 2 days) - urinary cortisol	CD: 90% cortisol suppression	predefined	100	0	70	15
Dichek	1994	6-day (2mg/6h for 2 days) - urinary cortisol 8mg overnight - serum cortisol	CD: 90% cortisol suppression	predefined	22	0	12	7
			CD: 68% cortisol suppression	ROC-based	24	0	10	7
			CD: 50% cortisol suppression	predefined	30	3	4	4
			CD: 80% cortisol suppression	predefined	20	0	14	7
Aron	1997	not reported	CD: 50% cortisol suppression	predefined	47	5	11	10
Al-Saadi	1998	8mg overnight - serum cortisol	CD: 50% cortisol suppression	predefined	15	0	11	2
		32mg overnight - serum cortisol (20 cases, 71%)	CD: 50% cortisol suppression	predefined	13	0	6	1
		32mg overnight - urinary cortisol (20 cases, 71%)	CD: 50% cortisol suppression	predefined	16	0	3	1
Teramoto	1998	8 mg/day - urinary cortisol	CD: cortisol suppression yes/no	predefined	32	2	3	3
Van Den Bogaert §	1999	7 mg ev – serum cortisol	CD: Δcortisol -190 nmol/L from baseline	predefined	74	3	4	5
Puig	1999	2mg/6h for 2 days - urinary and serum cortisol	CD: 50% cortisol suppression	predefined	41	2	4	1
Invitti	1999	2mg/6h for 2 days (62% urinary, 38% serum cortisol)	CD: 50% cortisol suppression	predefined	123	5	20	11
			CD: 80% cortisol suppression	predefined	72	0	71	16
Wiggam	2000	2mg/6h for 2 days - serum cortisol	CD: 50% cortisol suppression	predefined	41	0	3	1
			CD: 90% cortisol suppression	predefined	21	0	23	1

Supplementary Table 5. HDDST results from individual studies (continued 2/3).

First Author	Year	type of test	cutoff	type of cutoff	TP	FP	FN	TN
Isidori	2003	2mg/6h for 2 days - serum cortisol	CD: 50% cortisol suppression	predefined	159	6	28	26
			CD: 60% cortisol suppression	ROC-based	150	3	37	29
Reimondo	2003	8mg overnight - serum cortisol	CD: 50% cortisol suppression	ROC-based	38	4	11	6
Isidori (only EAS)	2006	2mg/6h for 2 days - serum cortisol	CD: 50% cortisol suppression	predefined		3		29
Salgado (only EAS)	2006	8mg overnight - serum cortisol	CD: 50% cortisol suppression	predefined		5		15
Hernandez (only EAS)	2006	8mg overnight - serum cortisol	CD: 68% cortisol suppression	ROC-based		0		8
Shah	2006	8/16/32 mg overnight - serum cortisol	CD: 50% cortisol suppression	predefined	46	1	20	7
Castinetti	2007	not reported	not reported	predefined	29	0	7	7
Tsagarakis	2007	2mg/6h for 2 days - serum cortisol	CD: 50% cortisol suppression	predefined	35	2	10	5
Gasinska (only CD)	2007	8mg overnight - serum cortisol	CD: 50% cortisol suppression	predefined	14		1	
Lin (only CD)	2007	6-day (2mg/6h for 2 days) - serum and urinary cortisol	CD: 50% serum cortisol suppression (day 3) or 10% UFC (day 2)	predefined	11		5	
Vilar	2008	8mg overnight - serum cortisol	CD: 50% cortisol suppression	predefined	31	2	8	5
			CD: 80% cortisol suppression	predefined	22	0	17	7
Esfahanian	2009	8mg overnight - serum cortisol	CD: 50% cortisol suppression	predefined	25	0	7	3
		6-day (2mg/6h for 2 days) - urinary cortisol	CD: 50% cortisol suppression	predefined	23	0	9	3
			CD: 90% cortisol suppression	predefined	29	0	3	3
Suda	2009	8mg overnight - serum cortisol	CD: 50% cortisol suppression	predefined	60	3	13	12
Shi	2011	6-day (2mg/6h for 2 days) - serum / urinary cortisol	CD: 50% cortisol suppression	predefined	38	0	26	5
Aytug (only CD)	2012	8mg overnight - serum cortisol (77 cases, 55%) or 2mg/6h for 2 days - urinary cortisol (64 cases, 45%)	CD: 50% serum cortisol suppression	predefined	73		4	
			CD: 80% serum cortisol suppression	predefined	48		29	
			CD: 90% urinary cortisol suppression	predefined	41		23	
Wang (only CD)	2012	2mg/6h for 2 days (89% urinary, 87% serum cortisol)	CD: 50% cortisol suppression	predefined	23		5	
Ammini	2014	2mg/6h for 2 days - serum cortisol	CD: 50% cortisol suppression	predefined	88	2	77	20
Ritzel	2015	8mg overnight - serum cortisol	CD: 50% cortisol suppression	predefined	55	4	9	10
			CD: 71% cortisol suppression	ROC-based	41	1	23	13

Supplementary Table 5. HDDST results from individual studies (continued 3/3).

First Author	Year	type of test	cutoff	type of cutoff	TP	FP	FN	TN
Barbot ^	2016	8mg overnight - serum cortisol	CD: 52.7% cortisol suppression	ROC-based	111	2	15	19
			CD: 75% cortisol suppression	ROC-based	96	0	30	21
Chen (only EAS)	2016	8mg overnight - serum cortisol	CD: 50% cortisol suppression	predefined		1		15
Davì (only EAS)	2017	not specified	CD: suppression	predefined		10		60
Polat Korkmaz (only CD)	2019	8mg overnight - serum cortisol	CD: 64% cortisol suppression	ROC-based	9		0	
Liu	2020	2mg/6h for 2 days - urinary cortisol	CD: 50% cortisol suppression	predefined	86	6	16	10
Chen	2020	2mg/6h for 2 days - urinary cortisol	CD: 50% cortisol suppression	predefined	174	11	32	10
Ferrante ¥	2021	8mg overnight - serum cortisol	CD: 50% cortisol suppression	predefined	45	4	3	7
Ding	2021	2mg/6h for 2 days - urinary cortisol	CD: 50% cortisol suppression	predefined	81	1	7	23
Qiao	2021	2mg/6h for 2 days – serum and urinary cortisol	CD: 50% urinary cortisol suppression	predefined	75	8	17	8
			CD: 62.7% urinary cortisol suppression	ROC-based	74	3	18	13
			CD: 51.2% serum cortisol suppression	ROC-based	61	3	31	13
Shi	2021	2mg/6h for 2 days - serum cortisol	CD: 50% cortisol suppression	predefined	71	4	30	14
			CD: 42.5% cortisol suppression	ROC-based	77	4	24	14

#: Pecori Giraldi Clin Endo 2001 reported 160 patients (148 CD, 12 EAS) included in Invitti JCEM 1999

§: Van Den Bogaert Clin Endo 1999 reported 121 patients included in their previous study Biemond Ann Intern Med 1990

^: Barbot Pituitary 2016 included patients (31 CD) reported in Testa Eur J Endocrinol 2007

$: Chen JCEM 2020 reported 227 cases (206 CD, 21 EAS, time span 2011-2013) Included in Feng 2017 World Neurosurgery (315 CD and no EAS, studied 2013-2015)

¥: Ferrante JENI 2021: considered only patients from Milan (those from Padova previously reported in Barbot Pituitary 2016 or Ceccato JCEM 2020)

Supplementary Table 6. Desmopressin test results from individual studies (continued 1/2).

First Author	Year	type of test	cutoff	type of cutoff	TP	FP	FN	TN
Malerbi	1993	5 µg (19%) or 10 µg (81%)	CD: Δcortisol +40%	predefined	15	0	1	1
Colombo	1997	10 µg	CD: ΔACTH +50%	predefined	17	0	0	1
			CD: Δcortisol +20%	predefined	16	0	1	1
Newell-Price	1997	10 µg	CD: ΔACTH +35%	predefined	12	3	5	2
			CD: Δcortisol +20%	predefined	14	1	3	4
Sakai	1997	5 µg	CD: ΔACTH +50%	predefined	10	0	0	3
Moro (only CD)	2000	10 µg	CD: ΔACTH ≥6 pmol/L	ROC-based	66		10	
Terzolo #	2001	10 µg	CD: ΔACTH +35%	predefined	17	3	2	2
			CD: ΔACTH +50%	predefined	16	3	3	2
Tsagarakis §	2002	10 µg	CD: ΔACTH +50%	predefined	21	3	5	2
			CD: Δcortisol +20%	predefined	19	3	7	2
Salgado (only EAS)	2006	10 µg	CD: ΔACTH +35%	predefined		6		7
			CD: Δcortisol +20%	predefined		5		8
Gasinska (only CD)	2007	10 µg	CD: ΔACTH +35%	predefined	10		3	
			CD: Δcortisol +20%	predefined	11		4	
Pecori (only CD)	2007	10 µg	CD: ΔACTH ≥6 pmol/L	predefined	22		5	
Marova	2008	10 µg	CD: ACTH response yes/no	predefined	16	1	5	10
			CD: Δcortisol +30%	predefined	16	1	5	10
Vilar	2008	10 µg	CD: ΔACTH +35%	predefined	18	1	3	3
			CD: ΔACTH +50%	predefined	16	0	5	4
			CD: Δcortisol +20%	predefined	16	1	5	3
			CD: Δcortisol +50%	predefined	10	1	11	3
Suda	2009	4 µg	CD: ΔACTH +50%	predefined	19	4	3	5
Tirabassi (only CD vs pseudo-CS) $	2010	10 µg	CD: basal cortisol >331 nmol/ L and ΔACTH >4 pmol/L	ROC-based	47		5	
Wang (only CD)	2012	10 µg	CD: ΔACTH +50%	predefined	27		2	
			CD: Δcortisol +20%	predefined	25		4	

Supplementary Table 6. Desmopressin test results from individual studies (continued 2/2).

First Author	Year	type of test	cutoff	type of cutoff	TP	FP	FN	TN
Rollin (only CD vs pseudo-CS)	2014	10 µg	CD: ΔACTH +98%	ROC-based	56		12	
			CD: Δcortisol +34%	ROC-based	54		14	
Barbot ^	2016	10 µg	CD: ΔACTH +32,3%	ROC-based	118	8	24	13
Davì (only EAS)	2017	not specified	EAS: no response	predefined		6		20
Frete	2020	10 µg	CD: ΔACTH +33%	ROC-based	143	6	24	21
Ferrante ¥	2021	10 µg	CD: ΔACTH +30%	predefined	34	2	14	5
			CD: Δcortisol +20%	predefined	33	2	14	5
Qiao	2021	10 µg	CD: ΔACTH +35%	predefined	85	5	7	11
			CD: ΔACTH +44.6%	ROC-based	84	4	8	12
			CD: Δcortisol +20%	predefined	78	2	14	14
			CD: Δcortisol +16.2%	ROC-based	80	2	12	14

Terzolo Clin Endo 2001: the reported data regarding HDDST and CRH test are included in Reimondo Clin Endo 2003

§: Tsagarakis JCEM 2002 reported patients included in Tsagarakis Clin Endo 1999 (25 CD 3 EAS)

*: Malerbi Clin Endo 1993 included 14 women with CD reported in Malerbi JCEM 1996

^: Barbot Pituitary 2016 included patients (31 CD) reported in Testa Eur J Endocrinol 2007

$: Tirabassi Clin Endo 2011 (30 CD) were included in Tirabassi JCEM 2010 (52 CD)

¥: Ferrante JENI 2021: considered only patients from Milan (those from Padova previously reported in Barbot Pituitary 2016 or Ceccato JCEM 2020)

Supplementary Table 7. Meta-regression of the Diagnostic Odds Ratio of Dynamic Diagnostic Tests for ACTH-dependent CS.

Diagnostic Odds Ratio (95% CI)		All other tests	p
Δ ACTH CRH	57.88 (43.25-77.47)	16.67 (12.88-21.56)	*<0.001*
Δ cortisol CRH	32.04 (16.91-60.72)	18.98 (14.68 – 24.55)	0.123
Δ serum cortisol HDDST	15.83 (10.81-23.18)	23.67 (17.43-32.14)	0.193
Δ urinary cortisol HDDST	16.2 (8.78-29.88)	21.79 (16.77-28.31)	0.326
Δ ACTH desmopressin	11.4 (6.86-20.26)	23.24 (17.83-30.31)	*0.036*
Δ cortisol desmopressin	13.51 (5.25-34.77)	21.5 (16.71-27.72)	0.318

Supplementary Table 8. QUADAS-2 methodological assessment of individual studies (continued 1/5).

First Author	Year	Setting	Type of study	Design	Risk of Bias				Applicability Concern		
					Patient selection	Index test	Reference Standard	Flow and Timing	Patient selection	Index test	Reference Standard
Blunt	1990	referral center	case-control (CD vs EAS)	retrospective	low	high	low	unclear	low	high	low
Tabarin	1990	referral center	case-control (CD vs EAS)	retrospective	low	high	low	unclear	low	high	low
Findling	1991	referral center	case-control (CD vs EAS)	retrospective	low	high	low	unclear	low	high	low
Flack	1992	referral center	case-control (CD vs EAS)	retrospective	low	low	low	low	low	low	low
Colao	1993	university hospital	case-control (CD vs EAS)	retrospective	low	unclear	high	unclear	low	high	high
Malerbi	1993	university hospital	case-control (CD vs EAS)	retrospective	low	high	low	unclear	high	high	low
Nieman	1993	referral center	case-control (CD vs EAS)	retrospective	low	low	low	unclear	low	low	low
Suda	1993	university hospital	case-control (CD vs EAS)	retrospective	low	low	low	unclear	high	low	low
Avgerinos	1994	referral center	case-control (CD vs EAS)	retrospective	low	low	low	low	low	low	low
Dichek	1994	referral center	case-control (CD vs EAS)	retrospective	low	low	low	unclear	low	low	low
Freda	1995	university hospital	case-control (CD vs EAS)	retrospective	low	low	low	unclear	low	low	low
Dickstein	1996	referral center	case-control (CD vs pseudo-CS)	retrospective	high	high	low	unclear	high	high	low
Aron	1997	university hospital	case-control (CD vs EAS)	retrospective	low	high	low	unclear	low	high	low
Colombo	1997	university hospital	case-control (CD vs EAS)	retrospective	low	low	low	low	low	low	low

Supplementary Table 8. QUADAS-2 methodological assessment of individual studies (continued 2/5).

First Author	Year	Setting	Type of study	Design	Risk of Bias				Applicability Concern		
					Patient selection	Index test	Reference Standard	Flow and Timing	Patient selection	Index test	Reference Standard
Newell-Price	1997	university hospital	case-control (CD vs EAS)	retrospective	low	low	low	low	low	low	low
Sakai	1997	university hospital	case-control (CD vs EAS)	retrospective	low	high	low	unclear	high	high	low
Al-Saadi	1998	university hospital	case-control (CD vs EAS)	retrospective	low	low	low	unclear	low	low	low
Teramoto	1998	university hospital	case-control (CD vs EAS)	retrospective	high	high	high	unclear	high	high	low
Invitti	1999	multicentric referral	case-control (CD vs EAS)	retrospective	low	low	low	unclear	low	low	low
Puig	1999	university hospital	case-control (CD vs EAS)	retrospective	low	low	low	unclear	low	low	low
Van Den Bogaert	1999	university hospital	case-control (CD vs EAS)	retrospective	low	low	low	unclear	low	low	low
Moro	2000	university hospital	case-control (CD vs pseudo-CS)	retrospective	high	high	low	unclear	high	high	low
Wiggam	2000	referral center	case-control (CD vs EAS)	retrospective	high	high	hlow	unclear	high	high	low
Terzolo	2001	university hospital	case-control (CD vs EAS)	retrospective	low	low	low	low	low	low	low
Newell-Price	2002	university hospital	case-control (CD vs EAS)	retrospective	low	low	low	low	low	low	low
Tsagarakis	2002	university hospital	case-control (CD vs EAS)	retrospective	low	low	low	low	low	low	low
Isidori	2003	university hospital	case-control (CD vs EAS)	retrospective	low	low	low	unclear	low	low	low
Reimondo	2003	university hospital	case-control (CD vs EAS)	retrospective	low	low	low	low	low	low	low

Supplementary Table 8. QUADAS-2 methodological assessment of individual studies (continued 3/5).

First Author	Year	Setting	Type of study	Design	Risk of Bias				Applicability Concern		
					Patient selection	Index test	Reference Standard	Flow and Timing	Patient selection	Index test	Reference Standard
Isidori	2006	university hospital	only EAS	retrospective	high	low	low	unclear	high	low	low
Shah	2006	university hospital	case-control (CD vs CS)	retrospective	high	high	high	unclear	high	low	high
Hernandez	2006	referral center	only EAS	retrospective	high	low	low	high	high	low	high
Salgado	2006	university hospital	only EAS	retrospective	high	low	low	unclear	high	low	low
Castinetti	2007	university hospital	case-control (CD vs EAS)	retrospective	low	high	low	unclear	low	high	low
Gasinska	2007	university hospital	only CD	retrospective	high	low	low	unclear	high	low	low
Lin	2007	university hospital	only CD	retrospective	high	low	low	unclear	high	low	low
Pecori Giraldi	2007	referral center	case-control (CD vs pseudo-CS)	retrospective	high	low	low	low	high	low	low
Tsagarakis	2007	university hospital	case-control (CD vs EAS)	retrospective	low	high	low	low	low	low	low
Marova	2008	referral center	case-control (CD vs EAS vs adrenal CS)	retrospective	high	high	high	unclear	high	low	high
Vilar	2008	university hospital	case-control (CD vs EAS)	retrospective	low	high	high	unclear	low	low	high
Arnaldi	2009	university hospital	case-control (CD vs EAS vs pseudo-CS)	retrospective	high	low	low	low	high	low	low
Esfahanian	2009	university hospital	case-control (CD vs EAS)	retrospective	low	low	high	high	high	low	high
Suda	2009	university hospital	case-control (CD vs EAS)	retrospective	low	high	high	unclear	high	high	high

Supplementary Table 8. QUADAS-2 methodological assessment of individual studies (continued 4/5).

First Author	Year	Setting	Type of study	Design	Risk of Bias				Applicability Concern		
					Patient selection	Index test	Reference Standard	Flow and Timing	Patient selection	Index test	Reference Standard
Tirabassi	2010	university hospital	case-control (CD vs pseudo-CS)	retrospective	high	low	low	low	high	low	low
Shi	2011	university hospital	case-control (CD vs EAS)	retrospective	low	low	high	unclear	low	low	low
Aytug	2012	university hospital	only CD	retrospective	high	low	low	unclear	high	low	low
Wang	2012	university hospital	only CD	retrospective	high	low	low	unclear	high	low	low
Ammini	2014	referral center	patients with CS	retrospective	high	high	high	unclear	high	low	high
Rollin	2014	university hospital	case-control (CD vs pseudo-CS)	retrospective	high	high	low	unclear	high	high	low
Ritzel	2015	university hospital	case-control (CD vs EAS)	retrospective	low	low	low	low	low	low	low
Barbot	2016	multicentric referral	case-control (CD vs EAS)	retrospective	low	low	low	unclear	low	low	low
Chen	2016	university hospital	only EAS	retrospective	high	unclear	high	unclear	high	unclear	low
Davì	2017	multicentric referral	only EAS	retrospective	high	unclear	high	unclear	high	unclear	high
Polat Korkmaz	2019	referral center	case-control (CD vs adrenal CS)	retrospective	high	low	low	high	high	low	high
Ceccato	2020	university hospital	case-control (CD vs EAS)	retrospective	low	low	low	low	low	low	low
Chen	2020	university hospital	case-control (CD vs EAS)	retrospective	low	low	low	unclear	low	low	low
Frete	2020	multicentric referral	case-control (CD vs EAS)	retrospective	low	low	low	unclear	low	low	low
Liu	2020	university hospital	case-control (CD vs EAS)	retrospective	low	low	low	unclear	low	low	low

Supplementary Table 8. QUADAS-2 methodological assessment of individual studies (continued 5/5).

First Author	Year	Setting	Type of study	Design	Risk of Bias				Applicability Concern		
					Patient selection	Index test	Reference Standard	Flow and Timing	Patient selection	Index test	Reference Standard
Ding	2021	university hospital	case-control (CD vs EAS)	retrospective	low	high	low	unclear	low	high	low
Ferrante	2021	university hospital	case-control (CD vs EAS)	retrospective	low	low	low	unclear	low	low	low
Gonzalez Fernandez	2021	university hospital	case-control (CD vs EAS)	retrospective	low	low	low	unclear	low	low	low
Qiao	2021	university hospital	case-control (CD vs EAS)	retrospective	low	unclear	low	unclear	low	unclear	low
Shi	2021	university hospital	case-control (CD vs EAS)	retrospective	low	low	low	unclear	low	low	low

Supplementary Figure 1. Forest Plots of the Sensitivity to detect CD in second-line tests for ACTH-dependent CS. Panel a: Δ ACTH after CRH test; panel b: Δ cortisol after CRH test.

a)

Author (Year)	Responders	CD	Proportion	95%-CI
cutoff = predefined				
Colao (1993)	18	18	1.00	[0.81; 1.00]
Suda (1993)	10	10	1.00	[0.69; 1.00]
Freda (1995)	17	17	1.00	[0.80; 1.00]
Dickstein (1996)	45	51	0.88	[0.76; 0.96]
Colombo (1997)	15	17	0.88	[0.64; 0.99]
Al-Saadi (1998)	21	24	0.88	[0.68; 0.97]
Teramoto (1998)	31	34	0.91	[0.76; 0.98]
Invitti (1999)	134	158	0.85	[0.78; 0.90]
Gasinska (2007)	12	14	0.86	[0.57; 0.98]
Lin (2007)	12	17	0.71	[0.44; 0.90]
Tsagarakis (2007)	39	47	0.83	[0.69; 0.92]
Vilar (2008)	15	16	0.94	[0.70; 1.00]
Suda (2009)	70	73	0.96	[0.88; 0.99]
Wang (2012)	14	29	0.48	[0.29; 0.67]
Ferrante (2021)	47	57	0.82	[0.70; 0.91]
Random effects model		582	0.89	[0.81; 0.93]
Heterogeneity: $I^2 = 58\%$, $\tau^2 = 0.6737$, $p < 0.01$				
cutoff = ROC-based				
Nieman (1993)	93	100	0.93	[0.86; 0.97]
Newell-Price (2002)	65	93	0.70	[0.60; 0.79]
Tsagarakis (2002)	19	26	0.73	[0.52; 0.88]
Reimondo (2003)	42	49	0.86	[0.73; 0.94]
Arnaldi (2009)	44	51	0.86	[0.74; 0.94]
Ritzel (2015)	65	78	0.83	[0.73; 0.91]
Barbot (2016)	113	149	0.76	[0.68; 0.82]
Polat Korkmaz (2019)	6	9	0.67	[0.30; 0.93]
Ceccato (2020)	40	42	0.95	[0.84; 0.99]
Frete (2020)	147	167	0.88	[0.82; 0.93]
Gonzalez Fernandez (2021)	19	19	1.00	[0.82; 1.00]
Random effects model		783	0.85	[0.78; 0.90]
Heterogeneity: $I^2 = 69\%$, $\tau^2 = 0.3307$, $p < 0.01$				
Random effects model		1365	0.87	[0.82; 0.91]
Heterogeneity: $I^2 = 62\%$, $\tau^2 = 0.4969$, $p < 0.01$				
Test for subgroup differences: $\chi^2_1 = 0.69$				

CRH ACTH Sensitivity (0.5 0.6 0.7 0.8 0.9 1)

b)

Author (Year)	Responders	CD	Proportion	95%-CI
cutoff = ROC-based				
Tabarin (1990)	18	21	0.86	[0.64; 0.97]
Nieman (1993)	88	97	0.91	[0.83; 0.96]
Newell-Price (2002)	85	100	0.85	[0.76; 0.91]
Tsagarakis (2002)	19	26	0.73	[0.52; 0.88]
Reimondo (2003)	30	49	0.61	[0.46; 0.75]
Arnaldi (2009)	51	51	1.00	[0.93; 1.00]
Ritzel (2015)	46	78	0.59	[0.47; 0.70]
Polat Korkmaz (2019)	7	9	0.78	[0.40; 0.97]
Ceccato (2020)	36	42	0.86	[0.71; 0.95]
Frete (2020)	151	167	0.90	[0.85; 0.94]
Random effects model		640	0.84	[0.72; 0.92]
Heterogeneity: $I^2 = 82\%$, $\tau^2 = 0.8041$, $p < 0.01$				
cutoff = predefined				
Colao (1993)	18	18	1.00	[0.81; 1.00]
Malerbi (1993)	9	10	0.90	[0.55; 1.00]
Dickstein (1996)	43	51	0.84	[0.71; 0.93]
Colombo (1997)	16	17	0.94	[0.71; 1.00]
Al-Saadi (1998)	24	24	1.00	[0.86; 1.00]
Invitti (1999)	93	158	0.59	[0.51; 0.67]
Wiggam (2000)	16	23	0.70	[0.47; 0.87]
Gasinska (2007)	14	15	0.93	[0.68; 1.00]
Vilar (2008)	13	16	0.81	[0.54; 0.96]
Wang (2012)	16	29	0.55	[0.36; 0.74]
Ferrante (2021)	50	57	0.88	[0.76; 0.95]
Gonzalez Fernandez (2021)	13	13	1.00	[0.75; 1.00]
Random effects model		431	0.88	[0.74; 0.95]
Heterogeneity: $I^2 = 67\%$, $\tau^2 = 1.3633$, $p < 0.01$				
Random effects model		1071	0.86	[0.78; 0.91]
Heterogeneity: $I^2 = 78\%$, $\tau^2 = 1.0176$, $p < 0.01$				
Test for subgroup differences: $\chi^2_1 = 0.39$				

CRH cortisol Sensitivity (0.5 0.6 0.7 0.8 0.9 1)

Supplementary Figure 1. Forest Plots of the Sensitivity to detect CD in second-line tests for ACTH-dependent CS. Panel c: serum cortisol suppression after HDDST; panel d: urinary cortisol suppression after HDDST.

c)

Author (Year)	Suppressors	CD	Proportion	95%-CI
cutoff = predefined				
Blunt (1990)	11	19	0.58	[0.33; 0.80]
Findling (1991)	16	20	0.80	[0.56; 0.94]
Colao (1993)	22	25	0.88	[0.69; 0.97]
Suda (1993)	10	10	1.00	[0.69; 1.00]
Aron (1997)	47	58	0.81	[0.69; 0.90]
Al-Saadi (1998)	15	26	0.58	[0.37; 0.77]
Van Den Bogaert (1999)	74	78	0.95	[0.87; 0.99]
Puig (1999)	41	45	0.91	[0.79; 0.98]
Wiggam (2000)	41	44	0.93	[0.81; 0.99]
Shah (2006)	46	66	0.70	[0.57; 0.80]
Castinetti (2007)	29	36	0.81	[0.64; 0.92]
Tsagarakis (2007)	35	45	0.78	[0.63; 0.89]
Gasinska (2007)	14	15	0.93	[0.68; 1.00]
Lin (2007)	11	16	0.69	[0.41; 0.89]
Vilar (2008)	22	39	0.56	[0.40; 0.72]
Esfahanian (2009)	25	32	0.78	[0.60; 0.91]
Suda (2009)	60	73	0.82	[0.71; 0.90]
Shi (2011)	38	64	0.59	[0.46; 0.71]
Aytug (2012)	73	77	0.95	[0.87; 0.99]
Wang (2012)	23	28	0.82	[0.63; 0.94]
Ammini (2014)	88	165	0.53	[0.45; 0.61]
Ferrante (2021)	45	48	0.94	[0.83; 0.99]
Random effects model		1029	0.82	[0.74; 0.87]
Heterogeneity: $I^2 = 81\%$, $\tau^2 = 0.6994$, $p < 0.01$				
cutoff = ROC-based				
Dichek (1994)	24	34	0.71	[0.53; 0.85]
Isidori (2003)	150	187	0.80	[0.74; 0.86]
Reimondo (2003)	38	49	0.78	[0.63; 0.88]
Ritzel (2015)	41	64	0.64	[0.51; 0.76]
Barbot (2016)	111	126	0.88	[0.81; 0.93]
Polat Korkmaz (2019)	9	9	1.00	[0.66; 1.00]
Shi (2021)	77	101	0.76	[0.67; 0.84]
Random effects model		570	0.79	[0.70; 0.85]
Heterogeneity: $I^2 = 62\%$, $\tau^2 = 0.1404$, $p = 0.01$				
Random effects model		1599	**0.81**	**[0.75; 0.85]**
Heterogeneity: $I^2 = 79\%$, $\tau^2 = 0.5531$, $p < 0.01$				
Test for subgroup differences: $\chi_1^2 = 0.43$				

HDDST serum Sensitivity

d)

Author (Year)	Suppressors	CD	Proportion	95%-CI
cutoff = predefined				
Blunt (1990)	16	21	0.76	[0.53; 0.92]
Flack (1992)	65	94	0.69	[0.59; 0.78]
Colao (1993)	20	25	0.80	[0.59; 0.93]
Avgerinos (1994)	100	170	0.59	[0.51; 0.66]
Dichek (1994)	22	34	0.65	[0.46; 0.80]
Freda (1995)	20	24	0.83	[0.63; 0.95]
Teramoto (1998)	32	35	0.91	[0.77; 0.98]
Al-Saadi (1998)	16	19	0.84	[0.60; 0.97]
Invitti (1999)	123	143	0.86	[0.79; 0.91]
Esfahanian (2009)	29	32	0.91	[0.75; 0.98]
Liu (2020)	86	102	0.84	[0.76; 0.91]
Chen (2020)	174	206	0.84	[0.79; 0.89]
Ding (2021)	81	88	0.92	[0.84; 0.97]
Random effects model		993	0.82	[0.75; 0.87]
Heterogeneity: $I^2 = 83\%$, $\tau^2 = 0.3278$, $p < 0.01$				
cutoff = ROC-based				
Qiao (2021)	74	92	0.80	[0.71; 0.88]
Random effects model		1085	**0.82**	**[0.75; 0.87]**
Heterogeneity: $I^2 = 81\%$, $\tau^2 = 0.2937$, $p < 0.01$				
Test for subgroup differences: $\chi_1^2 = 0.06$				

HDDST urinary Sensitivity

Supplementary Figure 1. Forest Plots of the Sensitivity to detect CD in second-line tests for ACTH-dependent CS. Panel e: ΔACTH after desmopressin test; panel f: Δcortisol after desmopressin test.

Supplementary Figure 2. Forest Plots of the Specificity to detect EAS in second-line tests for ACTH-dependent CS. Panel a: ΔACTH after CRH test; panel b: Δcortisol after CRH test.

a)

Author (Year)	Non responders	EAS	Proportion	95%-CI
cutoff = predefined				
Colao (1993)	1	2	0.50	[0.01; 0.99]
Suda (1993)	7	10	0.70	[0.35; 0.93]
Freda (1995)	1	1	1.00	[0.02; 1.00]
Colombo (1997)	1	1	1.00	[0.02; 1.00]
Al-Saadi (1998)	1	1	1.00	[0.02; 1.00]
Teramoto (1998)	4	4	1.00	[0.40; 1.00]
Invitti (1999)	13	13	1.00	[0.75; 1.00]
Isidori (2006)	18	18	1.00	[0.81; 1.00]
Salgado (2006)	2	2	1.00	[0.16; 1.00]
Tsagarakis (2007)	7	7	1.00	[0.59; 1.00]
Vilar (2008)	3	3	1.00	[0.29; 1.00]
Suda (2009)	11	15	0.73	[0.45; 0.92]
Davi (2017)	55	58	0.95	[0.86; 0.99]
Ferrante (2021)	10	11	0.91	[0.59; 1.00]
Random effects model		146	0.93	[0.80; 0.98]
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 1.0023$, $p = 0.79$				
cutoff = ROC-based				
Nieman (1993)	16	16	1.00	[0.79; 1.00]
Newell-Price (2002)	14	14	1.00	[0.77; 1.00]
Tsagarakis (2002)	5	5	1.00	[0.48; 1.00]
Reimondo (2003)	9	10	0.90	[0.55; 1.00]
Arnaldi (2009)	7	7	1.00	[0.59; 1.00]
Ritzel (2015)	17	18	0.94	[0.73; 1.00]
Barbot (2016)	21	21	1.00	[0.84; 1.00]
Ceccato (2020)	9	11	0.82	[0.48; 0.98]
Frete (2020)	22	27	0.81	[0.62; 0.94]
Gonzalez Fernandez (2021)	3	4	0.75	[0.19; 0.99]
Random effects model		133	0.94	[0.82; 0.98]
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0.6451$, $p = 0.99$				
Random effects model	279		0.94	[0.87; 0.97]
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0.8474$, $p = 0.99$				
Test for subgroup differences: $\chi^2_1 = 0.04$, df = 1 ($p = 0.85$)				

CRH ACTH Specificity

b)

Author (Year)	Non responders	EAS	Proportion	95%-CI
cutoff = ROC-based				
Tabarin (1990)	7	7	1.00	[0.59; 1.00]
Nieman (1993)	14	16	0.88	[0.62; 0.98]
Newell-Price (2002)	14	14	1.00	[0.77; 1.00]
Tsagarakis (2002)	5	5	1.00	[0.48; 1.00]
Reimondo (2003)	7	10	0.70	[0.35; 0.93]
Arnaldi (2009)	7	7	1.00	[0.59; 1.00]
Ritzel (2015)	17	18	0.94	[0.73; 1.00]
Ceccato (2020)	9	11	0.82	[0.48; 0.98]
Frete (2020)	23	27	0.85	[0.66; 0.96]
Random effects model		115	0.90	[0.81; 0.95]
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.94$				
cutoff = predefined				
Colao (1993)	1	2	0.50	[0.01; 0.99]
Colombo (1997)	1	1	1.00	[0.02; 1.00]
Al-Saadi (1998)	1	1	1.00	[0.02; 1.00]
Invitti (1999)	12	13	0.92	[0.64; 1.00]
Wiggam (2000)	1	1	1.00	[0.02; 1.00]
Salgado (2006)	2	2	1.00	[0.16; 1.00]
Vilar (2008)	2	3	0.67	[0.09; 0.99]
Ferrante (2021)	10	11	0.91	[0.59; 1.00]
Gonzalez Fernandez (2021)	2	2	1.00	[0.16; 1.00]
Random effects model		36	0.89	[0.70; 0.96]
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.93$				
Random effects model	151		0.89	[0.83; 0.94]
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.99$				
Test for subgroup differences: $\chi^2_1 = 0.01$, df = 1 ($p = 0.91$)				

CRH cortisol Specificity

Supplementary Figure 2. Forest Plots of the Specificity to detect EAS in second-line tests for ACTH-dependent CS. Panel c: serum cortisol suppression after HDDST; panel d: urinary cortisol suppression after HDDST.

c)

Author (Year)	Non suppressors	EAS	Proportion	95%-CI
cutoff = predefined				
Blunt (1990)	5	7	0.71	[0.29; 0.96]
Findling (1991)	6	9	0.67	[0.30; 0.93]
Colao (1993)	2	2	1.00	[0.16; 1.00]
Suda (1993)	9	10	0.90	[0.55; 1.00]
Aron (1997)	10	15	0.67	[0.38; 0.88]
Al-Saadi (1998)	2	2	1.00	[0.16; 1.00]
Van Den Bogaert (1999)	5	8	0.62	[0.24; 0.91]
Puig (1999)	1	3	0.33	[0.01; 0.91]
Wiggam (2000)	1	1	1.00	[0.02; 1.00]
Isidori (2006)	29	32	0.91	[0.75; 0.98]
Salgado (2006)	15	20	0.75	[0.51; 0.91]
Shah (2006)	7	8	0.88	[0.47; 1.00]
Castinetti (2007)	7	7	1.00	[0.59; 1.00]
Tsagarakis (2007)	5	7	0.71	[0.29; 0.96]
Vilar (2008)	7	7	1.00	[0.59; 1.00]
Esfahanian (2009)	3	3	1.00	[0.29; 1.00]
Suda (2009)	12	15	0.80	[0.52; 0.96]
Shi (2011)	5	5	1.00	[0.48; 1.00]
Ammini (2014)	20	22	0.91	[0.71; 0.99]
Chen (2016)	15	16	0.94	[0.70; 1.00]
Davi (2017)	60	70	0.86	[0.75; 0.93]
Ferrante (2021)	7	11	0.64	[0.31; 0.89]
Random effects model		280	0.83	[0.77; 0.88]
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0.0546$, $p = 0.71$				
cutoff = ROC-based				
Dichek (1994)	7	7	1.00	[0.59; 1.00]
Isidori (2003)	29	32	0.91	[0.75; 0.98]
Reimondo (2003)	6	10	0.60	[0.26; 0.88]
Hernandez (2006)	8	8	1.00	[0.63; 1.00]
Ritzel (2015)	13	14	0.93	[0.66; 1.00]
Barbot (2016)	19	21	0.90	[0.70; 0.99]
Shi (2021)	14	18	0.78	[0.52; 0.94]
Random effects model		110	0.88	[0.74; 0.95]
Heterogeneity: $I^2 = 10\%$, $\tau^2 = 0.2085$, $p = 0.35$				
Random effects model		**390**	**0.84**	**[0.80; 0.88]**
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0.1053$, $p = 0.67$				
Test for subgroup differences: $\chi_1^2 = 0.86$, df = 1 ($p = 0.36$)				

HDDST serum Specificity

d)

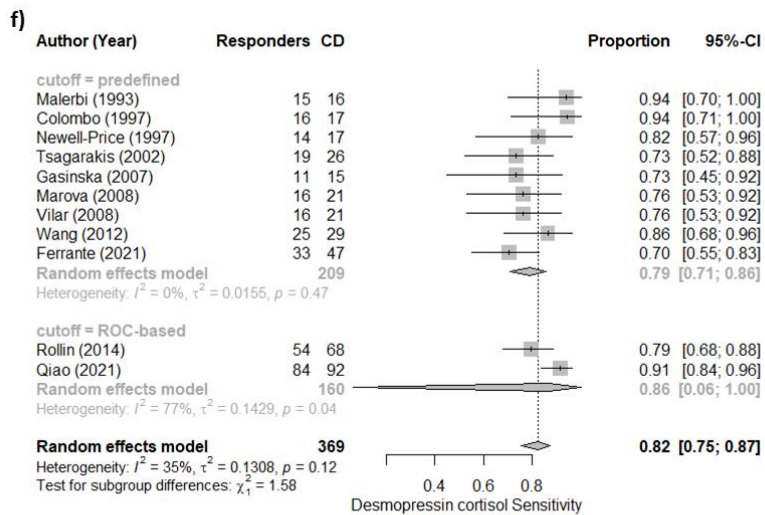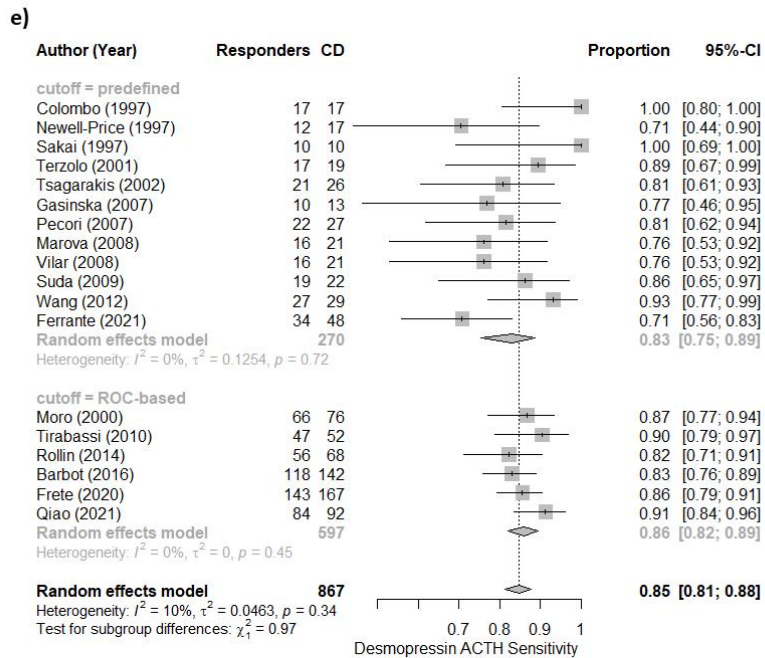| Author (Year)	Non suppressors	EAS	Proportion	95%-CI
cutoff = predefined				
Blunt (1990)	4	5	0.80	[0.28; 0.99]
Flack (1992)	10	10	1.00	[0.69; 1.00]
Colao (1993)	2	2	1.00	[0.16; 1.00]
Avgerinos (1994)	15	15	1.00	[0.78; 1.00]
Dichek (1994)	7	7	1.00	[0.59; 1.00]
Freda (1995)	1	1	1.00	[0.02; 1.00]
Teramoto (1998)	3	5	0.60	[0.15; 0.95]
Al-Saadi (1998)	1	1	1.00	[0.02; 1.00]
Invitti (1999)	11	16	0.69	[0.41; 0.89]
Esfahanian (2009)	3	3	1.00	[0.29; 1.00]
Liu (2020)	10	16	0.62	[0.35; 0.85]
Chen (2020)	10	21	0.48	[0.26; 0.70]
Ding (2021)	23	24	0.96	[0.79; 1.00]
Random effects model		126	0.89	[0.66; 0.97]
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 2.1050$, $p = 0.67$				
cutoff = ROC-based				
Qiao (2021)	13	16	0.81	[0.54; 0.96]
Random effects model		**142**	**0.88**	**[0.69; 0.96]**
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 1.5792$, $p = 0.60$				
Test for subgroup differences: $\chi_1^2 = 0.53$, df = 1 ($p = 0.47$)				

HDDST urinary Specificity

Supplementary Figure 2. Forest Plots of the Specificity to detect EAS in second-line tests for ACTH-dependent CS. Panel e: ΔACTH after desmopressin test; panel f: Δcortisol after desmopressin test.
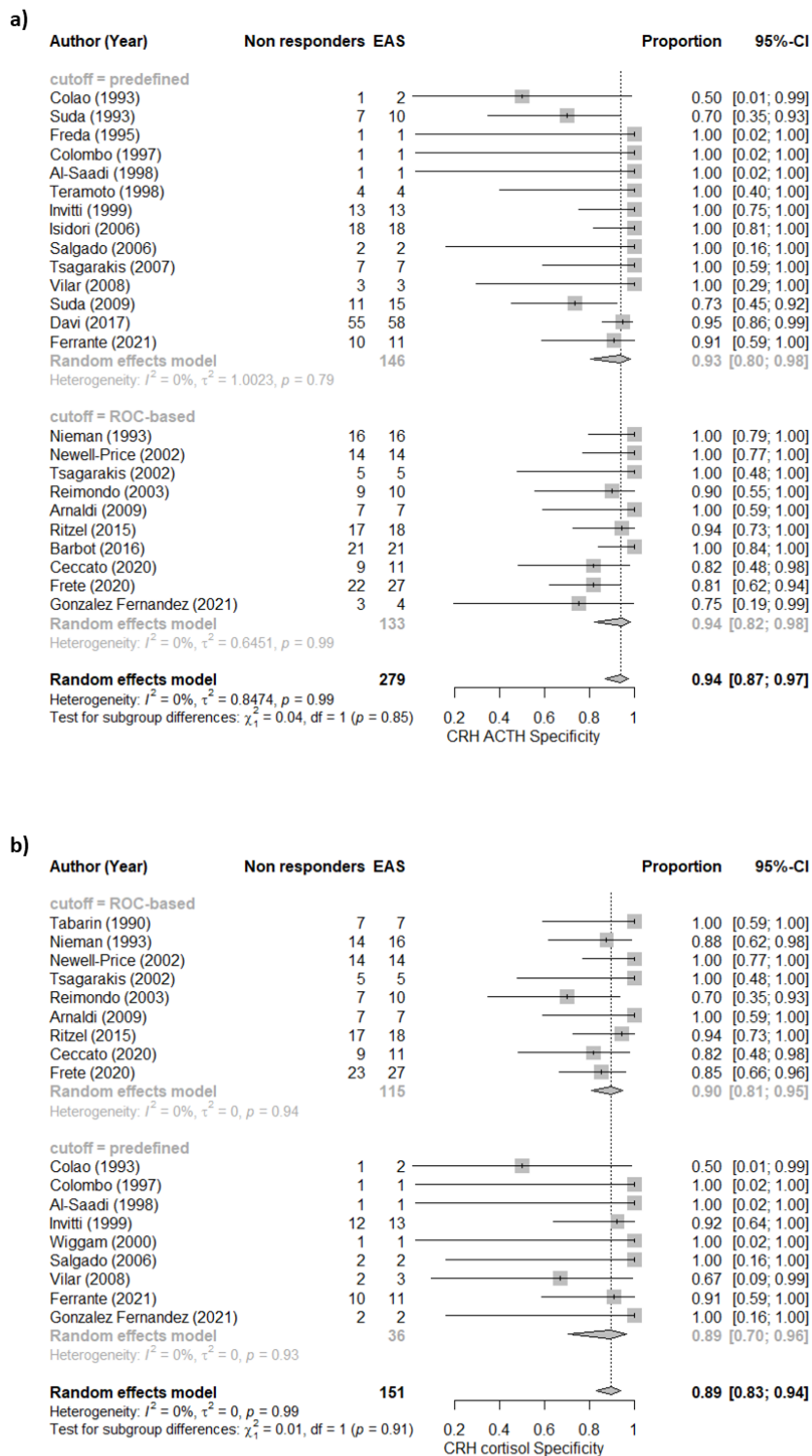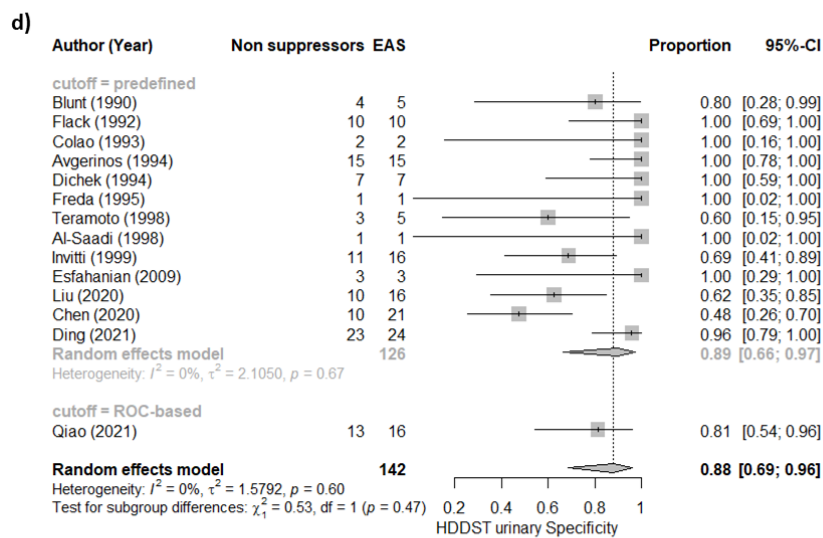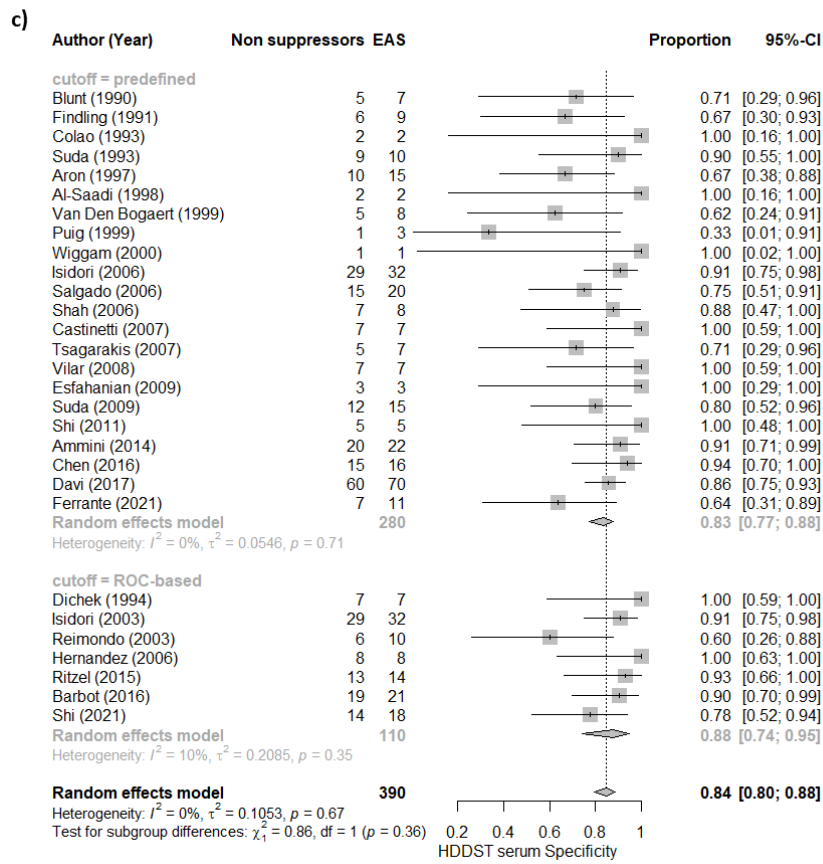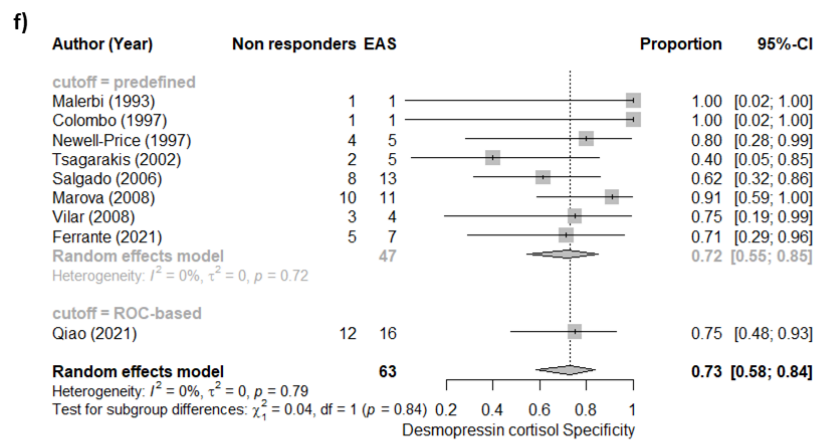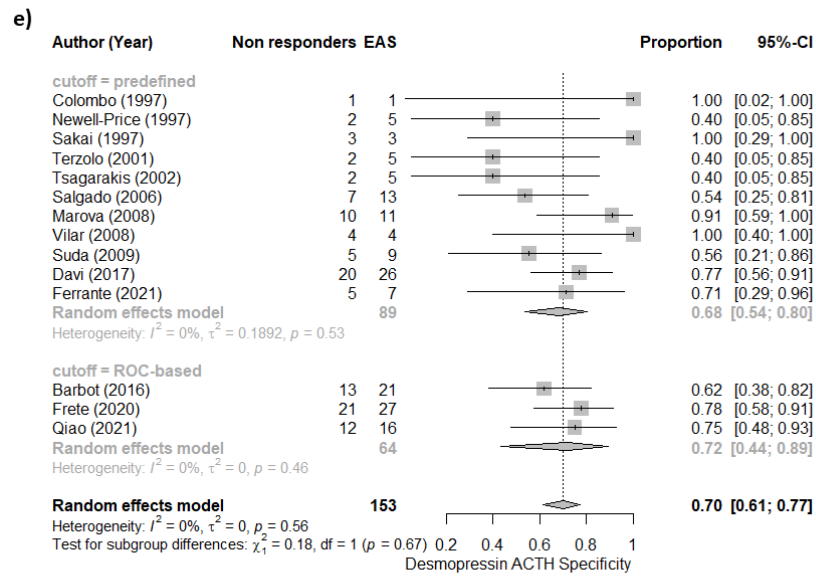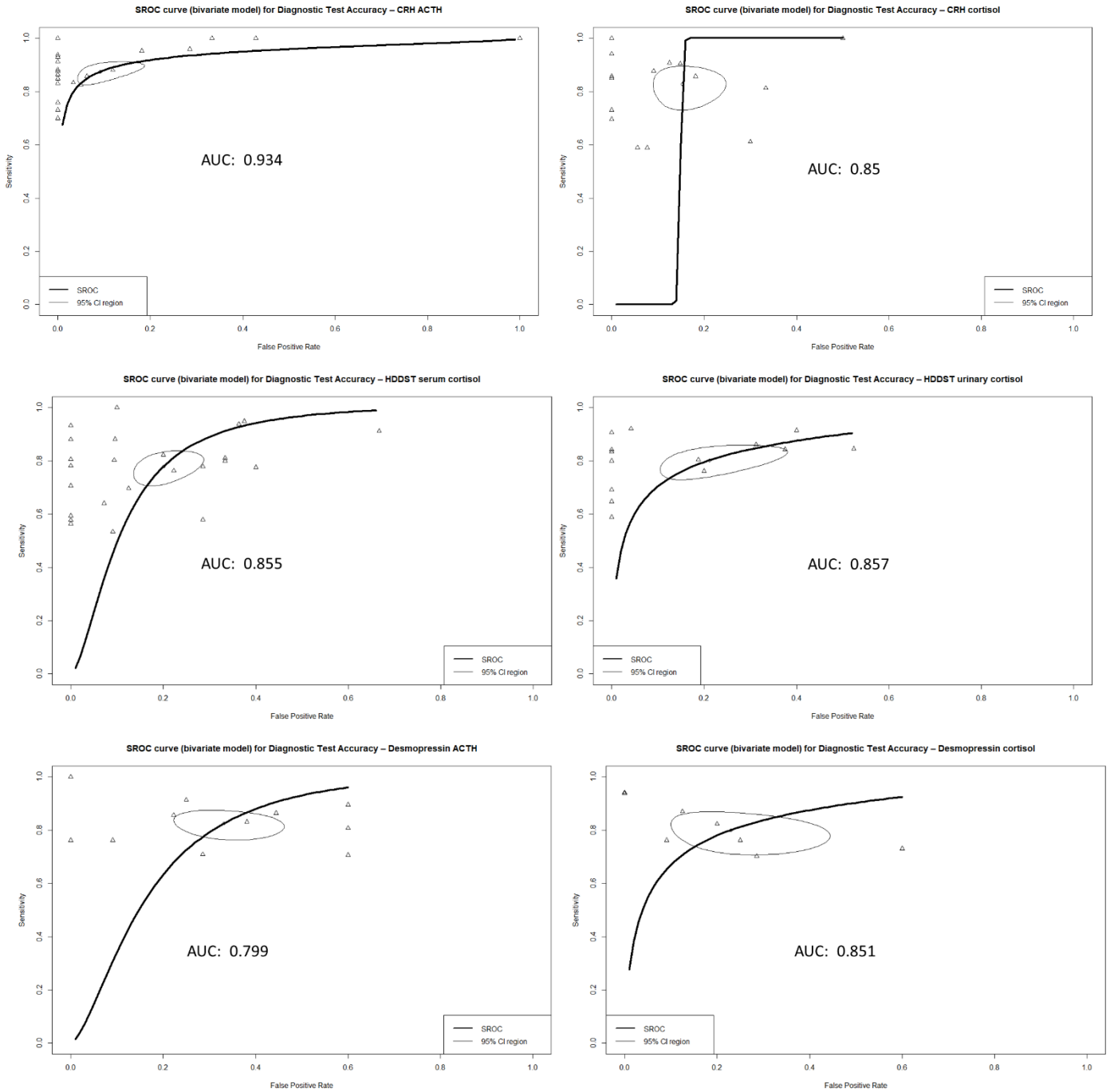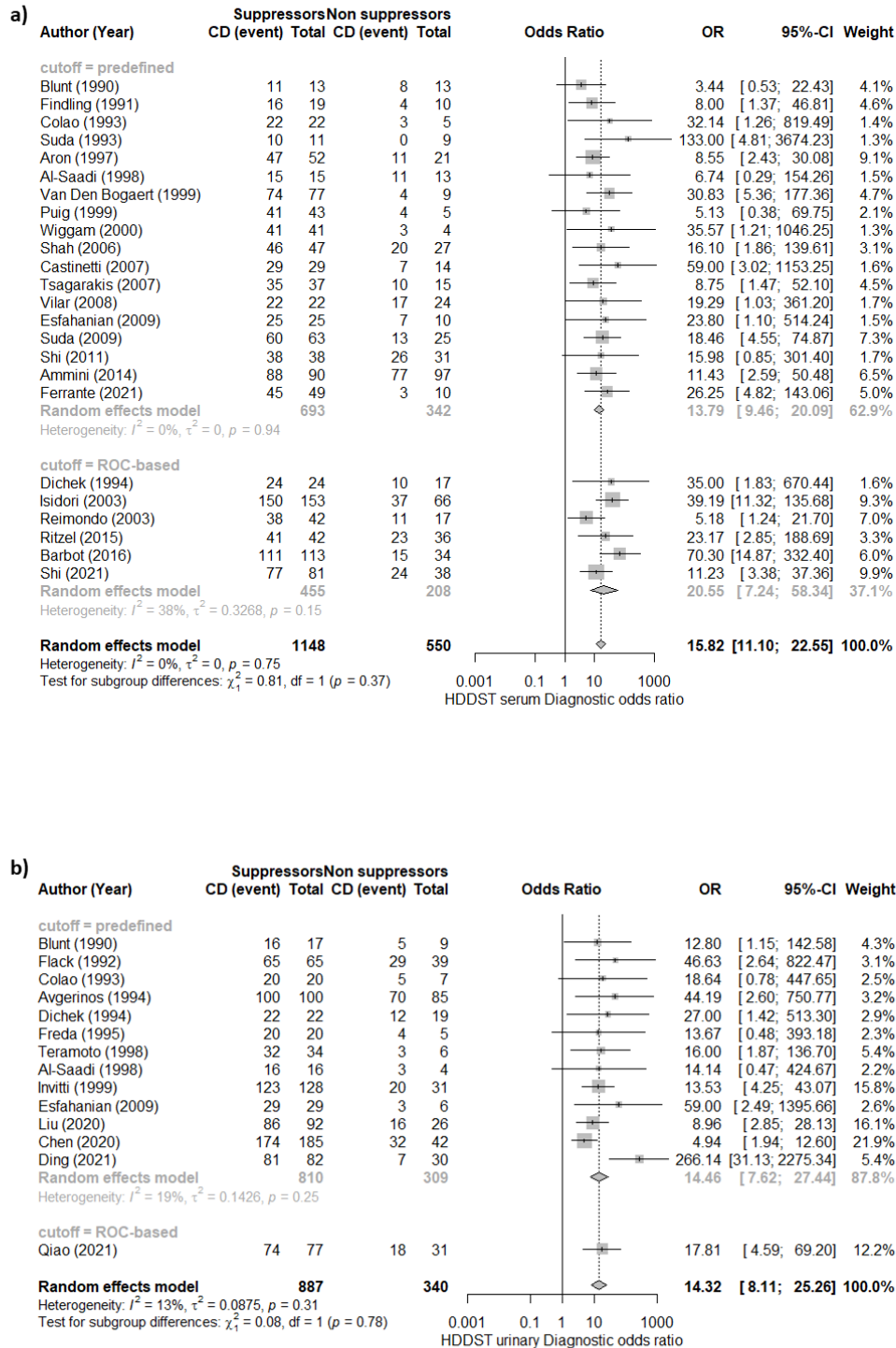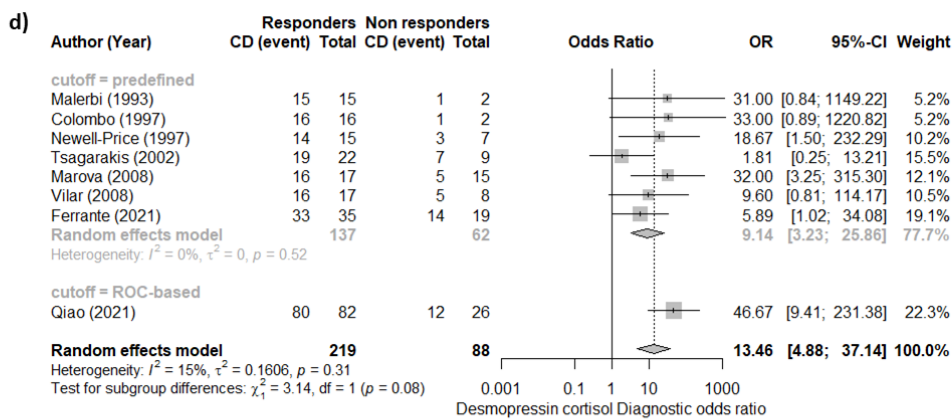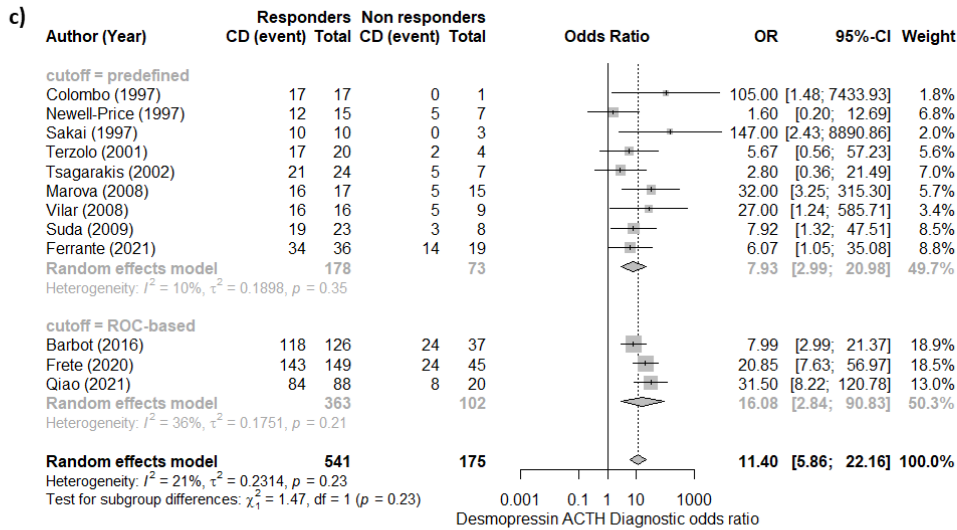
Supplementary Figure 3. Summary ROC curves and AUC of the included studies.

Supplementary Figure 4. Forest Plots of the Diagnostic Odds Ratio of HDDST (panel a: serum suppression; panel b: urinary suppression).

a)

Author (Year)	Suppressors CD (event)	Total	Non suppressors CD (event)	Total	Odds Ratio	OR	95%-CI	Weight
cutoff = predefined								
Blunt (1990)	11	13	8	13		3.44	[0.53; 22.43]	4.1%
Findling (1991)	16	19	4	10		8.00	[1.37; 46.81]	4.6%
Colao (1993)	22	22	3	5		32.14	[1.26; 819.49]	1.4%
Suda (1993)	10	11	0	9		133.00	[4.81; 3674.23]	1.3%
Aron (1997)	47	52	11	21		8.55	[2.43; 30.08]	9.1%
Al-Saadi (1998)	15	15	11	13		6.74	[0.29; 154.26]	1.5%
Van Den Bogaert (1999)	74	77	4	9		30.83	[5.36; 177.36]	4.7%
Puig (1999)	41	43	4	5		5.13	[0.38; 69.75]	2.1%
Wiggam (2000)	41	41	3	4		35.57	[1.21; 1046.25]	1.3%
Shah (2006)	46	47	20	27		16.10	[1.86; 139.61]	3.1%
Castinetti (2007)	29	29	7	14		59.00	[3.02; 1153.25]	1.6%
Tsagarakis (2007)	35	37	10	15		8.75	[1.47; 52.10]	4.5%
Vilar (2008)	22	22	17	24		19.29	[1.03; 361.20]	1.7%
Esfahanian (2009)	25	25	7	10		23.80	[1.10; 514.24]	1.5%
Suda (2009)	60	63	13	25		18.46	[4.55; 74.87]	7.3%
Shi (2011)	38	38	26	31		15.98	[0.85; 301.40]	1.7%
Ammini (2014)	88	90	77	97		11.43	[2.59; 50.48]	6.5%
Ferrante (2021)	45	49	3	10		26.25	[4.82; 143.06]	5.0%
Random effects model		693		342		13.79	[9.46; 20.09]	62.9%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.94$								
cutoff = ROC-based								
Dichek (1994)	24	24	10	17		35.00	[1.83; 670.44]	1.6%
Isidori (2003)	150	153	37	66		39.19	[11.32; 135.68]	9.3%
Reimondo (2003)	38	42	11	17		5.18	[1.24; 21.70]	7.0%
Ritzel (2015)	41	42	23	36		23.17	[2.85; 188.69]	3.3%
Barbot (2016)	111	113	15	34		70.30	[14.87; 332.40]	6.0%
Shi (2021)	77	81	24	38		11.23	[3.38; 37.36]	9.9%
Random effects model		455		208		20.55	[7.24; 58.34]	37.1%
Heterogeneity: $I^2 = 38\%$, $\tau^2 = 0.3268$, $p = 0.15$								
Random effects model		1148		550		15.82	[11.10; 22.55]	100.0%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.75$								
Test for subgroup differences: $\chi^2_1 = 0.81$, df = 1 ($p = 0.37$)								

0.001 0.1 1 10 1000
HDDST serum Diagnostic odds ratio

b)

Author (Year)	Suppressors CD (event)	Total	Non suppressors CD (event)	Total	Odds Ratio	OR	95%-CI	Weight
cutoff = predefined								
Blunt (1990)	16	17	5	9		12.80	[1.15; 142.58]	4.3%
Flack (1992)	65	65	29	39		46.63	[2.64; 822.47]	3.1%
Colao (1993)	20	20	5	7		18.64	[0.78; 447.65]	2.5%
Avgerinos (1994)	100	100	70	85		44.19	[2.60; 750.77]	3.2%
Dichek (1994)	22	22	12	19		27.00	[1.42; 513.30]	2.9%
Freda (1995)	20	20	4	5		13.67	[0.48; 393.18]	2.3%
Teramoto (1998)	32	34	3	6		16.00	[1.87; 136.70]	5.4%
Al-Saadi (1998)	16	16	3	4		14.14	[0.47; 424.67]	2.2%
Invitti (1999)	123	128	20	31		13.53	[4.25; 43.07]	15.8%
Esfahanian (2009)	29	29	3	6		59.00	[2.49; 1395.66]	2.6%
Liu (2020)	86	92	16	26		8.96	[2.85; 28.13]	16.1%
Chen (2020)	174	185	32	42		4.94	[1.94; 12.60]	21.9%
Ding (2021)	81	82	7	30		266.14	[31.13; 2275.34]	5.4%
Random effects model		810		309		14.46	[7.62; 27.44]	87.8%
Heterogeneity: $I^2 = 19\%$, $\tau^2 = 0.1426$, $p = 0.25$								
cutoff = ROC-based								
Qiao (2021)	74	77	18	31		17.81	[4.59; 69.20]	12.2%
Random effects model		887		340		14.32	[8.11; 25.26]	100.0%
Heterogeneity: $I^2 = 13\%$, $\tau^2 = 0.0875$, $p = 0.31$								
Test for subgroup differences: $\chi^2_1 = 0.08$, df = 1 ($p = 0.78$)								

0.001 0.1 1 10 1000
HDDST urinary Diagnostic odds ratio

Supplementary Figure 4. Forest Plots of the Diagnostic Odds Ratio of desmopressin test (panel c: Δ ACTH; panel d: Δ cortisol).

Supplementary Figure 5. Funnel Plots and small-study effect (p calculated with the Peters method).