**Chapter 2**

**Supplemental Data 5: Risk of bias assessment**

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| First author (year) | Consecutive patients  or random sample exposed | Eligibility criteria  reported | | Ascertainment  exposure | Cut-off value  cortisol\* | | | Assay cortisol | Number of patients lost to follow-up (%) |
| Carruthers (1975)72 | Unclear | No | | Unclear | 500 nmol/L | | | n.r. | n.a. |
| Allenby (1975)17 | Unclear | Yes | | Protocol | 500 nmol/L | | | Fluorimetry | n.r. |
| Bondarevsky (1976)53 | Unclear | No | | Unclear | 500 nmol/L | | | Fluorimetry | 1 (3.6%) |
| Wilson KS (1976)85 | Unclear | No | | Unclear | 550 nmol/L | | | Fluorimetry | n.a. |
| Krupin (1976)54 | Unclear | No | | Unclear | 200 nmol/L¥ | | | Fluorimetry | n.r. |
| Spiegel (1979)2 | Unclear | No | | Unclear | 500 nmol/L | | | RIA | n.r. |
| Smith (1983)73 | Unclear | No | | Unclear | 500 nmol/L | | | RIA | n.a. |
| Canafax (1983)55 | Unclear | No | | Unclear | 550 nmol/L | | | RIA | n.r. |
| Rodger (1986)1 | Unclear | No | | Unclear | 550 nmol/L | | | RIA | n.r. |
| Ruiz Muñoz (1988)74 | Yes | No | | Medical record | 550 nmol/L | | | RIA | n.a. |
| Shapiro (1990)76 | Unclear | No | | Unclear | 525 nmol/L | | | n.r. | n.a. |
| Brown\_1 (1990)75 | Unclear | No | | Unclear | 500 nmol/L | | | RIA | n.a. |
| Bromberg (1991)56 | Yes | Yes | | Unclear | 550 nmol/L | | | n.r. | n.r. |
| Brown\_2 (1991)77 | Unclear | No | | Unclear | 500 nmol/L | | | RIA | n.a. |
| Schlaghecke (1992)10 | Unclear | No | | Unclear | 552 nmol/L | | | RIA | n.a. |
| Svendsen (1992)18 | No | Yes | | Protocol | 500 nmol/L | | | n.r. | n.r. |
| Hirano (1993)57 | No | No | | Unclear | 500 nmol/L | | | Chromatography | n.r. |
| LaRochelle (1993)11 | Yes | Yes | | Medical record | 525 nmol/L | | | RIA | 0 |
| Carella (1993)20 | Unclear | Unclear | | Protocol | 500 nmol/L | | | RIA | n.r. |
| Brown\_3 (1993)19 | Unclear | Yes | | Protocol | 500 nmol/L | | | n.r. | 3 (6.1%) |
| Visscher (1995)21 | Unclear | No | | Protocol | 500 nmol/L | | | RIA | 0 |
| Kane (1995)78 | No | Unclear | | Unclear | 500 nmol/L | | | RIA | n.a. |
| Hanania (1995)80 | Unclear | Yes | | Unclear | 500 nmol/L | | | RIA | n.a. |
| Broide (1995)79 | Unclear | Yes | | Unclear | 500 nmol/L | | | RIA | n.a. |
| Greenberg (1996)23 | Unclear | Yes | | Protocol | 500 nmol/L | | | n.r. | 2 (2.9%) |
| Hasegawa (1996)58 | No | No | | Unclear | 500 nmol/L | | | n.r. | n.r. |
| Wasserman (1996)22 | Unclear | Yes | | Protocol | 500 nmol/L | | | n.r. | n.r. |
| Grebe (1997)59 | Unclear | Yes | | Unclear | 550 nmol/L | | | RIA | n.r. |
| Clark (1997)24 | Unclear | Unclear | | Unclear | 500 nmol/L | | | RIA | n.r. |
| Kos-Kudla\_1 (1998)81 | Unclear | No | | Unclear | 500 nmol/L | | | RIA | n.a. |
| Wilson AM\_1 (1998)25 | Unclear | Yes | | Protocol | 500 nmol/L | | | RIA | n.r. |
| Aaronson (1998)26 | Unclear | Yes | | Protocol | 500 nmol/L | | | Chromatography | n.r. |
| Vargas (1998)27 | Unclear | Yes | | Protocol | <2 SD$ | | | Chromatography | n.r. |
| Gazis (1999)28 | Unclear | No | | Protocol | 520 nmol/L | | | Enzyme assay | n.r. |
| Franz (1999)29 | Unclear | No | | Protocol | 500 nmol/L | | | n.r. | n.r. |
| Sorkness (1999)30 | Unclear | Yes | | Protocol | 500 nmol/L | | | n.r. | 1 (0.5%) |
| Nelson\_1 (1999)31 | Unclear | Yes | | Protocol | 500 nmol/L | | | n.r. | n.r. |
| Li (1999)32 | Unclear | Yes | | Protocol | 500 nmol/L | | | Chromatography | 1 (1.0%) |
| Wilson AM\_2 (1999)33 | Yes | Yes | | Protocol | 550 nmol/L | | | RIA | n.r. |
| Gellner (1999)60 | Unclear | Yes | | Unclear | 500 nmol/L | | | RIA | n.r. |
| Gupta (2000)34 | No | Yes | | Protocol | 500 nmol/L | | | RIA | n.r. |
| Henzen (2000)61 | Unclear | Yes | | Unclear | 550 nmol/L | | | Enzyme assay | n.r. |
| Affrime (2000)35 | Unclear | Yes | | Protocol | 500 nmol/L | | | RIA | n.r. |
| Nelson\_2 (2000)36 | Unclear | Yes | | Protocol | 500 nmol/L | | | n.r. | 11 (9.2%) |
| Patel\_1 (2001)82 | Yes | Yes | | Unclear | 500 nmol/L | | | Enzyme assay | n.a. |
| Skov (2002)62 | Yes | Yes | | Unclear | 500 nmol/L | | | Chromatography | n.r. |
| Boots (2002)37 | No | No | | Protocol | 550 nmol/L | | | Enzyme assay | n.r. |
| Niitsuma (2003)38 | Unclear | Unclear | | Unclear | 370 nmol/L§ | | | Chromatography | n.r. |
| Kos-Kudla\_2 (2003)63 | Unclear | Yes | | Unclear | 500 nmol/L | | | RIA | n.r. |
| Nguyen (2003)64 | Yes | Yes | | Protocol | 500 nmol/L | | | Chemiluminescence | n.r. |
| Patel\_2 (2004)39 | Yes | Yes | | Protocol | 500 nmol/L | | | Enzyme assay | n.r. |
| Lee (2004)40 | Unclear | Yes | | Protocol | 500 nmol/L | | | RIA | n.r. |
| Baz-Hecht (2005)65 | No | Yes | | Unclear | 500 nmol/L | | | n.r. | n.r. |
| Bonfils (2006)83 | Yes | Yes | | Unclear | 500 nmol/L | | | RIA | n.a. |
| Kirwan (2006)41 | Unclear | Yes | | Protocol | <2 SD# | | | Chromatography | n.r. |
| Schlessinger (2006)42 | Unclear | No | | Protocol | 500 nmol/L | | | n.r. | 0 |
| Andres (2006)43 | Unclear | Yes | | Protocol | 500 nmol/L | | | Fluorimetry | n.r. |
| White (2006)44 | Unclear | Yes | | Unclear | 500 nmol/L | | | Chemiluminescence | n.r. |
| Duclos (2007)45 | Unclear | Yes | | Protocol | 550 nmol/L | | | RIA | n.r. |
| Holme (2008)84 | Yes | Yes | | Unclear | 550 nmol/L | | | Chemiluminescence | n.a. |
| Gonzalez-Moles  (2010)66 | Yes | Yes | | Unclear | 500 nmol/L | | | RIA | 0 |
| Fleming (2010)46 | Unclear | Yes | | Protocol | 500 nmol/L | | | n.r. | n.r. |
| Neidert (2010)47 | Unclear | Yes | | Protocol | 550 nmol/L | | | Chemiluminescence | 1 (2.6%) |
| Moghaddam (2012)48 | Unclear | Yes | | Protocol | 600 nmol/L | | | Enzyme assay | 2 (3.2%) |
| Sandhu (2012)67 | Unclear | Yes | | Unclear | 550 nmol/L | | | Chemiluminescence | n.r. |
| Han (2012)68 | Yes | Yes | | Unclear | 500 nmol/L | | | RIA | 2 (1.9%) |
| Gilchrist (2013)69 | Unclear | Yes | | Unclear | 500 nmol/L | | | n.r. | n.r. |
| Habib\_1 (2013)49 | Yes | Yes | | Protocol | 500 nmol/L | | | Fluorimetry | n.r. |
| Kasayama (2013)70 | Unclear | Yes | | Unclear | 500 nmol/L | | | n.r. | n.r. |
| Silver (2013)50 | Unclear | Yes | | Protocol | 500 nmol/L | | | n.r. | n.r. |
| Jamilloux (2013)8 | Yes | No | | Unclear | 580 nmol/L | | | RIA | 19 (12.7%) |
| Sacre (2013)71 | Yes | Yes | | Unclear | 550 nmol/L | | | Chemiluminescence | n.r. |
| Habib\_2 (2014)51 | Yes | Yes | | Protocol | 500 nmol/L | | | Fluorimetry | n.r. |
| Habib\_3 (2014)52 | Yes | Yes | | Protocol | 500 nmol/L | | | Fluorimetry | n.r. |
| n.r.=not reported, n.a.=not applicable, RIA=radioimmunoassay | | | | | |  |  |  |  |
| \*used cut-off for this meta-analysis, presented in nmol/L | | | | |  | | |  |  |
| $-2 standard deviations below mean of placebo group | | | | |  | | |  |  |
| §lower cut-off due to assay technique | | |  | |  | | |  |  |
| #-2 standard deviations below pretreatment maximum value | | | | |  | | |  |  |
| ¥cut-off after metyrapone test | | | | |  | | |  |  |