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Supplementary Information 1: Critical appraisal tool for the quality assessment of included articles in systematic reviews

Checklist	Criteria*	Ratings**			
		Yes	No	Unclear	N/A
1	Was the sample characteristic of the specific population?				
2	Were patients recruited in an appropriate way?				
3	Was the sample size sufficient to power the study?				
4	Were the study participants described in detail and fosters comparison with other relevant studies?				
5	Was the data analysis undertaken with adequate description of the identified sample?				
6	Were objective and standard criteria used for the measurements?				
7	***Were the assessment and measurement methods used reliably?				
8	Were the statistical analyses used appropriate?				
9	Were relevant confounding factors described and accounted for?				
10	If sub-populations were identified, were they done according to objective criteria?				
11	****Was there a conflict of interest?				

Abbreviations: N/A (not applicable)

Notes:

* Adapted from Table 2 and Appendix 1 from Munn et al. (2014),³¹ and from Corchón et al. (2018).³²

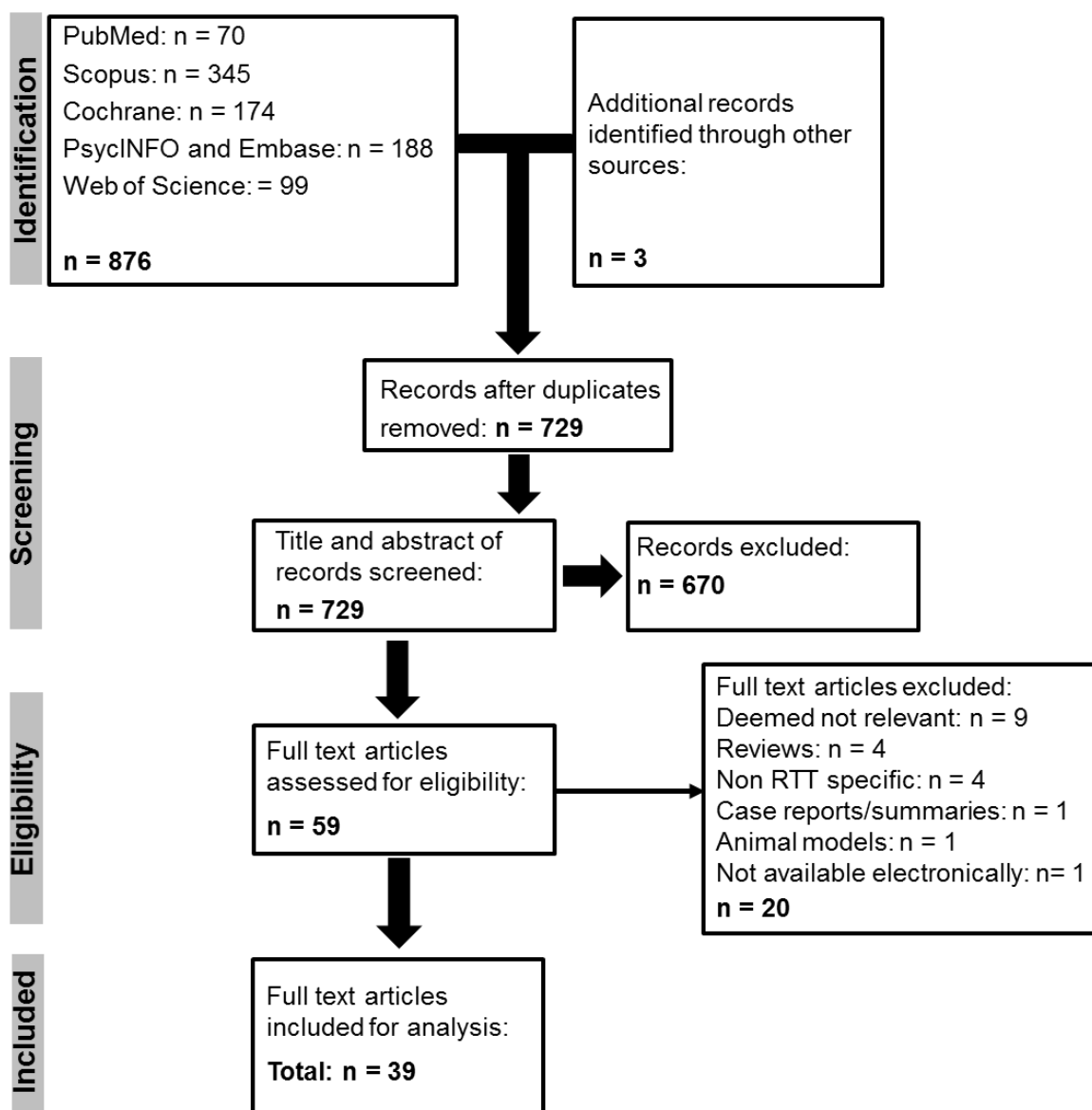
** Ratings were defined as Yes (meeting the criterion), No (not meeting the criterion), Unclear (unclear to whether the criterion was met) and N/A (criterion was not applicable).

*** There is no gold standard method for assessing autonomic function. In this instance, objective measures are those that measure autonomic function directly and provide a physiological assessment. Non-objective measures are defined as patient reported outcome measures such as questionnaires.

**** Conflict of interests are defined as factors that might raise the risk of bias in study design, analysis or reporting. This can include industry sponsorship and/or intellectual conflict.

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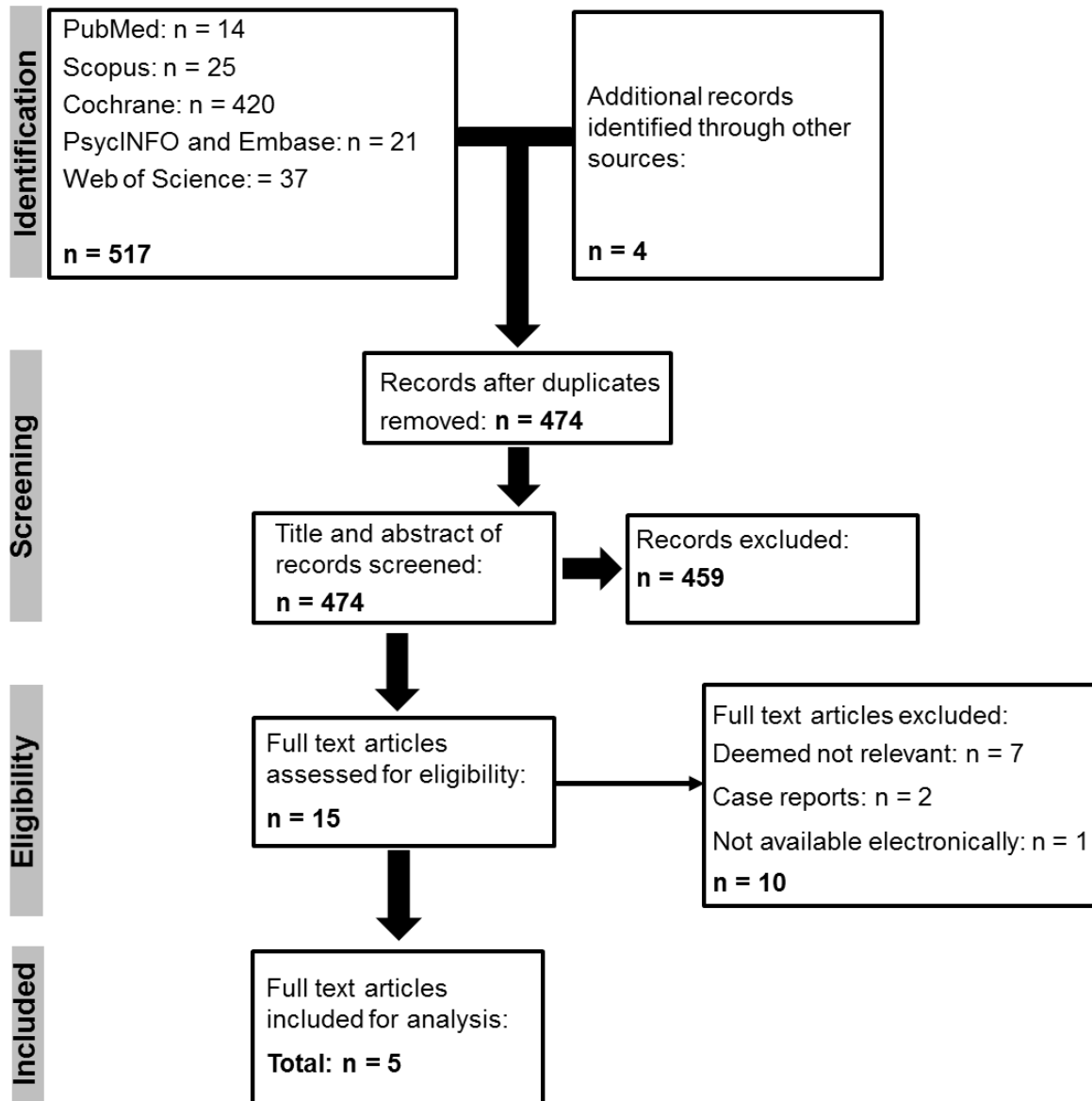
Supplementary Information 2: PRISMA flow-chart of systematic review 1: Autonomic dysfunction in Rett Syndrome



Abbreviation: RTT (Rett Syndrome)

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Supplementary Information 3: PRISMA flow-chart of systematic review 2: Sudden death and its causes in Rett Syndrome



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Supplementary Information 4: Baseline autonomic metrics in patients with Rett Syndrome and healthy/typically developed controls

Study ^a	RTT						Controls/Typically Developed					
	CSB (ms/mmHg)	MAP (mmHg)	CVT (LVS)	LF/HF	SDNN (ms)	pNN50 (%)	CSB (ms/mmHg)	MAP (mmHg)	CVT (LVS)	LF/HF	SDNN (ms)	pNN50 (%)
^a Acampa <i>et al.</i> (2008) ³⁷				4.2±3.2								
^a Bergström-Isacsson <i>et al.</i> (2014) ⁴¹	3.48 (2.88)	58.36 (14.81)	4.23 (2.90)				7.25 (8.59)	47.74 (5.83)	8.42 (9.05)			
^b Dotti <i>et al.</i> (2004) ⁴⁸				6-10						1.5–2.0		
^c Guideri <i>et al.</i> (1999) ⁴⁹				4±2.9						0.9±0.6		
^d Guideri <i>et al.</i> (2001) ⁵⁰				4.1±3.6						0.9±0.48		
^e Guideri <i>et al.</i> (2004) ⁵¹				3.6±3.08								
^a Guideri <i>et al.</i> (2005) ⁵²				4±2.6								
^a Halbach <i>et al.</i> (2016) ⁵⁴			4.50 ±2.53									
^f Julu <i>et al.</i> (2001) ⁵⁶	2.4 (0.5)		3.9 (0.4)									
^g Julu & Witt-Engerström (2005) ³⁵	4	76	5				6	86	9			
^h Kumar <i>et al.</i> (2017) ⁵⁷				2.43 (1.46, 4.70)	39.33 (29.87, 63.28)	2.18 (0.56- 8.62)				0.44 (0.30- 1.08)	62.56 (31.93, 72.21)	17.69 (1.74- 26.33)
ⁱ Larsson <i>et al.</i> (2013) ⁵⁹		68 (53–97)						77 (63–100)				
ⁱ Larsson <i>et al.</i> (2018) ⁶⁰	3 (1-14)	68 (53-97)	7 (2-14)				5 (2-10)	77 (63-100)	6 (3-11)			
Pini <i>et al.</i> (2016) ²⁰			ⁱ 5.88									

 Metric not assessed

(table notes appear on the next page)

Appendix 1 to Singh J, Lanzarini E, Santosh P. Autonomic dysfunction and sudden death in patients with Rett syndrome: a systematic review. *J Psychiatry Neurosci* 2019.

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[^] Studies are presented in alphabetical order by surname of first author (reference numbers are presented as superscripts).

Abbreviations: CSB (Cardiac Sensitivity to Baroreflex); CVT (Cardiac Vagal Tone); HF (power in High Frequency); LF (power in Low Frequency); LF/HF (ratio of LF and HF power components given as $LF[ms^2]/HF[ms^2]$); LVS (Linear Vagal Scale); MAP (Mean Arterial Blood Pressure); ms (milliseconds); N/A (not applicable); pNN50 (NN50 count divided by the total number of all NN intervals); RTT (Rett Syndrome); SD (standard deviation); SDNN (Standard deviation of all NN intervals)

^aValues presented as mean \pm SD.

^b LF/HF values for the RTT group were derived from 3 patients (MR49: 7; MR50: 10 and X308: 6). Normal values were obtained from the European Society of Cardiology Task Force (Eur. Heart J. 1996;17:354–381).

^cData was derived from 54 females with RTT, 28 female subjects and presented as mean \pm SD.

^dData was derived from 74 females with classic RTT, 40 female control subjects and presented as mean \pm SD.

^eValue given for the untreated (without anti-convulsant therapy) group.

^fValues are only presented for the up to 5-year-old age group and given as mean (standard error of the mean).

^gValues are approximate derived from Figure 2A & B in Julu & Witt-Engerström (2005).

^hValues presented as median (interquartile range).

ⁱValues presented as median (min-max) for individuals sitting.

^jCVT value at rest given as mean.

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Supplementary Information 5: Baseline cardiac metrics in patients with Rett Syndrome and healthy/typically developed controls

Study [^]	RTT			Controls/Typically Developed		
	R-R interval (ms ²)	Average QTc interval (ms)	Mean of longest QTc interval (ms)	R-R interval (ms)	Average QTc interval (ms)	Mean of longest QTc interval (ms)
^a Acampa <i>et al.</i> (2008) ³⁷	583 ± 82					
Crosson <i>et al.</i> (2017) ⁴³		422.60 ± 21.11				
^b Guideri <i>et al.</i> (1999) ⁴⁹	616 ± 101			725 ± 120		
^c Guideri <i>et al.</i> (2001) ⁵⁰	628 ± 108			728 ± 102		
^d Guideri <i>et al.</i> (2005) ⁵²	602 ± 121					
^e Kumar <i>et al.</i> (2017) ⁵⁷		346.4 (297.1, 392.6)	590.1 (535.55, 617.95)		363 (350.8, 370.5)	489.35 (457.35, 538.15)

 Metric not assessed

[^] Studies are presented in alphabetical order by surname of first author (reference numbers are presented as superscripts).

Abbreviations: ms (millisecond); QTc (corrected QT interval); R-R (time interval between two successive heart beats); RTT (Rett Syndrome); SD (standard deviation)

^aValues presented as mean (ms) ± SD.

^bValues are given for entire RTT cohort (n=54), female control subjects (n=28) and presented as mean ± SD.

^cValues are given for entire RTT cohort (n=74), female control subjects (n=40) and presented as mean ± SD.

^dBasal evaluation (untreated group) presented as mean ± SD.

^eValues presented as median (interquartile range).