Establishing Reference Ranges for Ambulatory Electrocardiography: A Meta-Analysis Supplementary Material

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eTable 1: MOOSE checklist for meta-analyses of observational studies

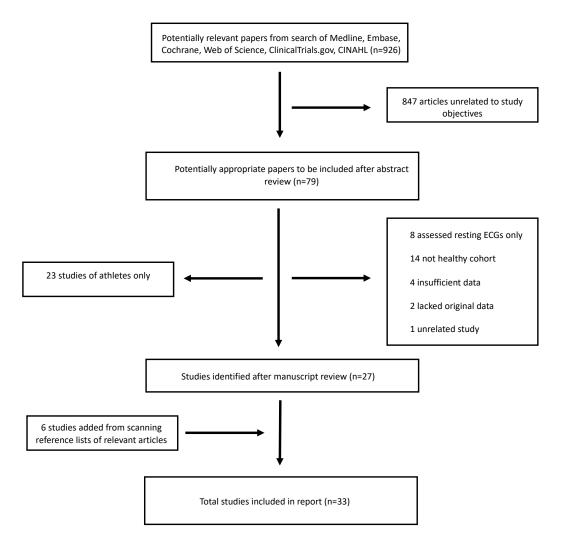
Item No	Recommendation	Reported on Page No		
Reporting	of background should include			
1	Problem definition	5		
2	Hypothesis statement	-		
3	Description of study outcome(s)	6		
4	Type of exposure or intervention used	6		
5	Type of study designs used	6		
6	Study population	6		
Reporting	of search strategy should include			
7	Qualifications of searchers (eg, librarians and investigators)	6		
8	Search strategy, including time period included in the synthesis and key words	Table e2		
9	Effort to include all available studies, including contact with authors	6		
10	Databases and registries searched	6		
11	Search software used, name and version, including special features used (eg, explosion)			
12	Use of hand searching (eg, reference lists of obtained articles)	6		
13	List of citations located and those excluded, including justification	Figure e1		
14	Method of addressing articles published in languages other than English	6		
15	Method of handling abstracts and unpublished studies	6		
16	Description of any contact with authors	6		
Reporting	of methods should include			
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	8, Table 1		
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	7		
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	7		
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	N/A		
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	7		
22	Assessment of heterogeneity	8		
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta- analysis) in sufficient detail to be replicated	8		
24	Provision of appropriate tables and graphics	Table 2, Figures		

Reporting of	of results should include	
25	Graphic summarizing individual study estimates and overall estimate	Figures and eFigures
26	Table giving descriptive information for each study included	Table 1
27	Results of sensitivity testing (eg, subgroup analysis)	N/A
28	Indication of statistical uncertainty of findings	9-11

eTable 2: Detailed search strategy:

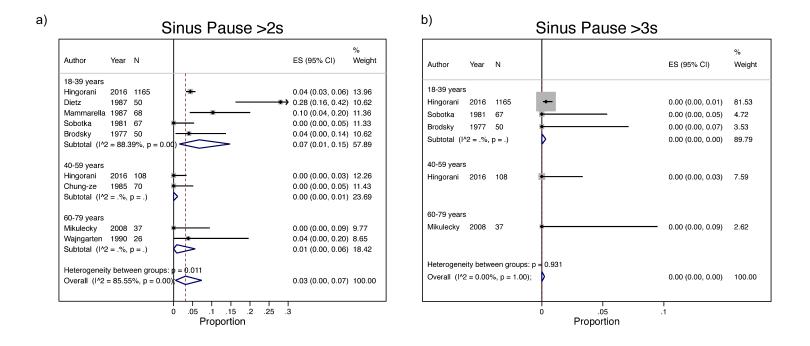
#	Searches
1	(healthy adult* or normal adult* or asymptomatic adult* or healthy participant* or asymptomatic participant* or normal participant* or healthy subject* or normal subject* or asymptomatic subject* or healthy population* or normal population* or asymptomatic population or free of heart disease or without apparent heart disease or active elderly or normal human or house officers or runner* or athlete* or healthy elderly).ti,ab.
2	exp electrocardiography/ or holter.mp. or ambulatory ECG.mp.
3	exp Arrhythmias, Cardiac/ or monitoring, physiologic.mp. or heart arrhythmia*.mp.
4	1 and 2 and 3
5	4 not (case report* or letter* or comment* or editorial* or review* or notes* or "conference abstract").pt.
6	5 not (exp infant/ or exp child/ or exp cells/)
7	limit 6 to humans
8	7 not (exp vascular diseases/ or exp cardiovascular infections/ or exp cardiovascular abnormalities/ or exp Carcinoid Heart Disease/ or exp Cardiac Output, High/ or exp Cardiac Output, Low/ or exp Cardiac Tamponade/ or exp Cardiomegaly/ or exp Cardiomyopathies/ or exp Endocarditis/ or exp Heart Aneurysm/ or exp Heart Arrest/ or exp Heart Defects, Congenital/ or exp Heart Failure/ or exp Heart Neoplasms/ or exp Heart Rupture/ or exp Heart Valve Diseases/ or exp Myocardial Ischemia/ or exp Myocardial Stunning/ or exp Pericardial Effusion/ or exp Pericarditis/ or exp Pulmonary Heart Disease/ or exp Rheumatic Heart Disease/ or exp Ventricular Dysfunction/ or exp Ventricular Outflow Obstruction/)
9	8 not (exp syncope/ or exp diving/ or exp physical exertion/ or exp Wolff- Parkinson-White/ or exp stroke/ or exp transient ischemic attack/ or exp cerebrovascular accident/ or exp sudden death/ or exp cardiac pathology/ or exp wandering pacemaker/ or exp metaraminol/ or exp ajmaline/ or exp quinidine/ or exp glycinexylidide/ or exp atropine/ or exp methscopolamine/ or exp hyperlipidemia/ or exp sinus node dysfunction/ or exp vasoregulatory abnormality/ or exp procainamide/ or exp propafenone/ or exp mexilitine/)

eFigure 1: Study selection



Abbreviations: CINAHL, Cumulative Index to Nursing and Allied Health Literature; ECG, electrocardiogram.

eFigure 2: Forest plots for the prevalence of sinus pauses of >2 and >3 seconds



ES (effect size) denotes prevalence of sinus pauses >2 seconds (panel a) and >3 seconds (panel b) for each study and the weighted mean prevalence by age group and overall. Note within age-group heterogeneity could not be tested for some groups due to the small number of studies and/or no events in some studies.

eFigure 3: Forest plot for the prevalence of first degree atrioventricular block

Author	Year	N		ES (95% CI)	% Weight
18-39 years					
Hingorani	2016	1165	•	0.01 (0.01, 0.02	11.92
Palatini	1992	40		0.05 (0.01, 0.17)	7.05
Dietz	1987	50		0.16 (0.07, 0.29	7.69
Sobotka	1981	67		0.09 (0.03, 0.18	8.49
Brodsky	1977	50		0.08 (0.02, 0.19	7.69
Subtotal (IA	2 = 89.	28%, p = 0.0		0.06 (0.01, 0.15	42.85
40-59 years					
Hingorani	2016		• <u>•</u>	0.01 (0.00, 0.05	
Chung-ze			<u>₹</u> +	0.00 (0.00, 0.05	
Adey	1978	189	1 H	0.01 (0.00, 0.03)) 10.57
Clarke	1976		•	0.01 (0.00, 0.06)	9.10
Subtotal (IA	2 = 0.0	0%, p = 0.80	0	0.01 (0.00, 0.02)	37.86
60-79 years					
Wajngarten			•	0.00 (0.00, 0.13)	
Manyari	1990		+	0.03 (0.00, 0.11)	
Subtotal (IA	2 = .%,	p = .)	\mathbf{P}	0.02 (0.00, 0.06)) 14.17
80+					
Manyari	1990	21		→ 0.19 (0.05, 0.42)	5.13
Untergane	the bath				
Heterogenei Overall (I^2				0.03 (0.01, 0.06)	100.00
			1		
			0 .05 .1 .15 .2	2.25.3	

Eirct Dogroo AV Block

ES (effect size) denotes prevalence of first degree atrioventricular block for each study and the weighted mean prevalence by age group and overall. Note within age-group heterogeneity could not be tested for some groups due to the small number of studies and/or no events in some studies.

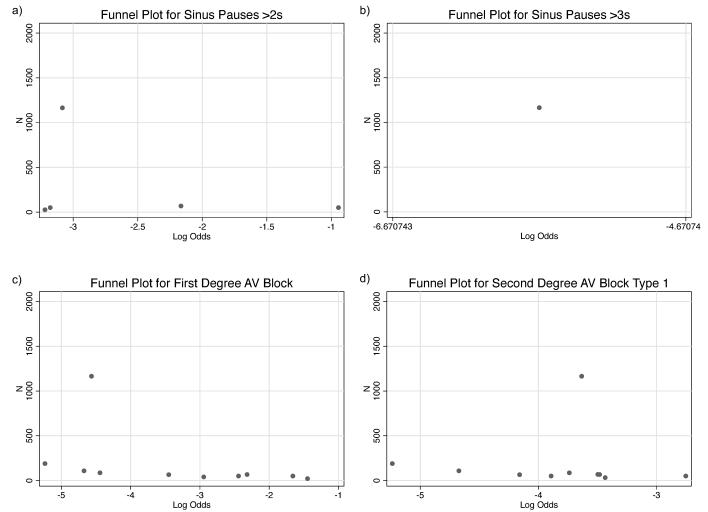
eFigure 4: Forest plot for the prevalence of second degree AV Block, type 1

Second Degree AV Block Type 1

			•		
Author	Year	N		ES (95% CI)	% Weight
18-39 years					
Hingorani	2016	1165	*	0.03 (0.02, 0.04)	47.70
Dietz	1987	50		0.06 (0.01, 0.17)	3.03
Mammarella	1987	68	• • · · · ·	0.03 (0.00, 0.10)	4.07
Sobotka	1981	67		0.03 (0.00, 0.10)	4.02
Brodsky	1977	50		0.06 (0.01, 0.17)	3.03
Subtotal (I^2	= 1.88%	%, p = 0.40)	0	0.02 (0.01, 0.03)	61.84
40-59 years					
Hingorani	2016		-	0.01 (0.00, 0.05)	6.35
Chung-ze	1985	70		0.00 (0.00, 0.05)	4.19
Adey	1978	189	•	0.01 (0.00, 0.03)	10.73
Clarke	1976	86		0.02 (0.00, 0.08)	5.11
Subtotal (I^2	= 0.00%	6, p = 0.51)	P	0.01 (0.00, 0.02)	26.37
60-79 years					
Wajngarten	1990	26		0.00 (0.00, 0.13)	1.60
Manyari	1990	65	•	0.02 (0.00, 0.08)	3.90
Andersson	1988	32	*	0.03 (0.00, 0.16)	1.96
Subtotal (I^2	= .%, p	= .)	\diamond	0.01 (0.00, 0.05)	7.46
80+			1		
80+ Manyari	1990	21		0.00 (0.00, 0.16)	1.30
Kantelip	1986	50	•	0.02 (0.00, 0.11)	3.03
Subtotal (I^2		= .)	\sim	0.01 (0.00, 0.06)	4.33
,		'		(,,	
Heterogeneity	/ betwee	en groups: p	= 0.102		
Overall (I^2 =	= 4.23%	p = 0.40);	Q	0.02 (0.01, 0.02)	100.00
				1	
		(0 .05 .1 .15 .2 .25 .	3	
			Proportion		

ES (effect size) denotes prevalence of second degree atrioventricular block, type 1, for each study and the weighted mean prevalence by age group and overall. Note within age-group heterogeneity could not be tested for some groups due to the small number of studies and/or no events in some studies.



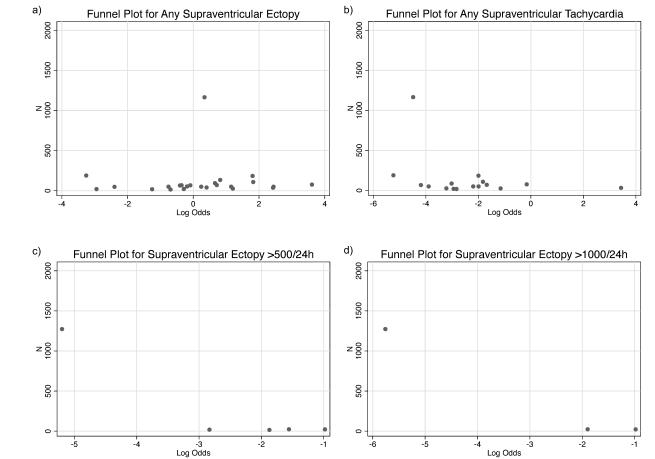


eFigure 6: Forest plot for the prevalence of any supraventricular ectopy

Any Supraventricular Ectopy

Author	Year	Ν	ES (95% CI)	% Weight
18-39 years			1	
Hingorani	2016	1165	0.58 (0.56, 0.61)	3.77
Palatini	1992	40	0.60 (0.43, 0.75)	3.56
Dietz	1987	50	0.76 (0.62, 0.87)	3.60
Mammarella	1987	68	0.41 (0.29, 0.54)	3.65
Romhilt	1984	48	0.08 (0.02, 0.20)	3.59
Sobotka	1981	67	0.48 (0.35, 0.60)	3.64
Brodsky	1977	50	0.56 (0.41, 0.70)	3.60
Raftery	1976	20	0.05 (0.00, 0.25)	3.37
Subtotal (I^2 = 93	.19%, p = 0.00)		0.43 (0.29, 0.58)	28.79
40-59 years				
Hingorani	2016	108	0.86 (0.78, 0.92)	3.69
Grosgogeat	1986	134	0.69 (0.61, 0.77)	3.71
Chung-ze	1985	70	0.67 (0.55, 0.78)	3.65
Matsuno	1985	94	0.66 (0.55, 0.75)	3.68
Romhilt	1984	53	0.45 (0.32, 0.60)	3.61
Bjerregaard	1982	184	0.86 (0.80, 0.91)	3.73
Adey	1978	189	0.04 (0.02, 0.07)	3.73
Raftery	1976	18	0.22 (0.06, 0.48)	3.33
Subtotal (I^2 = 98	.54%, p = 0.00)		0.56 (0.28, 0.82)	29.14
60-79 years Mikulecky	2008	37	0.92 (0.78, 0.98)	3.54
Wakida	1994	23	1.00 (0.85, 1.00)	3.42
Wajngarten	1990	26	0.77 (0.56, 0.91)	3.45
Manyari	1990	65	0.40 (0.28, 0.53)	3.64
Ribera	1989	50	0.92 (0.81, 0.98)	3.60
Neto	1988	50	0.32 (0.20, 0.47)	3.60
Andersson	1988	32	1.00 (0.89, 1.00)	3.51
Bjerregaard	1982	76	→ 0.97 (0.91, 1.00)	3.66
Raftery	1976	15	0.33 (0.12, 0.62)	3.26
Subtotal (I^2 = 95			0.80 (0.57, 0.96)	31.68
80+				
Manyari	1990	21	0.43 (0.22, 0.66)	3.39
Kantelip	1986	50	1.00 (0.93, 1.00)	3.60
Wakida	1994	22	1.00 (0.85, 1.00)	3.40
Subtotal (I^2 = .%	, p = .)		0.90 (0.47, 1.00)	10.39
Heterogeneity betw		= 0.023	-	
Overall (I^2 = 97.1	6%, p = 0.00);		0.64 (0.52, 0.76)	100.00
			<mark> </mark>	
			.75 1	

ES (effect size) denotes the weighted mean prevalence of any SVE, by age group and overall. Note within age-group heterogeneity could not be tested for some groups due to the small number of studies and/or no events in some studies.



eFigure 7: Funnel plots for meta-analyses of supraventricular ectopy and tachycardia

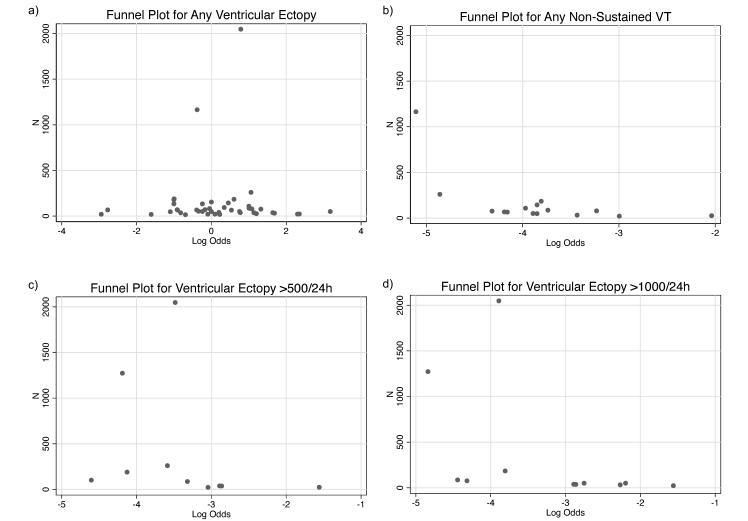
e11

eFigure 8: Forest plot for the prevalence with any ventricular ectopy

Any Ventricular Ectopy

Author	Year	Ν		ES (95% CI)	% Weight
18-39 years Von Rotz Hingorani Palatini Takada Suwa Dietz Mammarella Takeuchi Rasmussen Romhilt Bethge Sobotka Brodsky Raftery Zorzi Subtotal (I^2 =	2017 2016 1992 1988 1987 1987 1987 1985 1984 1983 1984 1983 1981 1977 1976 2018	$2048 \\ 1165 \\ 40 \\ 66 \\ 179 \\ 50 \\ 68 \\ 25 \\ 36 \\ 48 \\ 70 \\ 67 \\ 50 \\ 20 \\ 144 \\ 0 = 0.00)$	**************************************	$\begin{array}{c} 0.69 & (0.67, 0.71) \\ 0.41 & (0.38, 0.43) \\ 0.55 & (0.38, 0.71) \\ 0.29 & (0.18, 0.41) \\ 0.27 & (0.20, 0.34) \\ 0.50 & (0.36, 0.64) \\ 0.06 & (0.02, 0.14) \\ \bullet 1.00 & (0.86, 1.00) \\ 0.31 & (0.16, 0.48) \\ 0.25 & (0.14, 0.40) \\ 0.29 & (0.18, 0.41) \\ 0.40 & (0.28, 0.53) \\ 0.50 & (0.36, 0.64) \\ 0.55 & (0.36, 0.64) \\ 0.05 & (0.00, 0.25) \\ 0.61 & (0.53, 0.69) \\ 0.41 & (0.30, 0.53) \end{array}$	2.49 2.49 2.17 2.29 2.42 2.23 2.30 2.02 2.14 2.22 2.30 2.29 2.23 1.93 2.40 33,94
40-59 years Hingorani Bjerregaard Buershaper Takada Grosgogeat Takeuchi Rasmussen Chung-ze Matsuno Romhilt Bethge Bjerregaard Adey Clarke Raftery Zorzi Subtotal (I^2 =	2016 1991 1989 1986 1985 1985 1985 1985 1984 1983 1984 1983 1982 1978 1976 1976 1976 2018 2018	108 260 79 154 134 21 38 70 94 53 82 184 189 86 18 134 0 = 0.00)	◆↓ ◆ ◆ ◆ ◆ ◆ ◆ ◆ ◆ ◆ ◆	0.73 (0.64, 0.81) 0.74 (0.68, 0.79) 0.75 (0.64, 0.84) 0.50 (0.42, 0.58) 0.44 (0.35, 0.53) 0.48 (0.26, 0.70) 0.68 (0.51, 0.82) 0.46 (0.34, 0.58) 0.59 (0.48, 0.69) 0.42 (0.28, 0.56) 0.49 (0.38, 0.60) 0.65 (0.57, 0.72) 0.27 (0.21, 0.34) 0.73 (0.63, 0.82) 0.17 (0.24, 0.41) 0.27 (0.20, 0.35) 0.53 (0.43, 0.62)	2.37 2.44 2.32 2.41 2.39 1.95 2.16 2.30 2.35 2.25 2.33 2.42 2.34 1.88 2.39 36.72
60-79 years Mikulecky Wakida Wajngarten Manyari Ribera Neto Andersson Rasmussen Bethge Bjerregaard Bethge Subtotal (1 ^A 2 = 80+ Manyari	2008 1994 1990 1990 1988 1988 1985 1983 1985 1983 1982 1976 76.48%,	37 23 26 65 50 50 32 37 18 76 15 0 = 0.00)		0.76 (0.59, 0.88) 0.91 (0.72, 0.99) 0.77 (0.56, 0.91) 0.63 (0.50, 0.75) 0.68 (0.53, 0.80) 0.44 (0.30, 0.59) 0.84 (0.67, 0.95) 0.84 (0.68, 0.94) 0.56 (0.31, 0.78) 0.79 (0.68, 0.87) 0.33 (0.12, 0.62) 0.70 (0.61, 0.79) 0.52 (0.30, 0.74)	2.15 1.99 2.04 2.29 2.23 2.11 2.15 1.88 2.32 1.80 23.19
Kantelip Wakida Subtotal (I ² = Heterogeneity b Overall (I ² = S	between g		001	0.96 (0.86, 1.00) 0.91 (0.71, 0.99) 0.84 (0.54, 1.00) 0.55 (0.49, 0.61)	2.23 1.97 6.15 100.00

ES (effect size) denotes the weighted mean prevalence of any VE, by age group and overall. Note within age-group heterogeneity could not be tested for some groups due to the small number of studies and/or no events in some studies.



eFigure 9: Funnel plots for meta-analyses of ventricular ectopy and non-sustained ventricular tachycardia



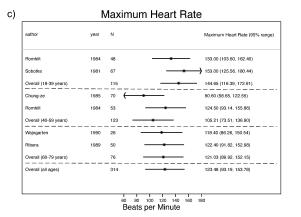
Heart Rate Analysis

Nine studies reported mean heart rate (eFigure 10a). There was no data in those \geq 80 years of age. The overall weighted mean heart rate was 78.1 beats per minute (bpm), with a central 95% range (2.5th to 97.5th percentile) from 61.2 to 95.0 bpm. The mean heart rate and 95% range was similar across all age groups. Similarly, the minimum heart rate (eFigure 10b) was similar across all age groups with overall weighted mean being 56.6 bpm (95% range from 41.2 to 72.0 bpm). However, lower 2.5th percentile for minimum heart rate varied with age and was 41.5 bpm in those 18-39, 43.4 bpm in those 40-59, and 37.4 with those 60-79 years. Maximum heart rate decreased with age (eFigure 10c), with a mean maximum heart rate of 123.5 bpm (95% range 93.2 to 153.8 bpm). One study in those 40-59 years, by Chung-Ze, was an outlier with a mean maximum heart rate of only 90.6 bpm. There was asymmetry in the funnel plots, particularly for minimum and maximum heart rate (eFigure 11) but the number of studies were small.

eFigure 10: Forest plots of mean, minimum and maximum Heart Rates

author	year	Ν		Mean Heart Rate (95%
Palatini	1992	40		- 79.00 (53.52, 104.48)
Romhilt	1984	48		82.40 (68.68, 96.12)
Sobotka	1981	67	x	82.00 (64.36, 99.64)
Brodsky	1977	50		73.00 (59.28, 86.72)
Overall (18-39 years)		205		79.31 (62.02, 96.61)
Chung-ze	1985	70 .		74.10 (53.13, 95.07)
Romhilt	1984	53	•	81.40 (67.68, 95.12)
Overall (40-59 years)		123		77.25 (59.40, 95.09)
Wajngarten	1990	26		75.30 (58.44, 92.16)
Ribera	1989	50		74.60 (60.10, 89.10)
Neto	1988	50		80.00 (64.32, 95.68)
Overall (60-79 years)		126		76.89 (61.43, 92.34)
Overall (all ages)		454		78.08 (61.15, 95.01)

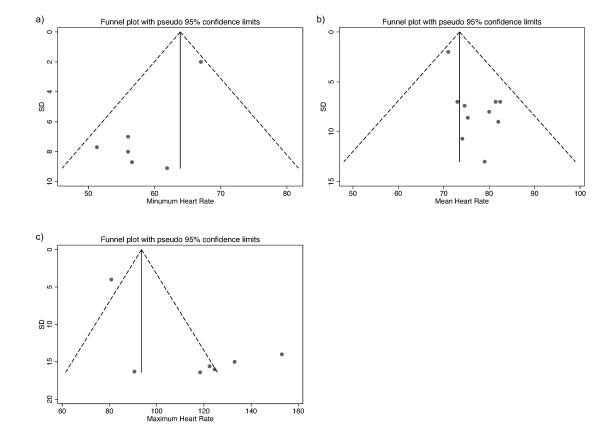
50 60 70 80 90 100 Beats per Minute



b) Minimum Heart Rate author vear Ν Minimum Heart Rate (95% range Romhilt 1984 48 56.00 (40.32, 71.68) Sobotka 1981 67 56.00 (42.28, 69.72) Overall (18-39 years) 115 56.00 (41.46, 70.54) ----Chung-ze 1985 70 61.90 (44.06, 79.70) Romhilt 1984 53 56.00 (42.28, 69.72) Overall (40-59 years) 59.36 (43.29, 75.40) 123 ·----Wajngarten 1990 26 56.60 (39.55, 73.65) 1989 50 Ribera 51.30 (36.21, 66.39) Overall (60-79 years) 53.11 (37.35, 68.87) 76 Overall (all ages) 314 56.62 (41.18, 72.04)



The weighted <u>average</u> mean (panel a), minimum (panel b) and maximum (panel c) heart rate for <u>each</u> study are presented, with central 95% ranges (2.5th to 97.5th percentile). The results are presented by age group and overall.



eFigure 11: Funnel plots for meta-analyses of mean, minimum and maximum heart rates

Heart

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