Global Normative Echo Data: The WASE Study
and
Thoughts on how to assess cardiac chamber sizes in the era of obesity

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no disclosures

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Is our normal echocardiography data appropriate ?

- We must understand what is normal before we can define abnormal
- Currently available reference values for cardiac structures and function do not reflect the diversity of populations from around the world
  - In the major studies used in guidelines
    - Most of subject are Causasian, few Blacks, no Latinos, Asians or Africans
  - All conducted in the US or Europe
- Studies from China, Japan, Iran show their normal heart dimensions and volumes to be smaller than the US/European studies
- Multi-Ethnic Study of Atherosclerosis (MESA)
  - Heart dimensions differ by ethnic groups in the US

Lack of diversity in data used in the ASE guidelines

Table 1 Basic demographic characteristics of studies supporting ASE/EACVI chamber quantification recommendations for normal reference values[2]

	Parasternal long-axis view	Apical four-chamber view	Apical two-chamber view	Biplane view
Total number	1,271	2,278	993	520
Data sources	Asklepios (1,019) Flemengho (252)	Cardia5 (1,027) Asklepios (1,006) Flemengho (245)	Cardia25 (588) Asklepios10 (161) Flemengho (244)	Padua (111) Asklepios10 (161) Flemengho (248)
Male, %	39	42	41	40
Race, %				
Male	100 white	80 white	84 white	100 white
Female	100 white	81 black	87 white	100 white
Age				
Male	45 ± 8	37 ± 10	50 ± 8	45 ± 8
Female	45 ± 7	37 ± 10	50 ± 7	

Asch et al, JASE 2019;3:157-162

- Currently available normal data mainly derived from middle aged adults
- There have been studies from other parts of the world
  - each study uses different imaging protocols + different measurement methods

Table 2 Characteristics of the main studies reporting normal values to date

	Population	n	2D/3D/Strain/Doppler	Chambers	Standard acquisition	Standard analysis by core lab	Multiethnic	Study design
NORRE[15]	European multicenter study	734	Y, all parameters	2D/3D LV RV LA RA	Guideline recommended echocardiographic approach	Y	N, mostly white European	Prosp
IRAN[8]	Iran, single center	368	2D Simpsons, M-mode diam, tissue Doppler imaging e'	LV RV LA diam	Y	N	N	Prosp, poor image excluded
India[16]	Indian residents, single center	100	2D, Doppler, diastolic function	LV diam and volumes, LA vol, diastolic function with tissue Doppler imaging	Y	N	N	Prosp
JAMP[7]	Japanese	700	LV linear dimension, LV volumes, LVEF, maximum LA volume, LV mass, aorta root diameters and mitral inflow and mitral annular velocities	LV, LA, and aorta	Y	Y	N	Prosp
EMINCA[6]	Han Chinese, multicenter	1,394	2D and M-mode	LV, LA, RV, RA, and Doppler	Y	Y	N	Prosp
South Korea[17,18]	South Korea	1,003	2D and Doppler	LV, LA, RV, RA, and Doppler	Y	Y	N	Prosp
Brazil[13]	One city	295, ages 25-64	M-mode	LV, RV, LA, aorta diam, LV mass	Y	N	N	Prosp
Nepal[14]	One city	126	2D and M-Mode	LV, RV, LA, aortic diam. LV mass	Y	N	N	Prosp

Asch et al, JASE 2019;32:157-162

- *Current normal values reported in ASE guidelines may not apply to all racial and ethnic groups*

What is the WASE Study ?

- World Association of Societies of Echocardiography (WASE)
  - Prospective, observation, cross-sectional study of healthy adults from sites around the world
  - Each site enrolls 100 patients evenly distributed by age and sex
  - Comprehensive image acquisition protocol
    - 2D, Doppler, 3D, longitudinal strain
    - All 4 chambers and aorta
  - Core lab measurements
  - Normal values
    - entire population
    - Subgroups
      - Nationality, race, ethnicity, age groups, sex

WASE Study: 2008 participants from 15 countries
43% White, 42% Asian, 10% Black, 6% Mixed/other

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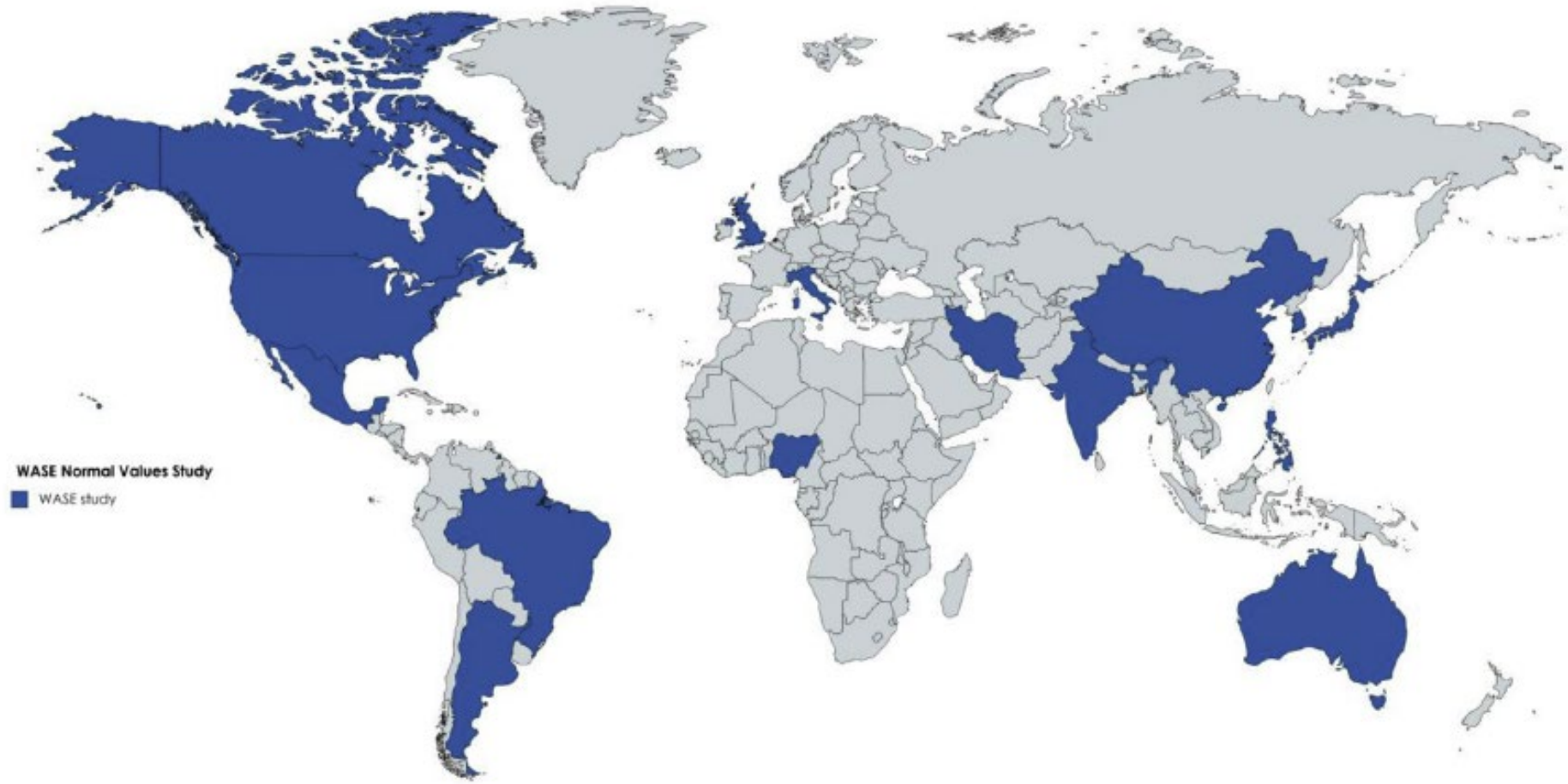

Asch et al, JASE 2019;32:1396-406

WASE LV size and function

Asch et al, JASE 2019;32:1396-406

- LV dimensions + volumes larger in males
- LVEF + GLS higher in females
- LV dimension normal ranges smaller than the ASE guidelines
- LV volumes ULN and LVEF LLN higher than ASE guidelines
- Intercountry variation even after indexing for body size
  - LV volumes largest in Australians, small in East Asian Indians (both sexes)
- Racial differences
  - Whites and blacks larger LV sizes than Asians or mixed race (after indexing)
- Country and Racial differences statistically but likely not clinically significant

WASE LV size and function

Asch et al, JASE 2019;32:1396-406

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Table 2 Normal ranges for the global WASE population by gender and its comparison with 2015 ASE/EACVI guidelines

Variable	WASE, LLN to ULN			Guidelines	
	Male	Female	*P*	Male	Female
LVIDd, mm	36 to 56	33 to 51	<.0001	42 to 58	38 to 52
Indexed LVIDd, mm/m^2	19 to 30	20 to 31	<.0001	22 to 30	23 to 31
LVIDs, mm	22 to 37	21 to 34	<.0001	25 to 40	22 to 35
Indexed LVIDs, mm/m^2	12 to 20	12 to 21	<.0001	13 to 21	13 to 21
IVSd, mm	6 to 12	5 to 10	<.0001	6 to 10	6 to 9
LVPWd, mm	6 to 11	5 to 10	<.0001	6 to 10	6 to 9
LV mass, g	74 to 204	55 to 148	<.0001	88 to 224	67 to 162
LV mass index, g/m^2	42 to 101	36 to 85	<.0001	49 to 115	43 to 95
LVEDV, mL	61 to165	47 to 122	<.0001	62 to 150	46 to 106
LVEDVI, mL/m^2	34 to 80	31 to 70	<.0001	34 to 74	29 to 61
LVESV, mL	21 to 65	17 to 47	<.0001	21 to 61	14 to 42
LVESVI, mL/m^2	12 to 32	11 to 28	<.0001	11 to 31	8 to 24
LVEF, %	57 to 68	58 to 69	<.0001	52 to 72	54 to 74
LV GLS, %	−17 to −24	−18 to −26	<.0001	NA	NA

WASE LV size and function

Asch et al, JASE 2019;32:1396-406

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Table 4 Normal ranges by race and gender

Race	Indexed LVIDd, mm/m-	Indexed LVIDs, mm/m^2	IVSd, mm	LVPWd, mm/m^2	LV Mass Index, g/m^2	LVEDVI, mL/m^2	LVESVI, mL/m^2	LVEF, %	GLS, %
Male									
White	19 to 29*	12 to 19*	6 to 12	6 to 11†	41 to 102	33 to 81*,†	11 to 32*,†	57 to 68*	–17 to –24
Black	18 to 29*	11 to 19*	6 to 11	7 to 12*,†	45 to 96	33 to 81*,†	13 to 33*	57 to 69	–17 to –25
Asian	20 to 30	13 to 20	6 to 12	6 to 11	43 to 102	31 to 72	12 to 29	58 to 69	–17 to –25
Other	19 to 30	13 to 19	5 to 11	6 to 10*	37 to 86*	34 to 68	12 to 27	58 to 67	–18 to –24
Female									
White	20 to 31*	12 to 20*	5 to 11†	6 to 10†	36 to 85†	32 to 76*,†	11 to 29*,†	58 to 69*	–18 to –26
Black	19 to 30*	11 to 21*	4 to 10	6 to 10†	33 to 76	32 to 69*,†	12 to 29*,†	56 to 68*	–18 to –26
Asian	21 to 31	13 to 21	5 to 11	5 to 11	36 to 89	29 to 66	10 to 24	59 to 69	–18 to –26
Other	20 to 31	13 to 20	5 to 9	5 to 9*	35 to 67*	26 to 62*	9 to 23	60 to 68	–19 to –25

WASE LV size and function

Asch et al, JASE 2019;32:1396-406

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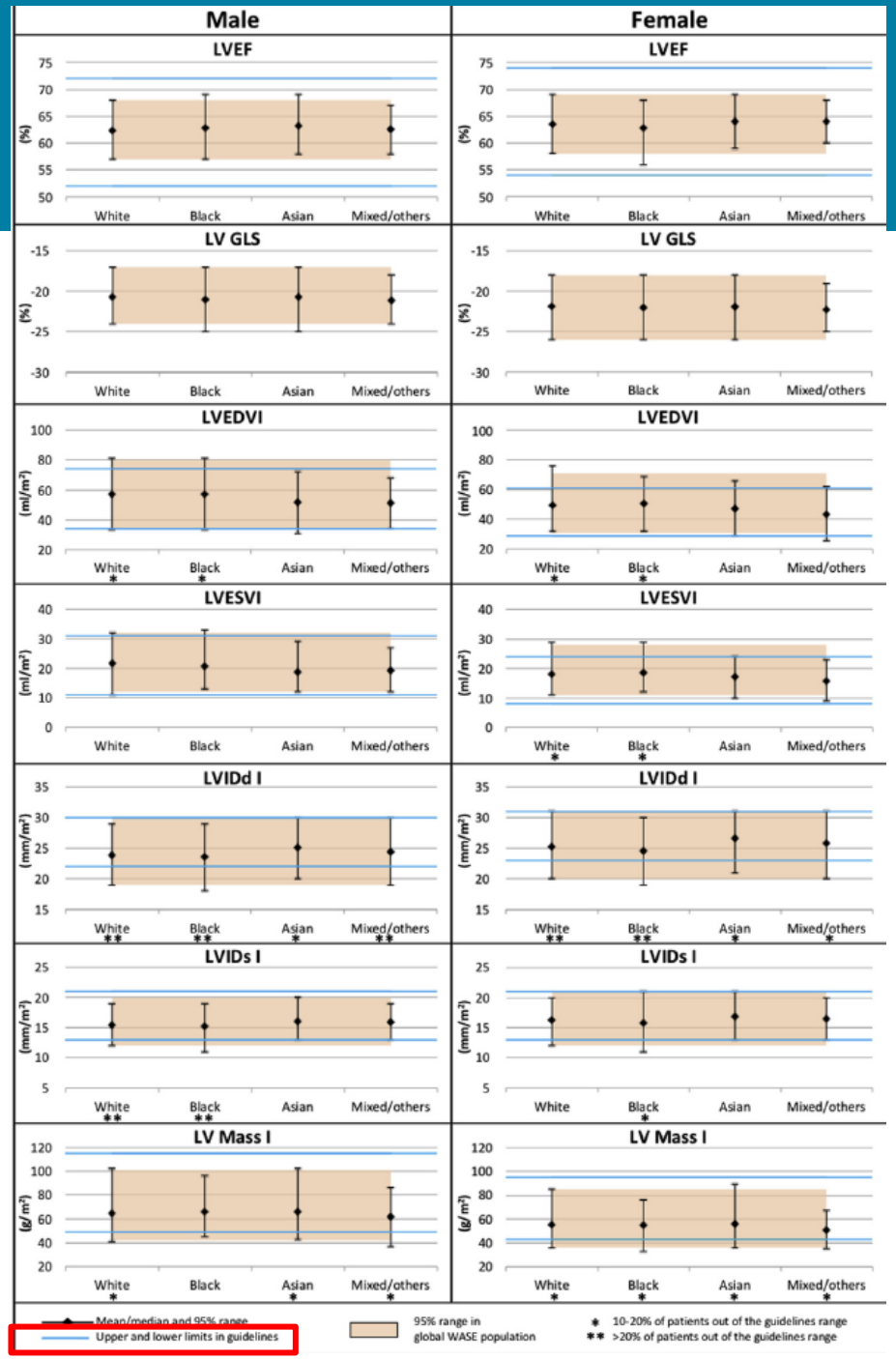
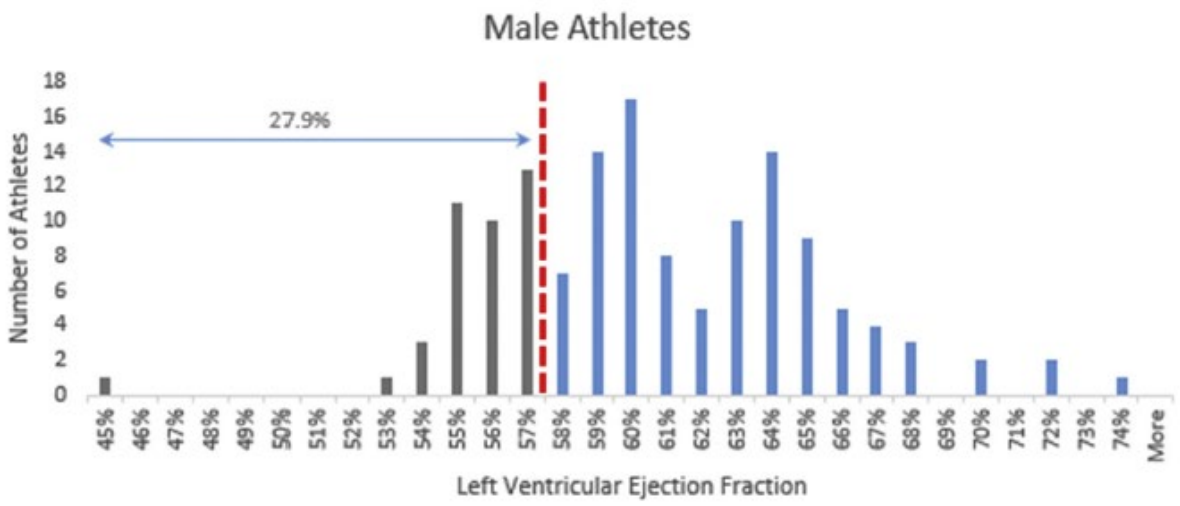
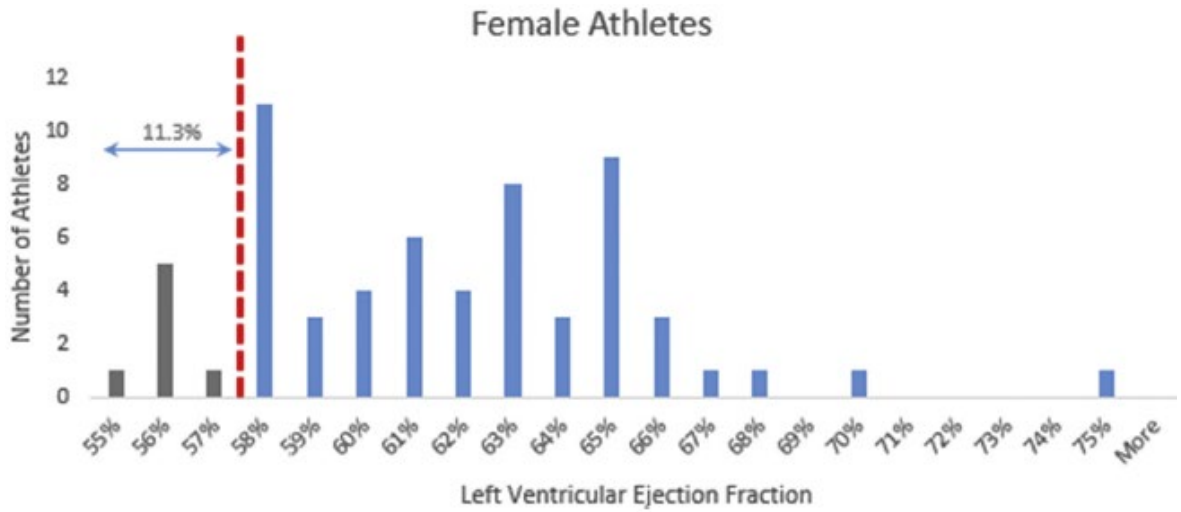


LVEF in athletes c/w WASE

Parizher et al, http://doi.org/10.1016/j.echo.2021.09.012 (Feb 2022 JASE issue)

- WASE excluded competitive athletes
- WASE LLN 58% (higher than 2015 ASE guidelines)
- 203 amateur to professional athletes from Cleveland Clinic Sports Center
  - Males 61 +/- 4.4% (52-69%); Females 62 +/- 3.9% (54-69%)

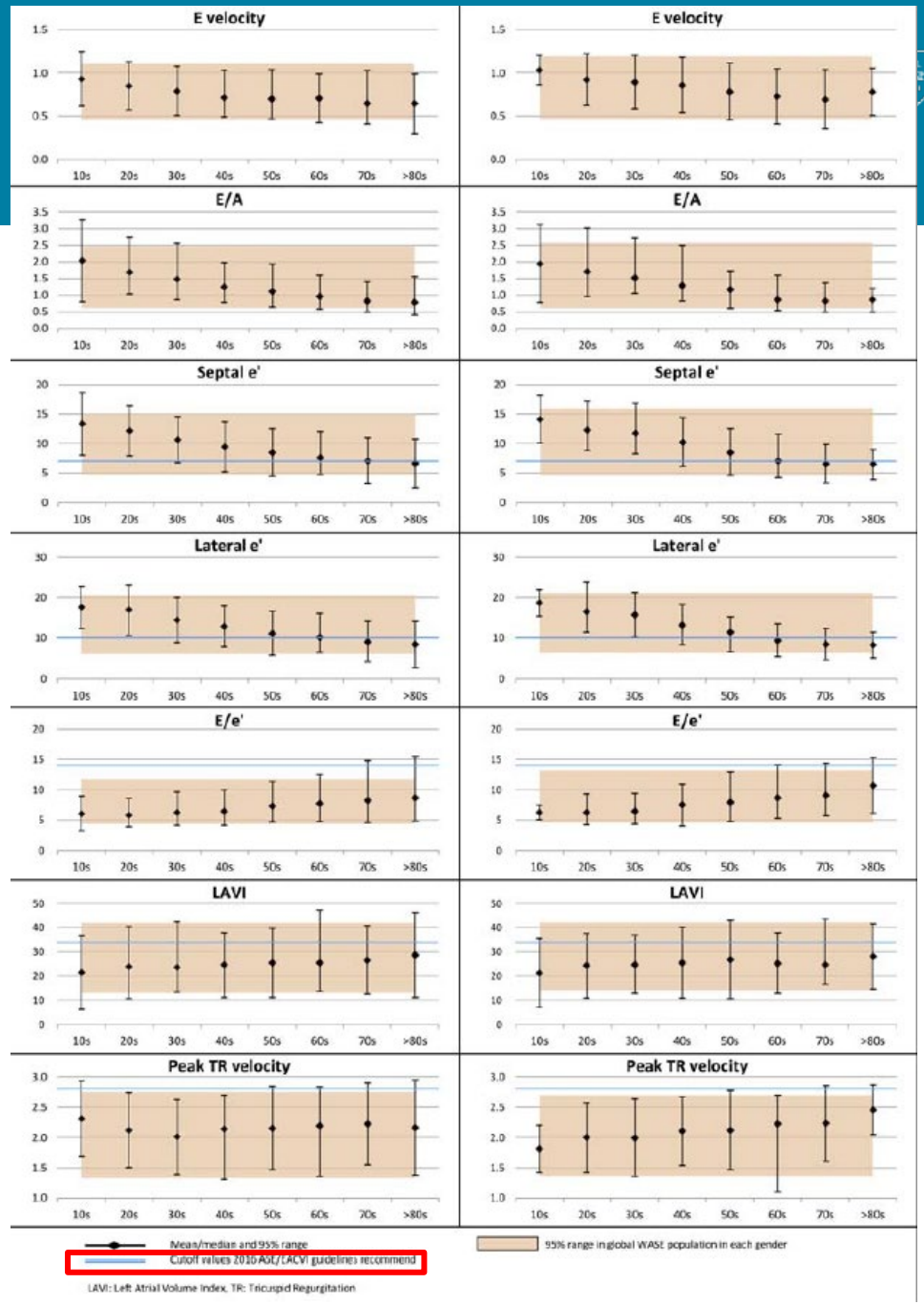




WASE LV diastolic function
Miyoshi et al, JASE 2020;33:1223-1233

- E + E/e' higher in females; LAVI similar
- As age increases
  - E/e' increases (in most countries was within guideline recommended range)
  - E/A, E, e' decreases (e' LLN lower in elderly c/w guidelines)
- LAVI ULN higher for all races and countries (but varied by country) ~ 41 ml/m^2
- E and E/A similar in all race all age groups
  - Asians lower septal/lateral e', higher E/e', smaller LAVI c/w whites
- When assessing diastolic function could consider a larger LAVI normal and in the elderly accept a lower e'

Miyoshi et al, JASE 2020;33:1223-1233



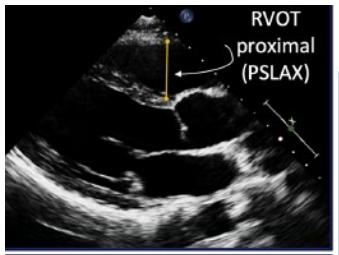
RV size and function

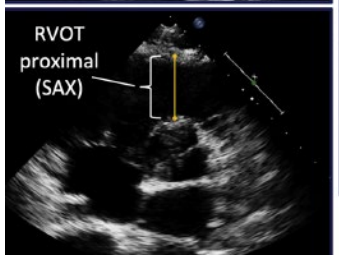
Addetia et al, JASE 2021;34:1148-57

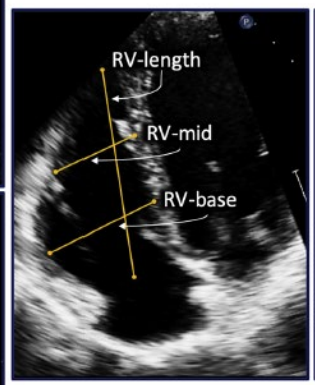
- Women – smaller RV areas (absolute + indexed), RV dimensions (absolute), higher FAC, free wall strain, RV GLS
- Age – RV area, length smaller > 65 yo
  - Other parameters of size and function: no or minimal decrease with age
- Ethnicity/Race –no meaningful difference in function parameters; RV size smallest in Asians

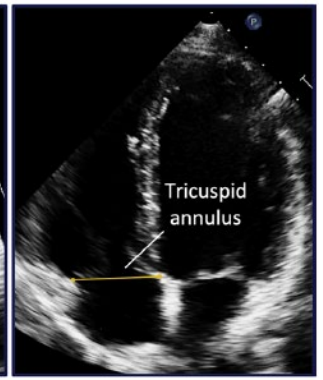
RV size and function

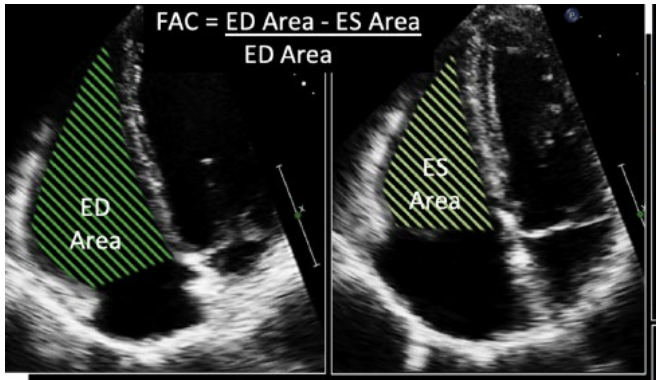
Addetia et al, JASE 2021;34:1148-57

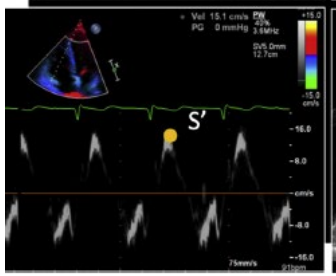


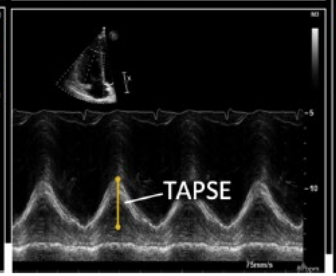


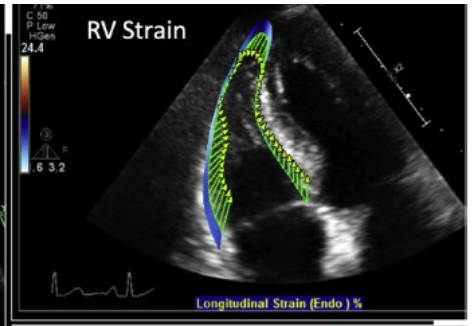


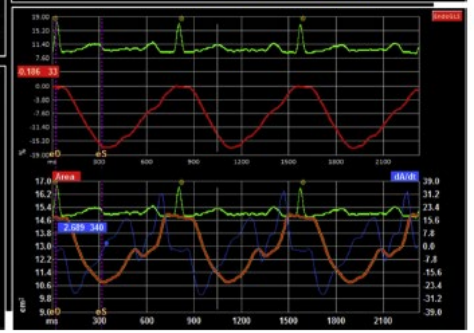


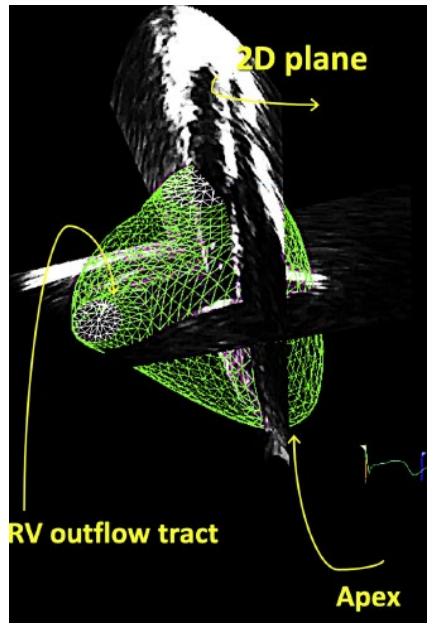












RV size and function

WASE data c/w 2015 ASE guidelines range

Addetia et al, JASE 2021;34:1148-57

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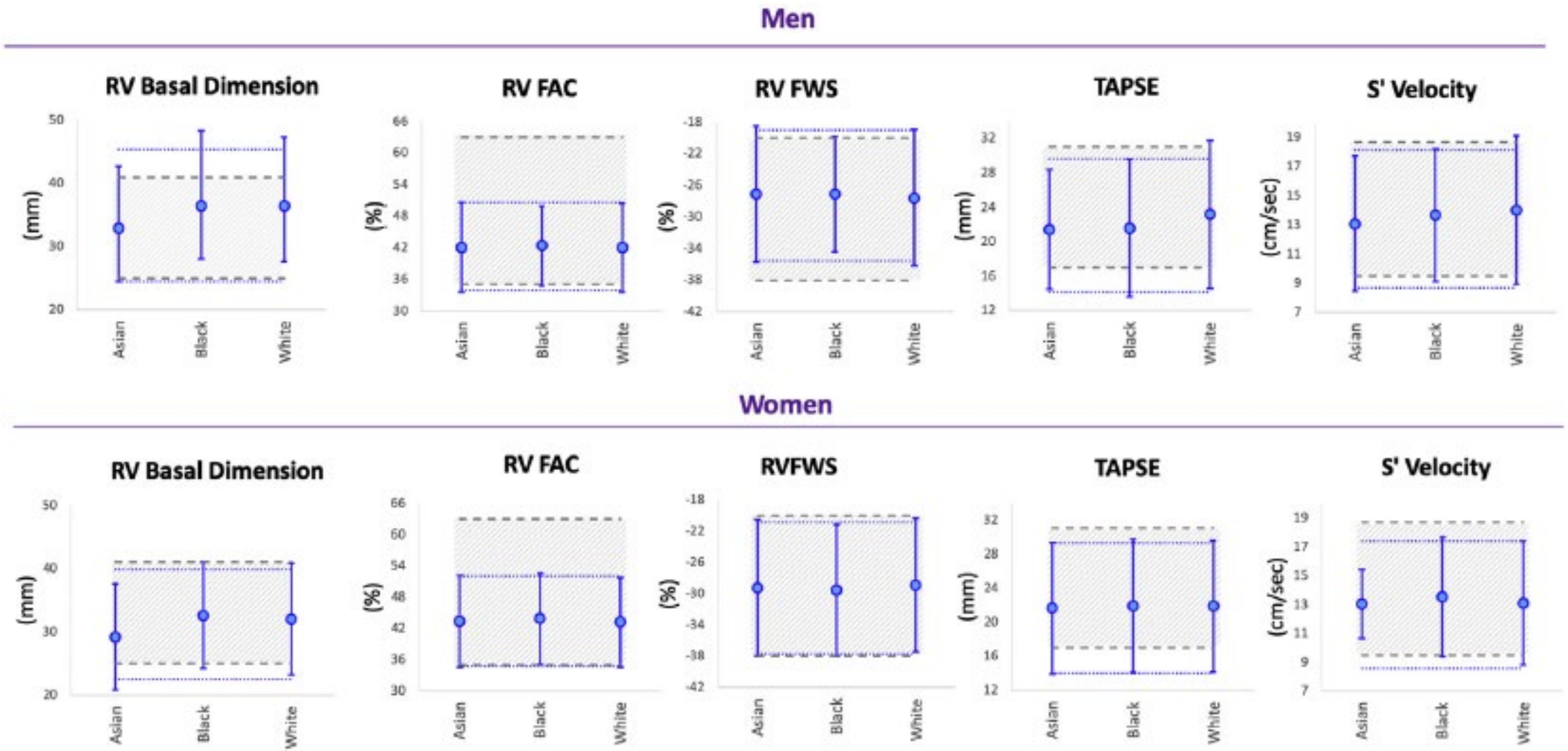

LA size and function

Singh et al, JASE http://doi.org/10.1016/j.echo.2021.08.008 (Feb 2022 issue)

- 3D maximum and minimum LV volumes adjusted for BSA similar for males and females
- Women higher emptying fractions
- 2D reservoir strains similar for both sexes
- Age associated with incremental increase in LA volumes
- Racial differences
  - LA volumes smaller for Asians
  - Some statistical but no clinically important differences for functional parameters

LA size and function

Singh et al, JASE http://doi.org/10.1016/j.echo.2021.08.008 (Feb 2022 issue)

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Table 3 Limits of normality for LA parameters

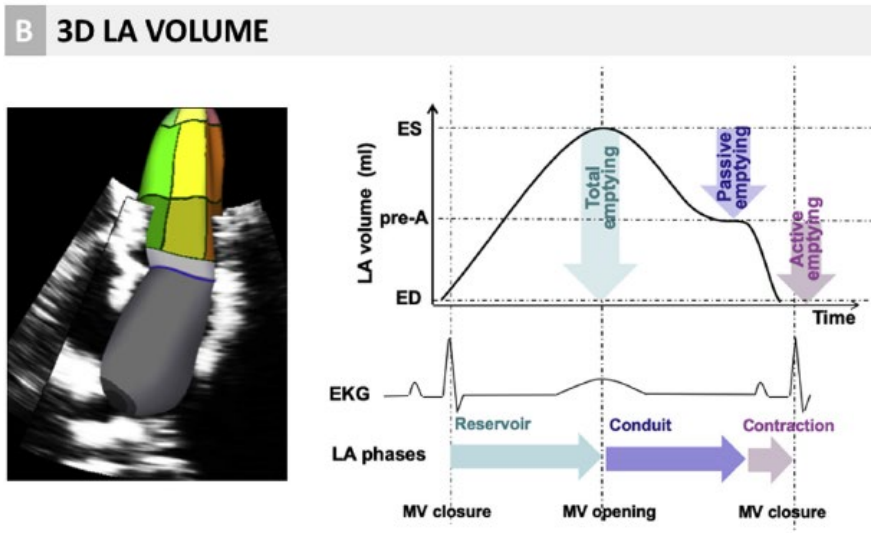
	Men			Women		
	18–40 y	41–65 y	>65 y	18–40 y	41–65 y	>65 y
	LLN–ULN	LLN–ULN	LLN–ULN	LLN–ULN	LLN–ULN	LLN–ULN
Size parameters						
2D maximum LAV, mL	22–82	22–91	22–84	21–71	21–78	20–80
2D maximum LAVi, mL/m^2	13–39	13–42	13–41	13–40	14–47	14–48
3D maximum LAV, mL	30–85	28–89	31–88	25–67	29–75	29–81
3D maximum LAVi, mL/m^2	16–41	16–46	18–48	17–39	18–43	18–47
3D minimum LAV, mL	9–37	10–38	11–42	8–27	9–36	10–36
3D minimum LAVi, mL/m^2	5–18	5–20	5–22	5–17	6–21	6–22
3D LA pre-A volume, mL	16–54	17–63	20–64	13–41	16–53	19–57
3D LA pre-A volume index, mL/m^2	9–26	10–31	11–34	9–23	10–30	13–35
3D LA reservoir volume, mL	16–55	16–56	17–53	15–45	16–45	16–46
3D LA reservoir volume index, mL/m^2	9–26	9–28	10–28	10–27	10–26	11–26
3D LA conduit volume, mL	9–35	8–32	7–31	9–32	7–27	5–25
3D LA conduit volume index, mL/m^2	5–18	4–16	4–16	5–19	4–16	3–16
Functional parameters						
2D LA EF, %	50–80	50–80	48–78	54–81	48–78	43–76
2D LA reservoir strain, %	25–63	23–61	24–57	29–62	22–56	21–56
2D LA conduit strain, %	18–50	12–43	10–36	19–52	12–42	9–36
2D LA booster strain, %	2–23	5–28	9–32	2–21	6–28	7–30
3D LA total EF, %	42–75	47–74	43–74	48–76	43–74	46–72
3D LA passive EF, %	21–55	16–48	14–47	26–63	20–52	14–48
3D LA active EF, %	17–54	26–59	24–60	18–54	21–56	27–59

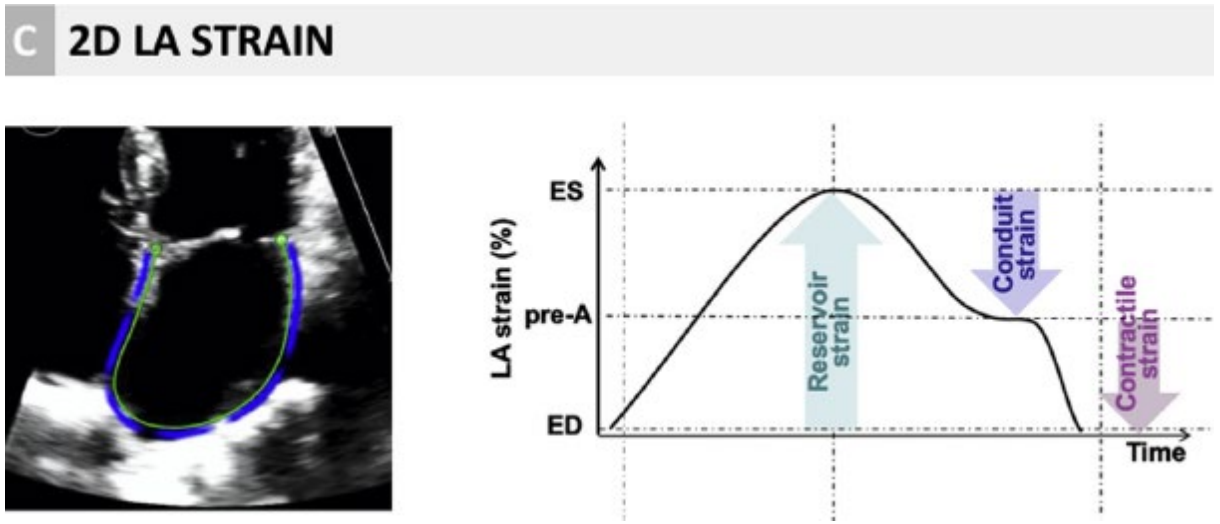
LLN, Lower limit of normal; *ULN*, upper limit of normal.

LA size and function

Singh et al, JASE http://doi.org/10.1016/j.echo.2021.08.008 (Feb 2022 issue)

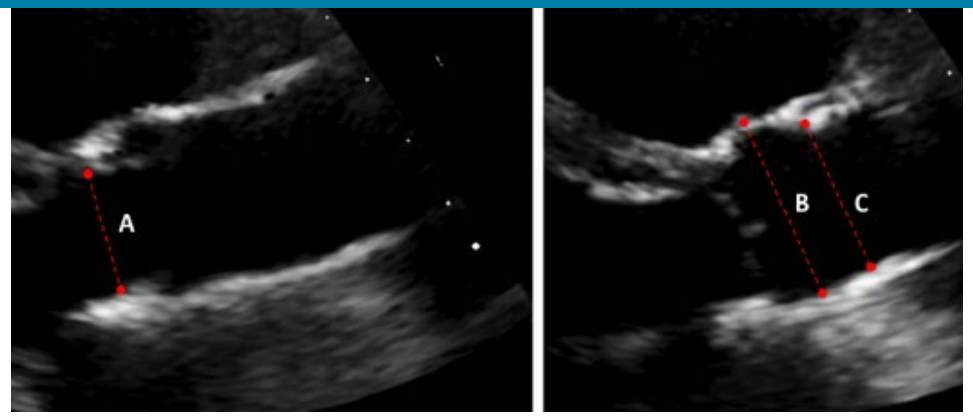
- similar normal values for LA volumes and strain can be used for both sexes
- LA size increases with age
- LA function shifts with age – rise in booster, decrease in passive





Aortic Root

Patel et al JASE https://doi.org/10.1016/j.echo.2021.09.011 (March 2022 issue)



annulus – inner edge to inner edge at mid systole

Sinuses of Valsalva, sinotubular junction
leading edge to leading edge at end diastole

- Aortic annulus, sinuses of Valsalva and sinotubular junction D dimensions larger in men c/w women
  - When indexed to BSA the measures are larger in women
  - When indexed to height the measures remain larger in men
- Aortic dimensions larger in the older age group
- Asians had the smallest nonindexed aortic dimensions

WASE data compared to 4 classic studies

Wong C et al https://doi.org/10.1016/j.echo.2021.12.001

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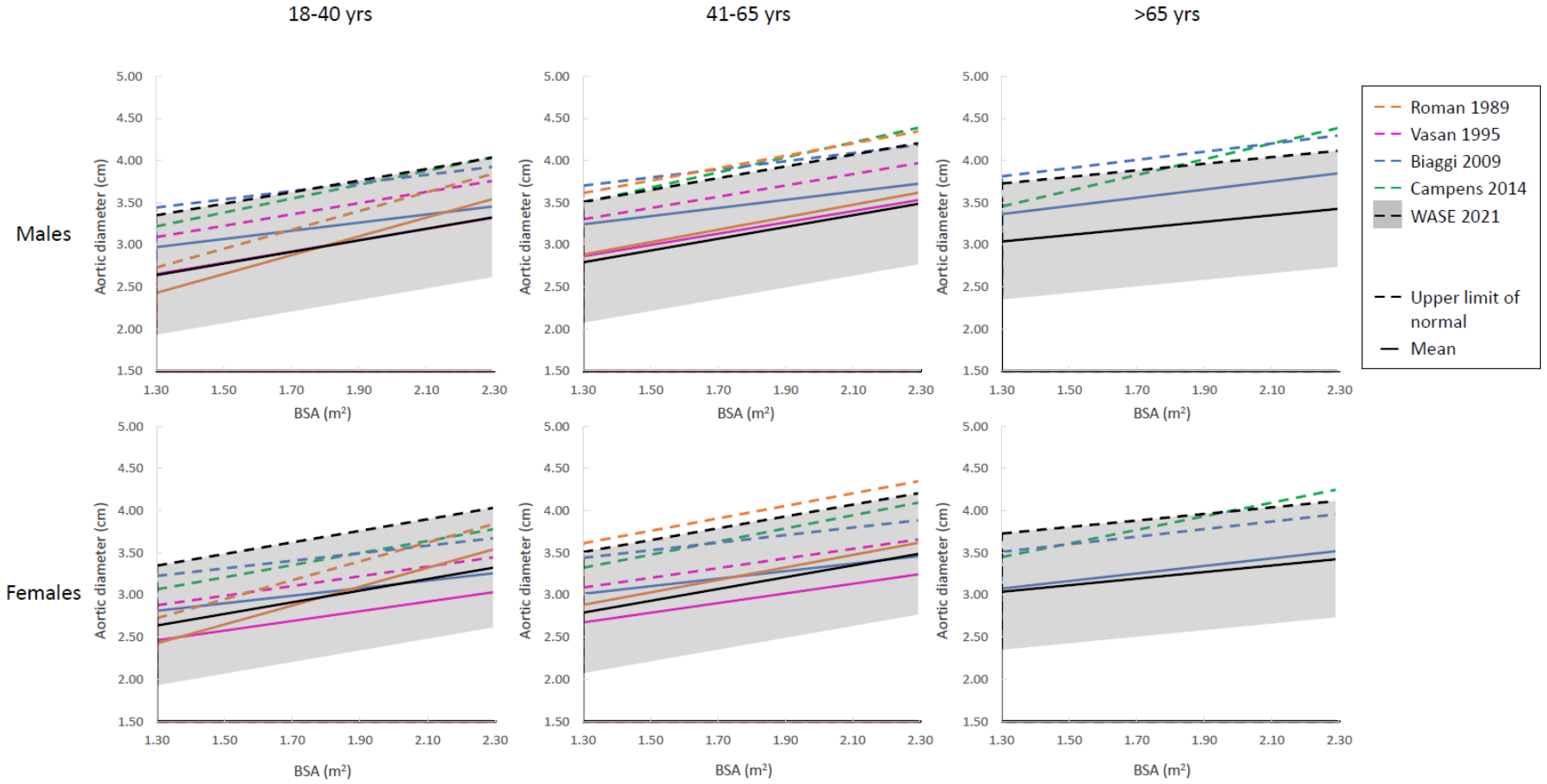
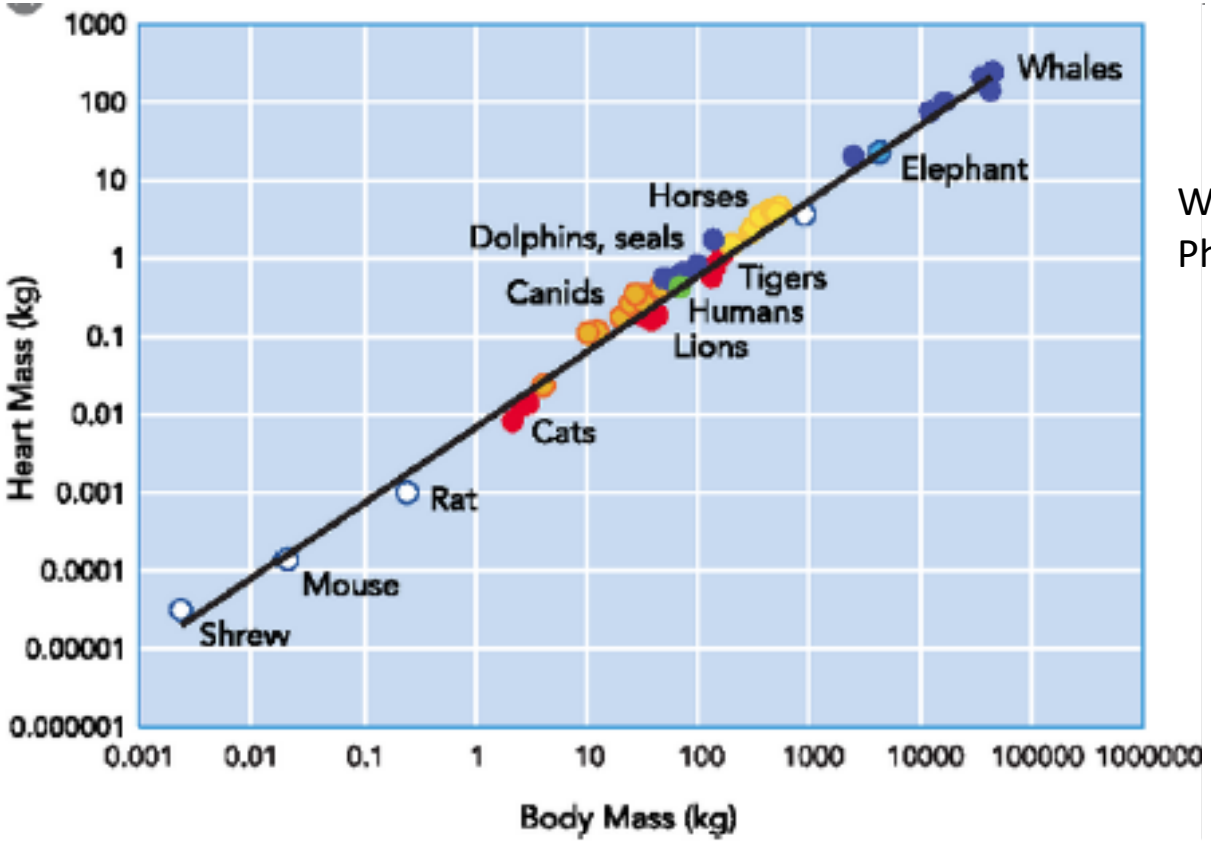


Defining upper limit of normal is critical to defining pathology

can be confusing since varies by BSA, age, sex, race/ethnicity

How should we index for body size ?

- Size of the heart is proportional to body size across species
  - Exponential with linear correlation between log body mass and heart mass



Williams et al. The Healthy Heart: Lessons from Nature's Elite Athletes. Physiology (Bethesda) 2015;30:349-57

Human adult heart size also influences by sex, age, race, ethnicity, exercise, body composition

How should we index for body size ?

- To account for differences in body size when determining if heart size is normal one needs to correct or index by an objective metric of body size
  - Most often linear or isometric scaling dividing by BSA
    - Advantage
      - Easy to comprehend and perform
    - Problems
      - The correlation between cardiac chamber size or mass is rarely linear
      - Body composition affects the relationship between body size and heart size
        - » When compared to normal values derived from patients with normal body size the ratio heart size/BSA gives different results when varying rates of adiposity
          - BSA in obese over-normalizes
          - Weight can change markedly over time

- Male, 275 lbs, 5’9”, BMI 40.6 kg/sq m, BSA 2.36 sqm
  - LA volume 75 ml LA volume index 31.8 ml/sq m
  - Bariatric surgery results in weight loss of 100 lbs
    - New BMI 25.8 kg/sq m; BSA 1.95 sq m
    - LA volume has not changed but indexing to BSA gives impression that it has
      - new LAVI is 38.5 ml/sqm

- The best parameter for indexing is fat-free mass (aka lean body mass)
  - Eliminates confounding effects of sex , different body builds
  - Difficult to measure

Alternatives to ratiometric scaling to BSA

- Allometric or non-linear scaling
  - Divide by measure of interest raised to an exponent

- Height rarely changes in adults so a better indicator body size
  - Height raised to power of 2.7 used in research studies
  - Human is closer to a cylinder than a sphere so recent studies have recommended height raised to 1.6-1.7

- Allometric indexing rarely applied
  - awkward and less intuitive

- Allometric indexing associatred with outcomes (Javier Olsen et al JASE http://doi.org/10.1016/j.echo.2021.10.010 (February 2022 issue)
  - LA max or min volumes indexed to height associated with future development of AF (median f/u 14 years)
  - LA max or min volume indexed to height raised to 1.65 even stronger association

Summary

- Normal values from the WASE study accounts for age, sex, race, ethnicity
- Some of the ULN values differ from current guidelines
  - Most are subtle and not clinically relevant difference
  - Except for Asians and some age-based differences
- Indexing helps remove effects of differing body size
  - BSA not a good scaling factor in the era of increasing obesity
  - Height or an allometric scale of height is better

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