ON-LINE APPENDIX: MATERIALS AND METHODS

Statistical Analysis

For each measurement of interest, age-specific reference intervals (normal ranges) are constructed from a parametric method[1] providing smooth centile curves and explicit formulae for the centile estimates. Let C_p $(0 < p < 1)$ be the curve corresponding to the 100qth centile of the distribution of the measurement of interest (Y) given the time (T) defined, in the normal model, by

$$C_p = \mu_T + q_p \sigma_T,$$

where T is continuous age expressed in years, μ_T and σ_T indicate the corresponding values of mean and SD at age T, q_p is the 100qth centile of the standard Gaussian distribution ($N[0,1]$). For example, determination of the third centile curve requires that $q_3 = -1.880794$. The estimated centile curves are calculated by substituting estimates of the parameter (μ and σ) curves into the above expression.

First, a smoothing of the studied variable against age depending on sex produces an overview of the shape of the mean curve and investigates the necessity to model each curve separately by sex. If the variable tends to have a stable level or asymptote as age increases, the following exponential transformation, which compresses the upper age range, is applied

$$X = exp\left\{\frac{T - T_1}{T_n - T_1}\log\rho\right\},$$

where T denotes the age, T_1 and T_n denote minimum and maximum ages, respectively, and ρ is a preselected constant for which a suitable value is 0.1. X is used in place of T in regression models for the parameter curves. Furthermore, data may require transformation (eg, logarithmic, Box-Cox) to achieve approximate normality.

Second, the mean μ_T is modelled as a fractional polynomial function of age. Fractional polynomial of degree m, $FP(m)$, is fitted by least-squares regression of the measurement of interest against age. Fractional polynomials are polynomials in which the powers of age are numbers chosen from the set $\{-2; -1; -0.5; 0; 0.5; 1; 2; 3\}$, where x^0 denotes a natural logarithm of x. The selection of an appropriate FP model is done by comparing the difference in deviance between models with a X^2 variate on 2 *df*. Then the mean is estimated by the fitted values from an appropriate fractional polynomial regression curve of the measurement of interest on age.

If the scaled absolute residuals appear to show no trend with age, the SD (σ_T) is estimated as the SD of the unscaled residuals. The scaled absolute residuals are defined as the absolute residuals multiplied by 1.25.[1] If there is a trend, fractional polynomial regression analysis is performed to estimate an appropriate curve in the same way as the mean.

Third, to check the model fitting, a normal probability plot of the z scores may help appreciate the degree to which the values follow a Gaussian distribution. The z scores are defined as

$$Z = \frac{Measurement - Mean}{SD}.$$

In addition, a scatterplot of the z scores against age is a usefull tool in assessing model fitting. Approximately, 90% of the values should lie between the limits ±1.645. If normality is accepted, no further modeling is required.

Eventually, if the normality is not reached, the exponential-normal or modulus-exponential-normal model may be used instead. The reader is referred to Royston and Wright, 2002[1] for more details about these 2 models. Such details are not presented here because these models were not required in our applications.

Last, estimated centiles and reference intervals are obtained by substituting the fitted curves of μ_T and σ_T into the equation of C_p.

REFERENCE

1. Royston P, Wright E. **A method for estimating age-specific reference intervals ('normal ranges') based on fractional polynomials and exponential transformation.** *Journal of the Royal Statistical Society Series A (Statistics in Society)* 2002;161:79–101 CrossRef

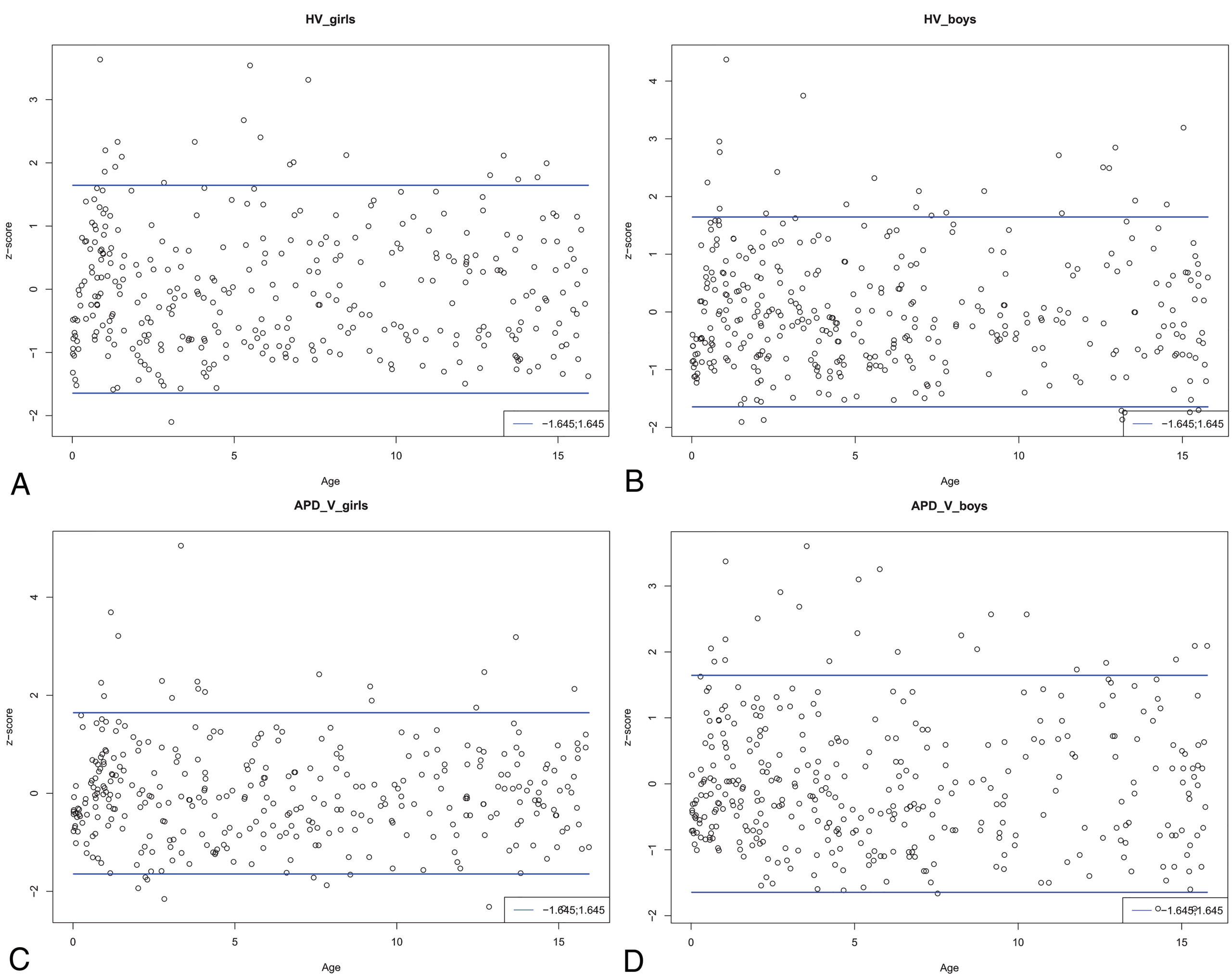
On-line Table 1: Median, third, and 97th percentiles for the different parameters as a function of age[a]

	Age (yr)																		
	0.25	0.5	1	1.5	2	2.5	3	4	5	6	7	8	9	10	11	12	13	14	15
H-V girls																			
Third	21.99	27.18	31.77	33.97	35.22	35.98	36.46	37.00	37.28	37.47	37.61	37.73	37.84	37.95	38.04	38.13	38.21	38.27	38.34
Median	34.58	36.71	39.35	40.90	41.88	42.53	42.99	43.56	43.91	44.16	44.34	44.49	44.61	44.71	44.80	44.87	44.94	45.00	45.04
97th	40.54	42.12	44.24	45.58	46.47	47.10	47.56	48.17	48.56	48.84	49.05	49.21	49.34	49.45	49.54	49.61	49.67	49.72	49.77
H-V boys																			
Third	20.94	27.92	33.17	35.53	36.82	37.56	38.02	38.49	38.74	38.93	39.11	39.31	39.53	39.76	40.00	40.24	40.49	40.74	40.99
Median	34.48	37.11	40.19	41.91	42.95	43.63	44.09	44.66	45.00	45.26	45.48	45.68	45.88	46.06	46.25	46.43	46.61	46.79	46.97
97th	40.39	42.31	44.79	46.29	47.26	47.92	48.40	49.02	49.43	49.73	49.97	50.18	50.37	50.54	50.71	50.86	51.01	51.16	51.30
APD-V girls																			
Third	10.88	13.65	16.77	18.47	19.48	20.10	20.49	20.90	21.07	21.14	21.17	21.18	21.18	21.19	21.19	21.19	21.19	21.19	21.19
Median	19.88	21.38	23.36	24.54	25.27	25.73	26.03	26.34	26.46	26.52	26.54	26.55	26.55	26.56		26.56	26.56	26.56	26.56
97th	25.57	26.70	28.26	29.21	29.81	30.19	30.43	30.69	30.80	30.84	30.86	30.87	30.87	30.87	30.87	30.87	30.88	30.88	30.88
APD-V boys																			
Third	9.67	13.43	17.14	19.04	20.13	20.80	21.21	21.64	21.81	21.89	21.91	21.93	21.93	21.93	21.94	21.94	21.94	21.94	21.94
Median	19.87	21.55	23.71	24.96	25.73	26.21	26.51	26.83	26.96	27.01	27.03	27.04	27.05	27.05	27.05	27.05	27.05	27.05	27.05
97th	25.54	26.76	28.40	29.40	30.01	30.40	30.65	30.91	31.01	31.06	31.08	31.08	31.09	31.09	31.09	31.09	31.09	31.09	31.09
APD-P girls																			
Third	12.58	13.29	14.32	15.02	15.50	15.85	16.11	16.48	16.76	17.00	17.22	17.43	17.64	17.85	18.06	18.26	18.46	18.67	18.87
Median	15.56	16.22	17.19	17.84	18.29	18.62	18.87	19.22	19.49	19.71	19.92	20.12	20.32	20.52	20.72	20.91	21.10	21.30	21.49
97th	18.36	18.97	19.89	20.51	20.94	21.25	21.49	21.83	22.08	22.30	22.50	22.69	22.88	23.07	23.26	23.44	23.63	23.82	24.00
APD-P boys																			
Third	12.99	13.82	14.98	15.71	16.19	16.52	16.75	17.08	17.32	17.55	17.77	17.99	18.22	18.46	18.69	18.93	19.17	19.41	19.65
Median	15.35	16.18	17.37	18.16	18.70	19.08	19.38	19.79	20.11	20.38	20.62	20.86	21.10	21.33	21.56	21.79	22.02	22.24	22.46
97th	17.47	18.32	19.56	20.40	21.00	21.44	21.78	22.28	22.65	22.96	23.23	23.49	23.73	23.96	24.19	24.41	24.63	24.84	25.05
APD-MP																			
Third	6.68	6.84	7.13	7.39	7.62	7.82	7.99	8.29	8.52	8.71	8.86	9.00	9.11	9.22	9.33	9.44	9.56	9.69	9.83
Median	8.40	8.57	8.89	9.16	9.40	9.62	9.81	10.12	10.37	10.57	10.73	10.87	11.00	11.11	11.23	11.35	11.47	11.60	11.75
97th	10.24	10.42	10.76	11.05	11.30	11.53	11.73	12.06	12.32	12.53	12.71	12.86	12.99	13.11	13.23	13.36	13.49	13.63	13.78

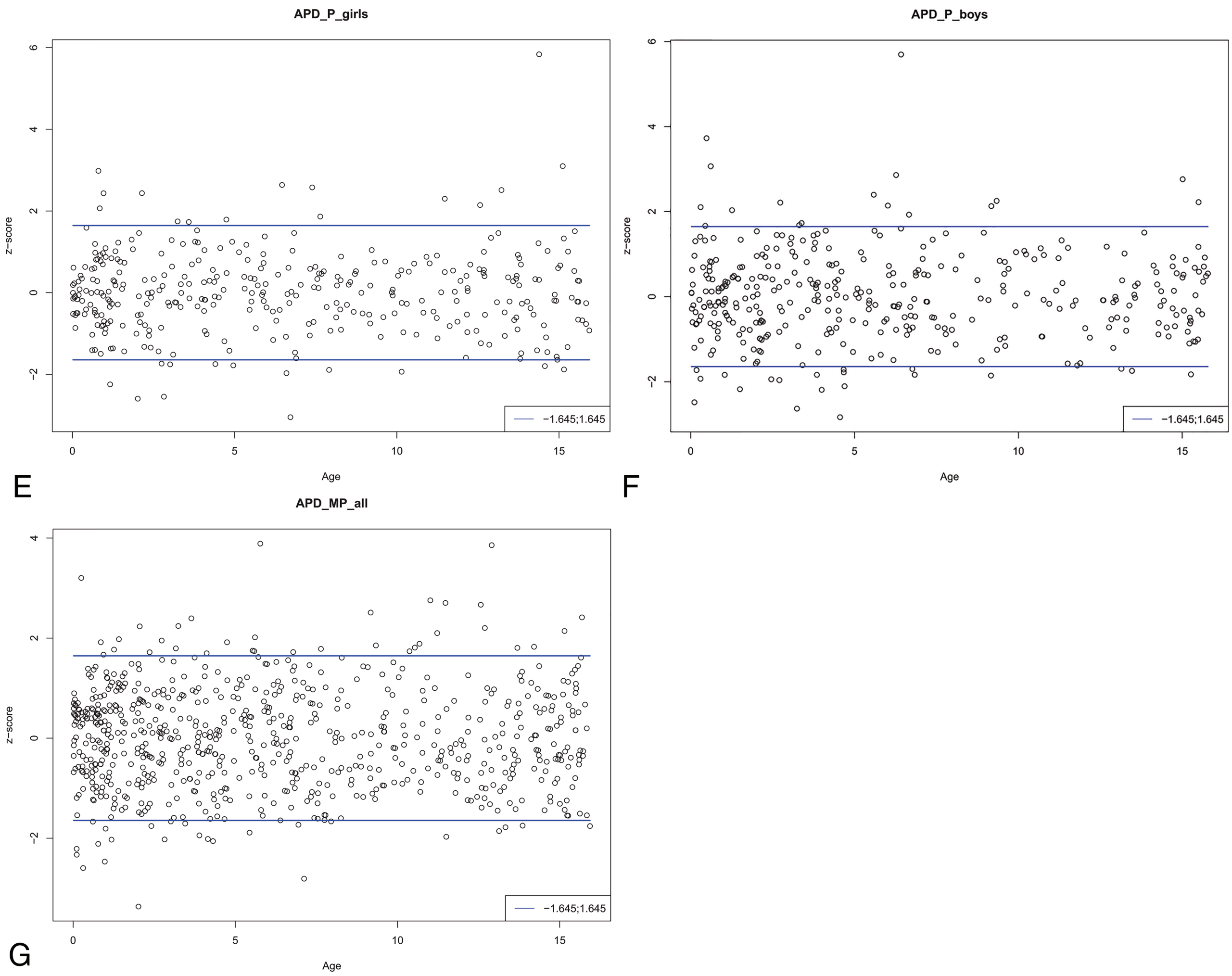
[a] The values of APD-MP were similar in both sexes.

On-line Table 2: Inter- and intraobserver agreement for MR imaging measurements performed on T1 or T2 sequences

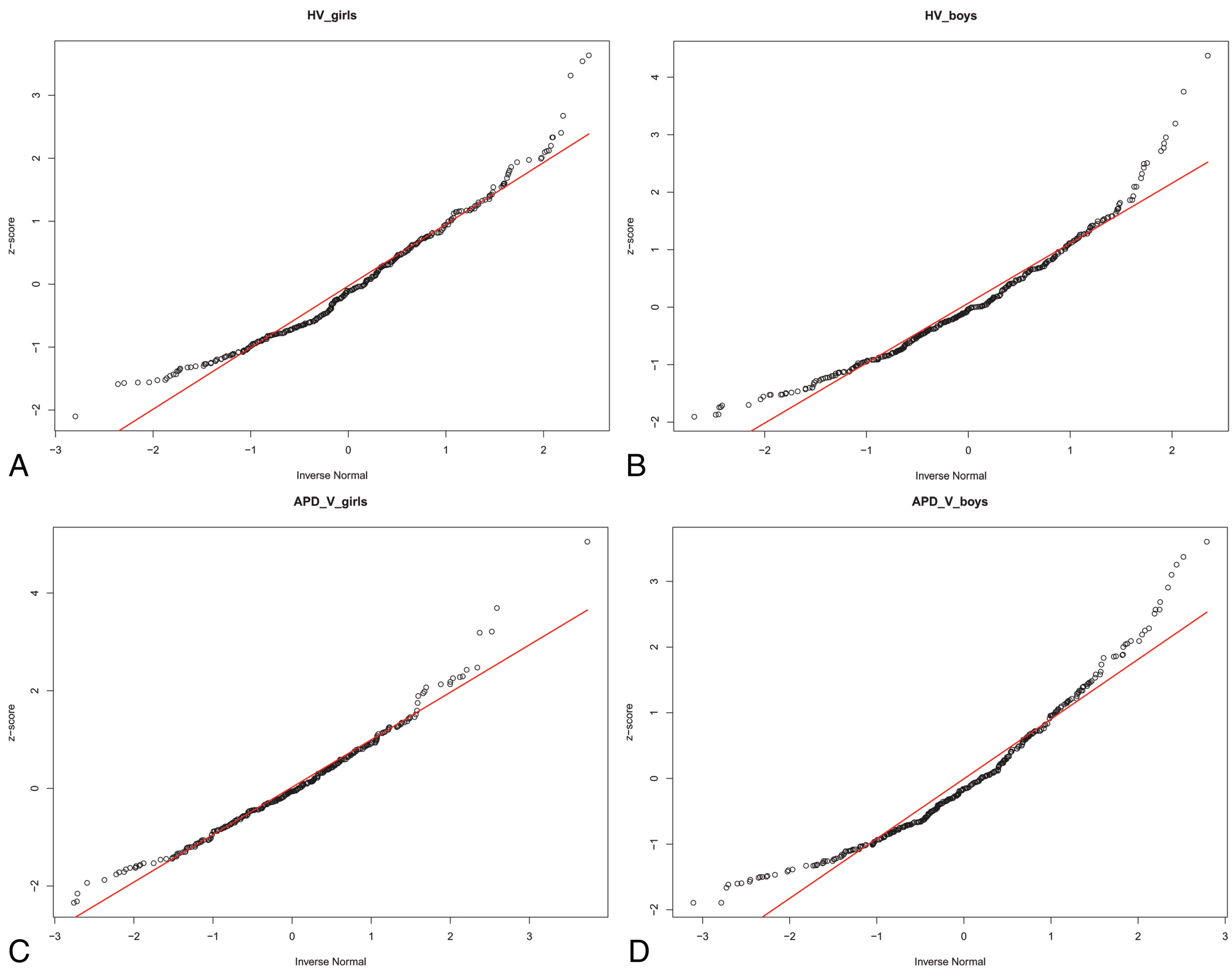
Parameter	Intraobserver Agreement			Interobserver Agreement		
	Mean Bias	95% Limits of Agreement	ICC (95% CI)	Mean Bias	95% Limits of Agreement	ICC (95% CI)
T1 images (*n* = 36)						
H-V	0.075	−0.817, −0.967	0.996 (0.983–0.999)	−0.286	−2.137, 1.567	0.982 (0.933–0.992)
APD-V	0.458	−1.611, 2.528	0.946 (0.841–0.970)	0.511	−2.634, 3.656	0.885 (0.721–0.949)
APD-P	0.133	−1.265, 1.532	0.897 (0.806–0.947)	0.214	−1.746, 2.175	0.811 (0.588–0.942)
APD-MP	0.047	−0.799, 0.894	0.986 (0.970–0.994)	0.397	−0.954, 1.749	0.963 (0.894–0.979)
T2 images (*n* = 14)						
H-V	0.364	−0.882, 1.611	0.992 (0.931–0.997)	−0.343	−2.170, 1.486	0.983 (0.879–0.995)
APD-V	0.007	−2.328, 1.168	0.943 (0.829–0.988)	−0.450	−3.011, 2.111	0.928 (0.793–0.977)
APD-P	0.014	−0.811, 0.840	0.955 (0.896–0.978)	−0.236	−1.298, 0.827	0.927 (0.769–0.971)
APD-MP	0.064	−0.541, 0.670	0.989 (0.975–0.996)	−0.350	−1.356, 0.657	0.966 (0.901–0.974)



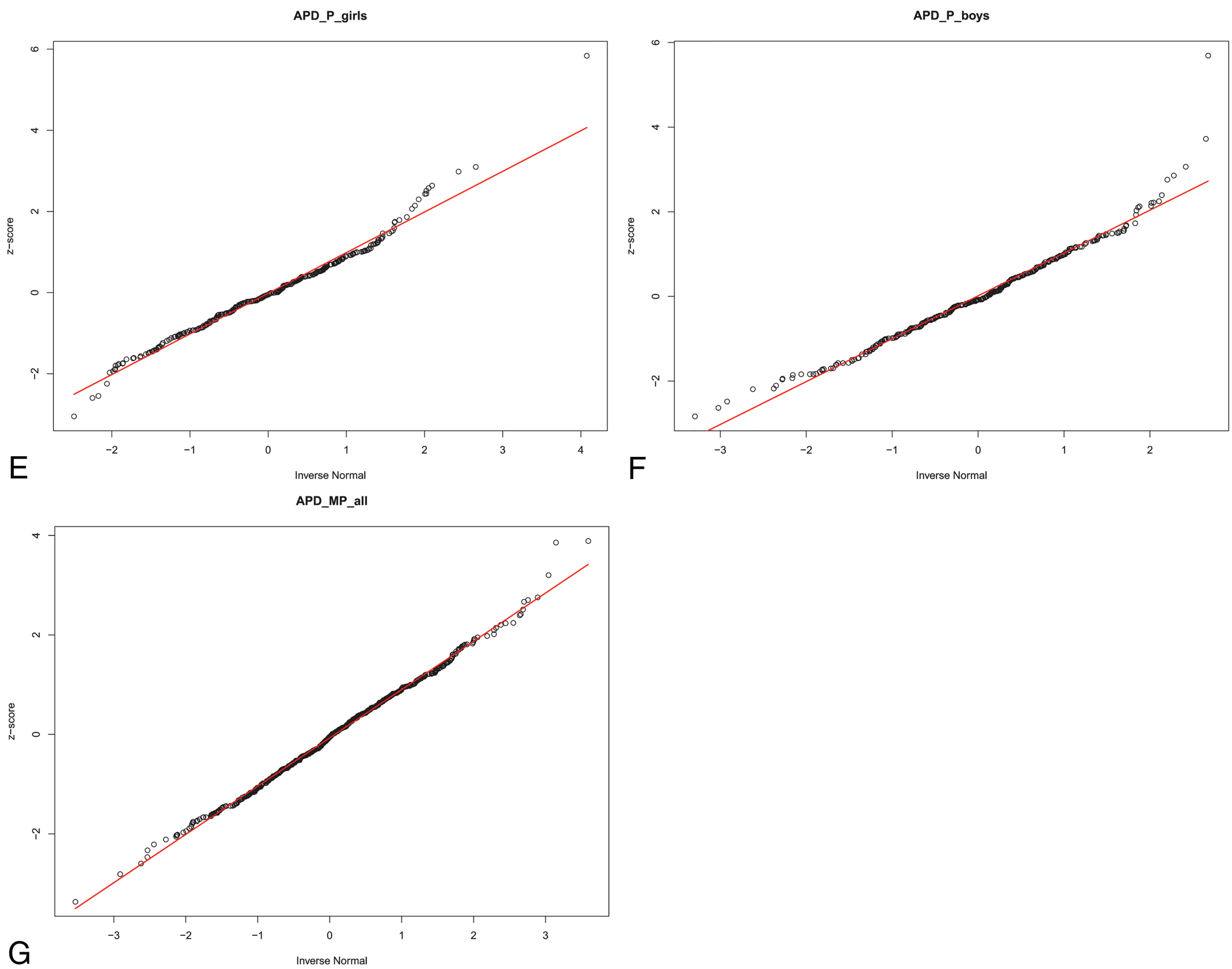
ON-LINE FIG 1. Scatterplots of *z* scores versus age. Tramlines were at −1.45; +1.45, from fitted models. Approximately 90% of the values should lie between the limits ± 1.645. The values of APD-MP were similar in both sexes.



ON-LINE FIG 1. Continued.



ON-LINE FIG 2. Normal plots of *z* scores from fitted models. The ordered *z* scores, when plotted against the corresponding ordered values from a standard Gaussian distribution with the same sample size, should lie roughly on a straight line. The values of APD-MP are similar in both sexes.



ON-LINE FIG 2. Continued.