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Centile reference chart for resting metabolic rate through the life course

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ABSTRACT

Objective Reference centile charts are widely used for the assessment of growth and have progressed from describing height and weight to include body composition variables such as fat and lean mass. Here, we present centile charts for an index of resting energy expenditure (REE) or metabolic rate, adjusted for lean mass versus age, including both children and adults across the life course.

Design, participants and intervention

Measurements of REE by indirect calorimetry and body composition using dual-energy X-ray absorptiometry were made in 411 healthy children and adults (age range 6–64 years) and serially in a patient with resistance to thyroid hormone α (RTH α) between age 15 and 21 years during thyroxine therapy.

Setting NIHR Cambridge Clinical Research Facility, UK.

Results The centile chart indicates substantial variability, with the REE index ranging between 0.41 and 0.59 units at age 6 years, and 0.28 and 0.40 units at age 25 years (2nd and 98th centile, respectively). The 50th centile of the index ranged from 0.49 units (age 6 years) to 0.34 units (age 25 years). Over 6 years, the REE index of the patient with RTH α varied from 0.35 units (25th centile) to 0.28 units (<2nd centile), depending on changes in lean mass and adherence to treatment.

Conclusion We have developed a reference centile chart for an index of resting metabolic rate in childhood and adults, and shown its clinical utility in assessing response to therapy of an endocrine disorder during a patient's transition from childhood to adult.

INTRODUCTION

Describing the physiological phenotypes of uncommon genetic disorders brings the challenge of determining the extent to which characteristics differ from those of a healthy population. This becomes more challenging when the individual is both developing through age and undergoing treatment. Measurement of resting energy expenditure (REE), a physiological variable dependent on body composition, which can change in catabolic (eg, critical illness) or endocrine (eg, hyperthyroidism or hypothyroidism) states, is useful in determining nutritional, energy intake or drug therapy.^{1–4} We have previously reported relationships between REE and body composition, using linear regression modelling and Z-scores, separately in healthy children and adults.^{3,5} As in many other sets of linear prediction equations, REE predictions are not easily

WHAT IS ALREADY KNOWN ON THIS TOPIC?

- ⇒ Centile charts for height and weight are widely used in the clinical setting to describe the normality of a measurement.
- ⇒ Resting energy expenditure (REE) or metabolic rate, being dependent on lean body mass, changes throughout childhood and adult life.

WHAT THIS STUDY ADDS

- ⇒ We have developed a centile chart for REE, based on lean mass and age, across childhood and adult life.
- ⇒ The centile chart will enable best comparison of this physiological parameter with normality during growth and adolescence, including in response to interventions (eg, thyroid hormone therapy) that govern this variable.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ Centile charts may be most appropriate when comparing other biological parameters that change with human physical growth, with normality.

interpreted when development moves an individual from one regression segment to another. For example, REE regressions by Schofield⁶ and Henry⁷ which are based on weight and height exhibit this effect. Here, we present an approach to the challenge of describing REE in terms of body composition with a continuous, unsegmented relationship through the 6 to 65 years age range.

Reference, growth centile charts are widely used in paediatric clinical settings to assess measurements such as height, weight and head circumference through childhood.⁸ The current UK-WHO growth charts^{9,10} consist of reference data based on the British 1990 (UK90)¹¹ and the WHO standards for weight, length, body mass index (BMI) and head circumference from 2 weeks of age up to 4 years. The UK90 data were also used to construct new charts for birth between 23 and 42 weeks' gestation.⁸ They are valuable for defining and detecting altered growth in an individual, due to, for example, small for gestational age,^{12,13} childhood obesity,¹⁴ rapid weight gain,¹⁵ malnutrition¹⁶ and epidemiology of childhood health at a population level.¹⁷

More informatively, body composition reference charts, including data for total body water, fat mass



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and fat-free mass (FFM) for UK children, adolescents and young adults¹⁸ and UK infants and children, have emerged.¹⁹ Body composition can be tracked from infancy to childhood and into adulthood and can be related to many clinical conditions and poor health outcomes. Reference charts allow clinicians to interpret observations across a wide range of diseases, conditions and treatments^{20–22} and are therefore an invaluable tool, contributing to assessment of nutritional status and management in clinical populations.

The advent of genome sequencing,²³ with earlier diagnosis of heritable metabolic disorders, has enabled commencement of therapies in childhood. Resistance to thyroid hormone alpha (RTH α) or congenital, non-goitrous hypothyroidism 6 (OMIM 614450), due to heterozygous mutations in thyroid hormone receptor α (TR α), is characterised by childhood developmental and growth retardation and a relative hypothyroid state in hormone-resistant TR α -expressing tissues, resulting in reduced REE.^{24 25} Like conventional childhood hypothyroidism, thyroxine therapy alleviates many symptoms and can promote normal growth and development.² However, due to feedback regulation within the pituitary-thyroid axis being mediated by a different, normal thyroid hormone receptor subtype (TR β), circulating thyroid-stimulating hormone (TSH) is not a useful biomarker in assessing response to thyroxine therapy.^{2 24 25}

When monitoring therapy of these patients longitudinally, defining expected REE using current methods is difficult. The LMS method fits growth references to data by assuming that the data at each age are distributed as skew normal.^{26 27} The method summarises the reference data with three smooth curves: the power transformation *lambda* needed to normalise the data (the L curve), the median *mu* or 50th centile (M curve), and the coefficient of variation of the distribution *sigma* (the S curve). The three curves allow any required centile to be drawn. The LMS method is a special case of the Generalised Additive Models for Location Scale and Shape (gamlss) family of models²⁸ which can be fitted using the gamlss package in R.

The LMS method has been widely used to construct reference data. Wells *et al*^{18 19} used it to derive reference centiles for body composition (total body water, FFM and fat mass) and four-component body composition variables from the age of 6 weeks to 20 years. They produced charts with the 25th, 50th, 75th, 91st and 98th centiles.

Using this method, we first sought to construct reference centiles for REE to describe the variation in REE and body composition across childhood and adulthood, providing uniformity across the age spectrum; second, we used the centile chart to plot the change in REE index of a patient with RTH α , evaluating its value in assessing the response to thyroid hormone therapy in this disorder.

METHODS

The REE measurement protocols used have been described previously.^{3 5} All measurements in each participant were made on a single occasion, on waking after an overnight stay in the National Institute for Health and Care Research (NIHR) Cambridge Clinical Research Facility. All investigations were part of ethically approved protocols (RTH: Cambridgeshire LREC 98/154; REC 06/Q0108/84; REC 14/EE/0092) or were clinically indicated and undertaken with prior, informed written consent and assent for children under the age of 16. The healthy participants were free from disease and non-smoking; they were excluded from the study if they were pregnant or receiving any metabolism-influencing medications. Recruitment and data collection took

place between 2014 and 2019. Energy expenditure was calculated from the corrected gas exchange volumes (Gem Nutrition, Daresbury, UK) using the derivations of Elia and Livesey.²⁹ Body composition was assessed using dual energy X-Ray absorptiometry (DXA, Lunar iDXA, enCORE V.18). Precision of the instruments has been previously reported as iDXA precision for lean mass; 0.4% coefficient of variation (CV), REE precision 3.8% CV.^{5 30}

To present the normality of the healthy paediatric (age 6–16 years) data, height, weight and BMI were converted into centiles using the British 1990 WHO reference child data using the excel LMS function.

Statistical analysis

Statistical analysis was performed using R V.4.0.5 and gamlss package V.5.3–4.

Scatterplots and Pearson's correlations were examined for all variables (age, height, weight, BMI, bone mass, fat mass and lean mass) considered influential in explaining the variation in REE. Gamlss was used to model the mean and variance of REE as functions of age and body size. Preference was given to log transformed body size variables, to best represent the allometric relationships between them. Age was fitted as a penalised cubic B-spline curve, with age logged to improve the fit by stretching the age range for children relative to adults. Interactions between sex, age and body size were also tested for.

The gamlss package was used to fit the regression models, and the optimal model was identified as that minimising the Bayesian information criterion (BIC). This method has been described elsewhere.³¹

Centile chart

A centile chart describing the distribution of the REE index (REE/LM^{0.67}, kJ/min/kg) was generated from the optimal model, where the centiles were spaced exactly two-thirds of an SD apart, giving the rounded centiles 2, 9, 25, 50, 75, 91 and 98.³²

RESULTS

Descriptive characteristics of the healthy children (n=204) and adults (n=126), from which the models were derived, are presented in online supplemental table 1. The participant flow chart is detailed in online supplemental figure 1. The mean BMI SDS for the children in our dataset (aged 6–16.9 years) was 0.41 units for females and 0.27 units for males, when compared with the British 1990-WHO reference child.

The correlations between variables were greater with the variables log-transformed, with the single exception of bone mass versus lean mass (r=0.69 vs 0.76) (online supplemental table 2). Lean mass was the strongest predictor of REE (r=0.77).

The optimal gamlss model predicted log REE as a combination of log lean mass and a spline curve in log age. The coefficient for log lean mass=0.67 SE 0.02, which means that antilogged, the model was equivalent to the index REE/LM^{0.67} (REE index) plotted against age. Adding interaction terms did not reduce the BIC. There was also no evidence of heteroscedasticity—the residual SD was 0.092, corresponding to a residual coefficient of variation in REE of 9.2%, with this residual not depending on age or lean mass.

Age-specific centile curves (2nd, 9th, 25th, 50th, 75th, 91st and 98th) and LMS values for the REE index were plotted (figure 1) with the data reported in online supplemental table 3. From age 6 to 25 years, it can be seen that the 50th centile falls by approximately 30% from an REE index of 0.493 units

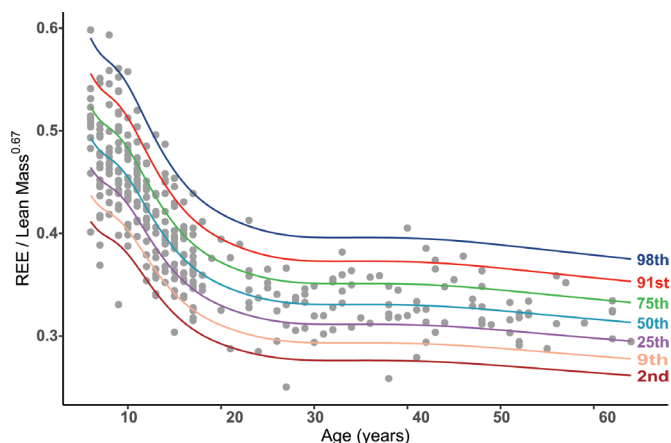


Figure 1 Resting energy expenditure (REE) index centile curves for the 2nd through to the 98th centile plotted against age.

to 0.335 units and then remains relatively constant throughout adulthood. We also observe a large degree of variation within each age, with the 2nd and 98th REE index centiles at age 6 being 0.412 units and 0.590 units, respectively, corresponding to a range of four residual SDs of 9.2%.

To illustrate utility of the chart in a clinical setting, serial REE measurements in a patient with RTH α , diagnosed in adolescence and treated with thyroid hormone therapy into adulthood, were superimposed on the centile chart. To monitor the biochemical response to treatment, thyroid function tests (thyroid stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3) and creatine kinase (CK), a marker of thyroid hormone action in skeletal muscle) were measured (figure 2).

At baseline (age 15 years), the patient's REE index was subnormal (REE index 0.348 units, between 9th and 25th centiles) and associated with thyroid biochemistry (low FT4, high FT3, normal TSH), characteristic of RTH α . Initially, thyroxine therapy (62.5 mcg daily) raised circulating FT4 and

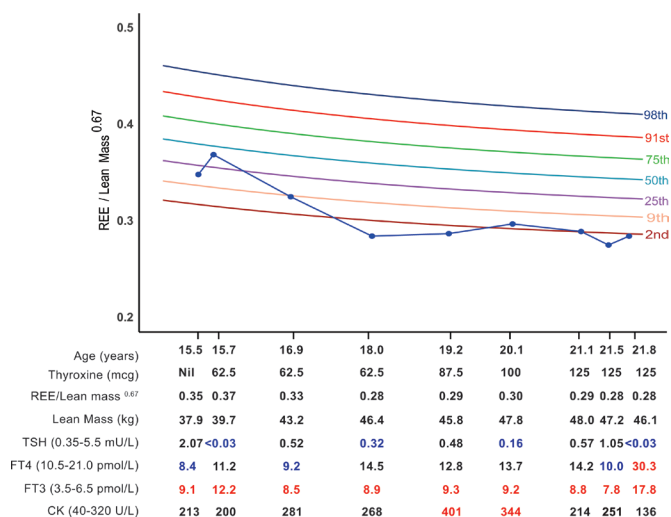


Figure 2 Serial measurements of REE index and biochemical parameters in a patient with RTH α treated with thyroxine therapy over 6 years, superimposed on the centile chart. Biochemical measurements outside the reference range are highlighted blue (low) or red (high). CK, creatine kinase; FT3, free triiodothyronine; FT4, free thyroxine; REE, resting energy expenditure; RTH α , resistance to thyroid hormone α ; TSH, thyroid-stimulating hormone.

FT3 concentrations, with a concomitant increase in REE index (0.369 units) of one centile. However, from age 16 to 18 years, his REE index fell sharply (0.284 units, <2nd centile), in association with a marked gain (7kg) of lean mass that was not matched by an increase in thyroxine dosage, reflected in falling circulating FT3 and rising CK levels. Subsequently, stepwise increases in thyroxine dosage until age 21.1 years, did augment his REE index (0.297 units, above second centile), with concomitant increases in circulating FT3 followed by normalisation of raised CK. At age 21.5 years, a sharp decline in REE index (0.289 to 0.275 units) in the context of stable thyroxine dosage and lean mass suggested that the patient was not adherent with therapy, with biochemical measurements (lower circulating FT4 and FT3, higher CK) confirming this. Latest measurements at age 21.8 years, showing a rise in REE index (0.284 units) and improvement in biochemical indices (higher FT4 and FT3, fall in CK), suggest that adherence with thyroxine therapy has been restored.

DISCUSSION

We present REE centiles adjusted for lean mass and age over a childhood and adult (age 6 to 65 years) period. Further, we illustrate utility of the REE centile chart in treating a patient with RTH α , a type of congenital hypothyroidism in which this physiological variable best measures the response to thyroxine therapy.

The centile chart consists of the 2nd to the 98th centiles of an REE index, modelled using gamlss. Compared with the UK-WHO reference child, the children in our dataset were mostly representative of a healthy population; however, in 7-year-old girls and 9-year-old boys, the mean centile for BMI was >72. Our results highlight a decline in REE, adjusted for body composition, during childhood and a plateau through adulthood. At each age, we observe a wide degree of variation, with a CV of 9.2%.

Recently, Pontzer *et al.*³³ reported similar findings to the present study, such that both total energy expenditure (TEE) and basal energy expenditure when adjusted for FFM decline in childhood and reach a plateau at 20 years of age. At 60 years of age, a second break point was apparent when adjusted TEE and basal energy expenditure declined further, potentially linked to a decline in fat mass and FFM.

The reported rapid increase in adjusted TEE during the first year of life has been documented by Reichman *et al.*³⁴ who have published centile charts for TEE using the LMS method in infants from 1 to 12 months of age. They observed a curvilinear increase in TEE whether expressed as MJ/day or relative to body weight or FFM (MJ/day/kg) throughout this period of rapid growth. Similar to the current study, they observed a large degree of variation at each age and they concluded that a large proportion of the reported variation is biological and not error of measurement.

Our previous linear regression equation for predicting REE in children included lean mass and sex as contributory variables. However, in adults, we and others^{3 33 35–37} have found that fat mass also contributes to variation in REE. In our current work, which combines child and adult datasets (with children comprising 61% of the total), the contribution of fat mass from the adult dataset is insufficient to influence the overall REE index. Whether the centile chart is not appropriate in individuals with grossly deranged fat mass (eg, lipodystrophy) is unclear, but it should be used with caution in such contexts.

We acknowledge that our healthy participant sample is smaller than that recommended for constructing centiles for use at a

population level. The WHO growth standards required at least 200 children per sex per 3-month age group for a cross-sectional study.³⁸ Other growth reference studies such as the Fourth Dutch Growth Study and the Cuban and First Dutch growth study ranged from 14 500 to 55 000 in sample size.³¹ However, they were focused on height and weight, where the measurements are relatively easy to obtain, whereas capturing REE and lean mass require much more complex technologies. Nevertheless, to address this limitation, we will continue to develop our dataset to close relative paucity of measurements within our sample.

Our application of the centile chart to RTH α , a disorder in which REE is a better marker of thyroid status in TR α -expressing peripheral tissues than circulating TSH measurements,² illustrates its clinical utility. Thus, a decline in REE from age 16 to 18 years accompanied by an increase in lean mass of ~6.7 kg prompted a further increase in dosage of thyroxine therapy to account for growth. Subsequently, a marked fall in REE index (at age 21.5 years) despite stable body composition and thyroxine dosage suggested non-adherence with therapy and biochemical indices (fall in FT4 and FT3) supported this notion. Once non-adherence was rectified, both REE index and biochemical markers improved. Overall, this centile chart enables the impact of both altered body composition and thyroxine therapy on this physiological parameter (REE) to be discerned at the same time. However, when measuring this parameter as a baseline characteristic of RTH α , we suggest that, rather than REE index, deviation of measured REE from a predicted value to derive a Z-score, is a more appropriate but complementary approach.²⁴

In conclusion, we have produced an REE index centile chart, adjusted for body composition and age, covering children and adults. This chart enables seamless monitoring of a physiological parameter (REE) that changes with growth, in relation to age-appropriate control data from childhood into adult life. The chart also provides a useful approach to discern the effects of a therapeutic intervention which changes growth, body composition and REE.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Cambridge Central Ethics Committee LREC 98/154, REC 06/Q0108/84, Cambridge South Ethics Committee REC 14/EE/0092. Participants gave informed consent to participate in the study before taking part.

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Supplementary Table 1. Descriptive characteristics of the healthy participants.

Children	Males (N = 95)		Females (N = 109)	
	Mean \pm SD	Range	Mean \pm SD	Range
Age (years)	11.2 \pm 3.1	6.0 to 16.0	10.5 \pm 2.9	6.0 to 16.0
Height (cm)	152.4 \pm 20.2	116.8 to 188.2	145.9 \pm 17.2	110.7 to 177.2
Weight (kg)	43.7 \pm 15.2	20.0 to 78.6	41.1 \pm 13.8	18.2 to 84.4
BMI (kg/m ²)	18.2 \pm 2.7	14.0 to 29.1	18.7 \pm 3.10	13.1 to 28.9
Bone (kg)	1.74 \pm 0.70*	0.81 to 3.43	1.53 \pm 0.54	0.70 to 2.95
Fat (kg)	9.7 \pm 4.2*	3.3 to 26.9	12.3 \pm 5.7	4.0 to 32.7
Lean (kg)	32.5 \pm 12.3*	16.1 to 62.4	27.4 \pm 8.8	13.0 to 49.3
REE (kJ/min)	4.40 \pm 0.85*	2.97 to 6.96	3.92 \pm 0.64	2.43 to 5.38
Adults	Males (N = 57)		Females (N = 69)	
	Mean \pm SD	Range	Mean \pm SD	Range
Age (years)	31.9 \pm 15.0*	17.0 to 64.0	36.2 \pm 12.3	17.0 to 62.0
Height (cm)	177.3 \pm 7.0	161.8 to 191.1	164.2 \pm 7.7	147.0 to 182.9
Weight (kg)	76.0 \pm 16.6*	46.6 to 124.0	64.8 \pm 12.8	37.7 to 115.0
BMI (kg/m ²)	24.1 \pm 4.6	16.7 to 37.2	23.9 \pm 3.7	17.4 to 36.3
Bone (kg)	2.96 \pm 0.51*	2.06 to 4.20	2.41 \pm 0.38	1.53 to 3.32
Fat (kg)	17.5 \pm 8.7	5.1 to 43.6	22.1 \pm 7.8	6.8 to 48.6
Lean (kg)	56.2 \pm 10.2*	36.4 to 91.0	40.7 \pm 6.7	24.7 to 64.4
REE (kJ/min)	5.09 \pm 0.80*	3.88 to 7.06	3.98 \pm 0.56	2.72 to 5.92

Both child and adult datasets have been described in detail previously (3, 5, 29).

*Significant differences between males and females, $P < 0.05$.

BMI, Body Mass Index; REE, Resting Energy Expenditure.

Supplementary Table 2. Correlation coefficients for the un-logged and log-transformed variables.

	Height	Weight	Age	BMI	Bone	Fat	Lean	REE
Height	1.00	0.86	0.55	0.53	0.92	0.47	0.91	0.71
Weight	0.91	1.00	0.69	0.88	0.92	0.79	0.94	0.71
Age	0.71	0.80	1.00	0.65	0.65	0.57	0.62	0.21
BMI	0.57	0.86	0.70	1.00	0.69	0.91	0.71	0.51
Bone	0.95	0.95	0.79	0.70	1.00	0.55	0.96	0.70
Fat	0.57	0.81	0.64	0.90	0.64	1.00	0.53	0.37
Lean	0.96	0.96	0.77	0.72	0.97	0.61	1.00	0.78
REE	0.72	0.71	0.34	0.51	0.70	0.40	0.77	1.00

Upper triangle unlogged correlations, lower triangle log-transformed correlations.
BMI, Body Mass Index; REE, Resting Energy Expenditure.

Supplementary Table 3. REE index and LMS values for children and adults by centile, adjusted for lean mass and age.

Age (years)	2nd	9th	25th	50th	75th	91st	98th	Mu	Sigma
6	0.412	0.437	0.464	0.493	0.523	0.556	0.590	-0.707	0.090
7	0.401	0.426	0.453	0.481	0.510	0.542	0.576	-0.733	0.090
8	0.395	0.420	0.446	0.473	0.503	0.534	0.567	-0.748	0.090
9	0.389	0.413	0.439	0.466	0.495	0.525	0.558	-0.764	0.090
10	0.380	0.403	0.428	0.455	0.483	0.513	0.544	-0.788	0.090
11	0.368	0.391	0.415	0.440	0.468	0.497	0.527	-0.820	0.090
12	0.355	0.377	0.400	0.425	0.451	0.479	0.509	-0.856	0.090
13	0.342	0.364	0.386	0.410	0.435	0.462	0.491	-0.891	0.090
14	0.331	0.352	0.374	0.397	0.421	0.447	0.475	-0.925	0.090
15	0.322	0.341	0.363	0.385	0.409	0.434	0.461	-0.954	0.090
16	0.313	0.333	0.353	0.375	0.398	0.423	0.449	-0.980	0.090
17	0.306	0.325	0.346	0.367	0.390	0.414	0.439	-1.003	0.090
18	0.301	0.319	0.339	0.360	0.383	0.406	0.431	-1.021	0.090
19	0.296	0.315	0.334	0.355	0.377	0.400	0.425	-1.037	0.090
20	0.292	0.310	0.330	0.350	0.372	0.395	0.419	-1.050	0.090
21	0.289	0.307	0.326	0.346	0.368	0.390	0.414	-1.061	0.090
22	0.286	0.304	0.323	0.343	0.364	0.387	0.410	-1.071	0.090
23	0.284	0.301	0.320	0.340	0.361	0.383	0.407	-1.079	0.090
24	0.282	0.299	0.318	0.337	0.358	0.381	0.404	-1.086	0.090
25	0.280	0.297	0.316	0.335	0.356	0.378	0.402	-1.092	0.090
26	0.279	0.296	0.314	0.334	0.354	0.376	0.400	-1.097	0.090
27	0.278	0.295	0.313	0.333	0.353	0.375	0.398	-1.101	0.090
28	0.277	0.294	0.312	0.332	0.352	0.374	0.397	-1.104	0.090
29	0.277	0.294	0.312	0.331	0.352	0.373	0.397	-1.105	0.090
30	0.276	0.293	0.312	0.331	0.351	0.373	0.396	-1.106	0.090
31	0.276	0.293	0.311	0.331	0.351	0.373	0.396	-1.107	0.090
32	0.276	0.293	0.311	0.331	0.351	0.373	0.396	-1.107	0.090
33	0.276	0.293	0.311	0.331	0.351	0.373	0.396	-1.107	0.090
34	0.276	0.293	0.311	0.331	0.351	0.373	0.396	-1.107	0.090
35	0.276	0.293	0.311	0.331	0.351	0.373	0.396	-1.107	0.090
36	0.276	0.293	0.311	0.331	0.351	0.373	0.396	-1.107	0.090

37	0-276	0-293	0-311	0-331	0-351	0-373	0-396	-1.107	0.090
38	0-276	0-293	0-311	0-331	0-351	0-373	0-396	-1.107	0.090
39	0-276	0-293	0-311	0-330	0-351	0-373	0-396	-1.108	0.090
40	0-276	0-293	0-311	0-330	0-351	0-372	0-395	-1.108	0.090
41	0-276	0-293	0-311	0-330	0-350	0-372	0-395	-1.109	0.090
42	0-275	0-292	0-310	0-330	0-350	0-372	0-395	-1.110	0.090
43	0-275	0-292	0-310	0-329	0-350	0-371	0-394	-1.111	0.090
44	0-275	0-291	0-310	0-329	0-349	0-371	0-394	-1.113	0.090
45	0-274	0-291	0-309	0-328	0-348	0-370	0-393	-1.114	0.090
46	0-274	0-290	0-308	0-328	0-348	0-369	0-392	-1.116	0.090
47	0-273	0-290	0-308	0-327	0-347	0-369	0-391	-1.118	0.090
48	0-272	0-289	0-307	0-326	0-346	0-368	0-391	-1.120	0.090
49	0-272	0-289	0-306	0-325	0-346	0-367	0-390	-1.123	0.090
50	0-271	0-288	0-306	0-325	0-345	0-366	0-389	-1.125	0.090
51	0-270	0-287	0-305	0-324	0-344	0-365	0-388	-1.127	0.090
52	0-270	0-286	0-304	0-323	0-343	0-364	0-387	-1.130	0.090
53	0-269	0-286	0-303	0-322	0-342	0-363	0-386	-1.133	0.090
54	0-268	0-285	0-303	0-321	0-341	0-362	0-385	-1.135	0.090
55	0-268	0-284	0-302	0-321	0-340	0-361	0-384	-1.138	0.090
56	0-267	0-284	0-301	0-320	0-339	0-361	0-383	-1.140	0.090
57	0-266	0-283	0-300	0-319	0-339	0-360	0-382	-1.143	0.090
58	0-266	0-282	0-299	0-318	0-338	0-359	0-381	-1.146	0.090
59	0-265	0-281	0-299	0-317	0-337	0-358	0-380	-1.148	0.090
60	0-264	0-281	0-298	0-316	0-336	0-357	0-379	-1.151	0.090
61	0-264	0-280	0-297	0-316	0-335	0-356	0-378	-1.153	0.090
62	0-263	0-279	0-296	0-315	0-334	0-355	0-377	-1.156	0.090
63	0-262	0-278	0-296	0-314	0-333	0-354	0-376	-1.158	0.090
64	0-262	0-278	0-295	0-313	0-333	0-353	0-375	-1.161	0.090

Supplementary Figure 1. Participant flow chart of the study.