



OXFORD MATERNAL
AND PERINATAL
HEALTH INSTITUTE



Maternal Health Task Force



INTERGROWTH-21st course on maternal, fetal and newborn growth monitoring

Course overview



This Course overview will:

Discuss some of the **conceptual issues** about fetal and newborn growth monitoring.

Introduce the INTERGROWTH-21st Project: **rationale, aim, design and implementation.**

Present the **key findings** from INTERGROWTH-21st Project on the likeness of early human growth.

Introduce the **INTERGROWTH-21st growth standards.**

Highlight challenges in standardising the measurement of fetuses and newborns around the world.



Conceptual issues

Growth monitoring (GM) is an essential aspect of evidence-based antenatal and newborn care worldwide, as it is for infants and children.

- Poor growth places babies at risk of perinatal mortality and, longer term metabolic and cardiovascular disease.
- Overgrowth increases risks of birth trauma, need for operative delivery and childhood obesity.

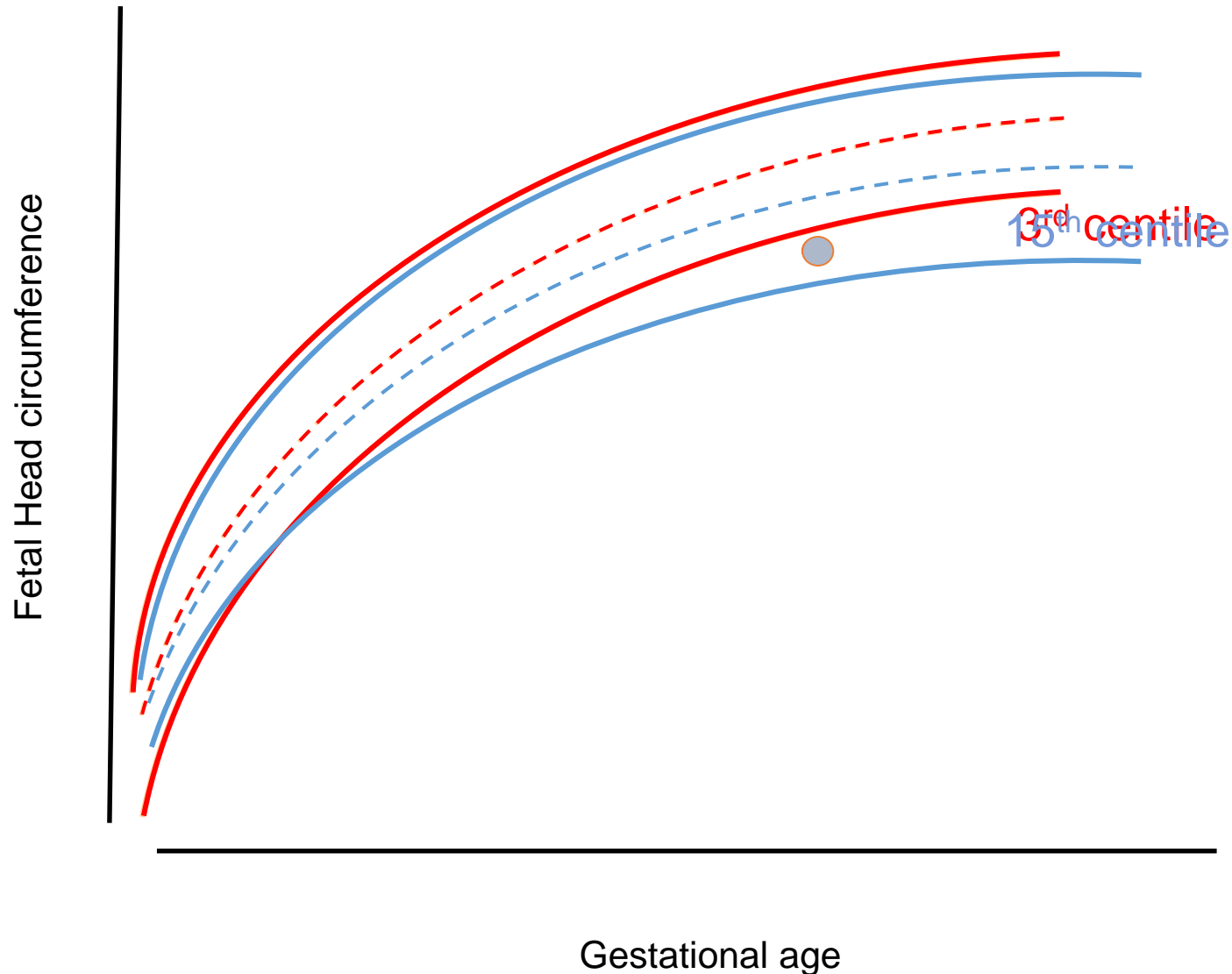
There is currently no agreement on the definition of 'normal' or 'abnormal' growth around the world. (Bhutta, 2013; Villar et al., 2015).

Systematic reviews demonstrate over 100 charts in use around the world to measure the size of babies in the womb; with a further 100 for measuring newborn size at birth.

This has resulted in a situation where parents may be told their baby is small on one chart, only to be then told it is normal if a different chart is used. (Villar et al., 2015).



The difference the choice of chart can make in fetal growth monitoring





Conceptual issues

Growth is a continuum from conception, embryonic and fetal life, to early neonatal life and infancy, until childhood and adolescence.

The first 1000 days, from conception until age 2, is recognised as a crucial window for programming life long growth and development.

Integrated standards to measure growth from fetal life through to childhood would:

- Enable longitudinal assessment of skeletal growth (i.e. fetal head circumference or postnatal length) and fat-related markers (i.e. fetal abdominal circumference or postnatal weight).
- Improve our understanding of the effects of in-utero growth problems on later life outcomes.
- Integrate maternity, neonatal and paediatric clinical care delivery.



Standards for growth monitoring

In 1994 the World Health Organization (WHO) recommended the use of **prescriptive standards** to monitor human growth.

Standards describe growth observed under optimal conditions (nutrition, medical, environmental, social), and by definition are independent of time of place. They are prescriptive as they describe how growth *should* be, rather than how it actually is.

In contrast, most growth charts in use are **references**, derived from observing growth in a particular time of place, and are not necessarily relevant to other populations or the same population over time.

Standards have been widely accepted and adopted in child growth monitoring.



Standards in child growth monitoring

1994 WHO Technical group advised the use of normative standards in human growth monitoring.

1996 The WHO Multicentre Growth Reference Study (MGRS) established to monitor growth from birth until 5 years. 8000 healthy children selected from 5 countries that were breast fed for 6 months and from non socially deprived parents.

2006 The MGRS demonstrated the growth of children to be remarkably similar around the world justifying the release of the WHO Child Growth Standards.

2016 The WHO Child growth Standards have been adopted by over 140 member states of the United Nations.



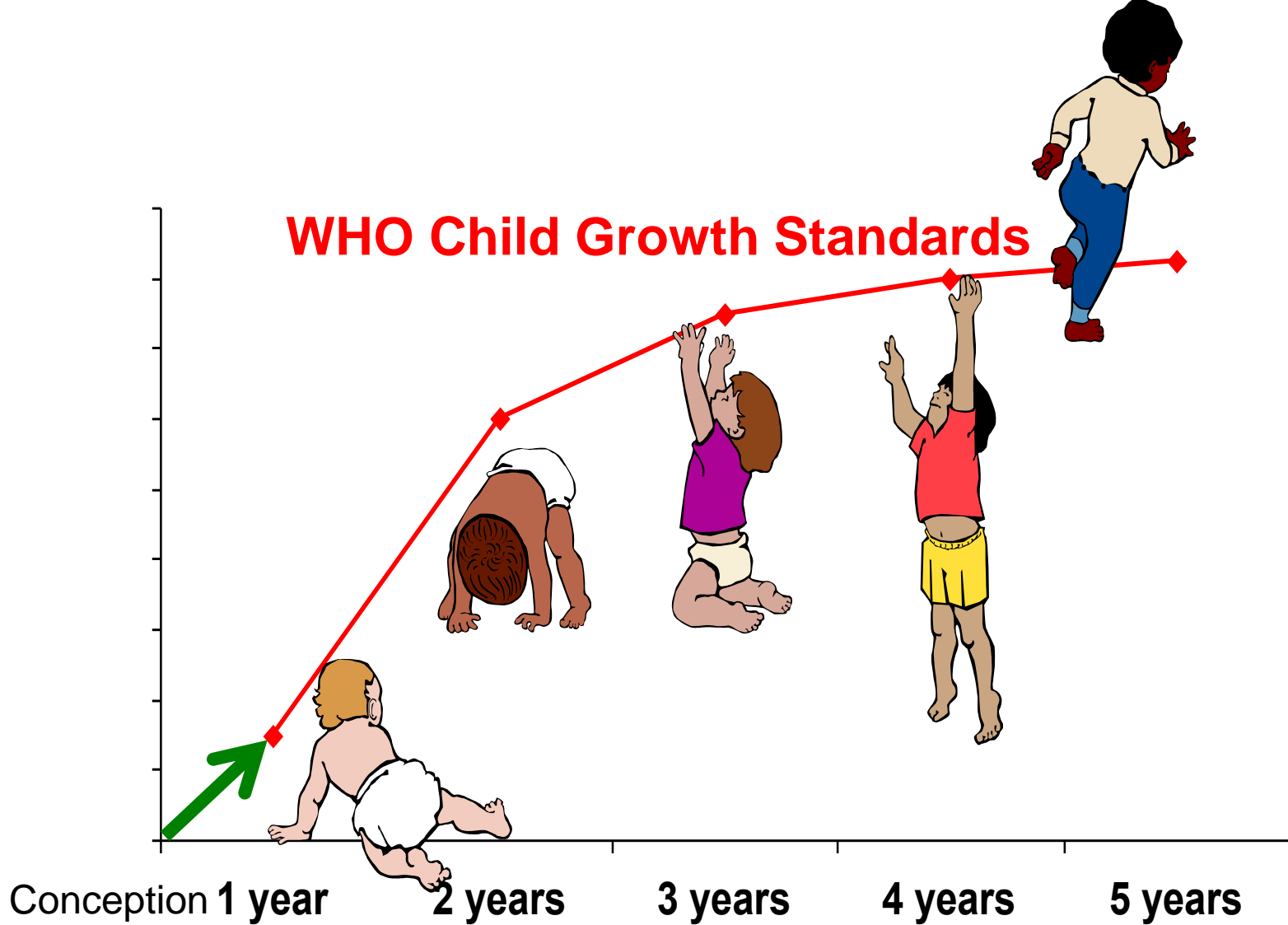
The INTERGROWTH-21st Project

The INTERGROWTH-21st Project was established to determine whether fetal and newborn growth are similar enough around the world to produce international standards for growth monitoring.

This would enable a *unified approach* to growth monitoring from conception until 5 years of age.

- This short [video](#) introduces the INTERGROWTH-21st Project.
- Watch a Webinar on the INTERGROWTH-21st Project [here](#).

WHO Child Growth Standards



INTERGROWTH-21st



The hypothesis of the INTERGROWTH-21st Project was:

The variability in skeletal growth **WITHIN** a population is larger than the variability **BETWEEN** populations when nutrition and health needs are met.

The INTERGROWTH-21st Project was done to prove this hypothesis and produce fetal and newborn growth standards that would be applicable to women everywhere.





The aim of the INTERGROWTH-21st Project was:

To produce prescriptive growth standards, which conceptually extend the World Health Organization (WHO) Multicentre Growth Reference Study (MGRS), to cover fetal and newborn life to describe:

1. Fetal growth assessed by clinical and ultrasound measures.
2. Postnatal growth of term and preterm infants up to 2 years of age.
3. The relationship between birthweight, length and head circumference, gestational age and perinatal outcomes.



The INTERGROWTH-21st Project design:

The INTERGROWTH-21st Project was a **prospective, population-based, multi-ethnic** study.

The study had 3 main components:

1. **The Newborn Cross-Sectional Study (NCSS)**: a study of all newborns born in the INTERGROWTH-21st study sites over 12 months.
2. **The Fetal Growth Longitudinal Study (FGLS)**: a detailed study of fetal growth from $<14^{+0}$ weeks to birth, with follow-up to age 2 in women individually at low risk of fetal growth and nutritional problems.
3. **The Preterm Postnatal Follow-up Study (PPFS)**: a detailed study of the growth of all preterm infants born to women in FGLS until age 2.



Selection of study sites

Study sites were selected to represent diverse geographic, cultural and ancestral groups where environmental and socio-economic constraints on growth were low, and women received up-to-date, evidence-based, medical care and appropriate nutrition.

Pelotas Brazil	Beijing China	Nagpur India	Turin Italy
Nairobi Kenya	Muscat Oman	Oxford United Kingdom	Seattle USA

INTERGROWTH-21st Project sites



INTERGROWTH-21st sites

BILL & MELINDA
GATES *foundation*



The INTERGROWTH-21st Project implementation

The selection of the populations occurred on two levels- **cluster** and **individual**.

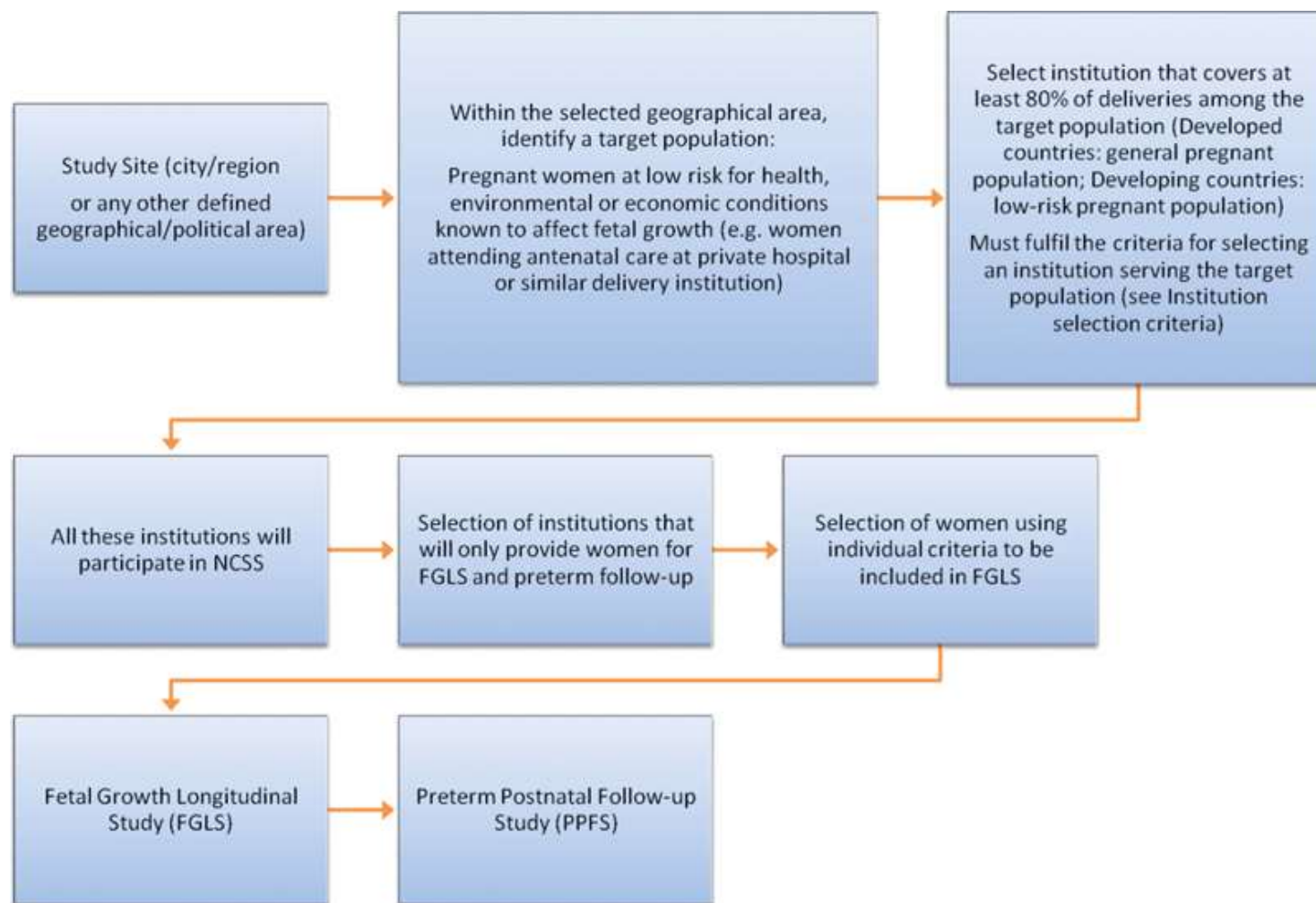
The cluster level involved selecting a geographical area (e.g. city or part of a city with clear political or geographical limits) followed by the selection, within each area, of health institutions where women at low-medium risk for impaired fetal growth attend for antenatal/delivery care and infant follow-up.

The individual level involved selecting, within these populations and hospitals, women or newborns with specific characteristics required for the project's different components.

The institutions selected in each geographical area delivered >80% of the eligible women in the target population with >1000 deliveries per year.



Selection of populations for the INTERGROWTH-21st Project





The Fetal Growth Longitudinal Study (FGLS):

The study aimed to develop new, international, fetal growth standards using 2D ultrasound to measure the most commonly acquired dimensions of fetal size, and a new, international, symphyseal-fundal height standard.

The study population were a group of apparently healthy women who could follow basic antenatal care models.

In the initial screening process, specific factors commonly used to identify women who would benefit from low-risk routine antenatal care were selected.

To accurately determine fetal growth, accurate knowledge of gestational age was essential. In the INTERGROWTH-21st Project sites, dating by first trimester ultrasound was implemented. (Papageorgiou et al., 2014; Villar et al., 2013).



Inclusion criteria in FGLS to ensure accurate determination of gestational age

Certain last menstrual period

Regular 24–32-day menstrual cycles

No hormonal contraception use or breastfeeding in the preceding 2 months

Spontaneous conception

CRL measurement between 9⁺⁰ and 13⁺⁶ weeks of gestation

Discrepancy between CRL and last menstrual period estimates ≤ 7 days

“Healthy” mother criteria for Fetal Growth Longitudinal Study

- a) aged ≥ 18 and ≤ 35 years;
- b) BMI ≥ 18.5 and < 30 kg/m²;
- c) height ≥ 153 cm;
- d) singleton pregnancy;
- e) a known LMP with regular cycles (defined as a 26-30 day cycle in the previous 3 months), without hormonal contraceptive use, pregnancy or breastfeeding in the 3 months before pregnancy;
- f) natural conception
- g) no relevant past medical history (refer to screening form), with no need for long-term medication (including fertility treatment and over the counter medicines, but excluding routine iron, folate, calcium, iodine or multivitamin

Criteria defining a low-risk study population as healthy and well-nourished (both before and during pregnancy) to ensure that fetal growth is optimal.

- pregnancy or congenital disease or fetal anomaly;
- n) no previous pregnancy affected by pre-eclampsia/eclampsia, HELLP syndrome or a related pregnancy-associated condition;
- o) no clinically significant atypical red cell alloantibodies;
- p) negative urinalysis;
- q) systolic blood pressure < 140 mmHg and diastolic blood pressure < 90 mmHg;
- r) haemoglobin ≥ 11 g/dl;
- s) negative syphilis test and no clinical evidence of any other sexually transmitted diseases, including clinical Trichomoniasis;
- t) not in an occupation with risk of exposure to chemicals or toxic substances, or very physically demanding activity to be evaluated by local standards. Also women should not be conducting vigorous or contact sports, as well as scuba diving or similar activities





Fetal Growth Longitudinal Study (FGLS)

N = 4,607

Pregnancy

Birth

1 year

2 years



Ultrasound measures:
9-14 weeks
Then every 5 ± 1 weeks

Anthropometric measurements:

Length/height
Weight
Head circumference

Neurodevelopment

assessment:

Psychometric tests
Wireless EEG
Actigraphy

Fetal Growth Longitudinal Study (FGLS)

Scans every 5 ± 1 weeks

Measurements at each scan $>14^{+0}$ weeks:

Biparietal diameter

Occipito-frontal diameter

Head circumference

Transverse abdominal diameter

Anterio-posterior abdominal diameter

Abdominal circumference

Femur length

Philips HD9



Measurements obtained 3 times from 3 separately obtained images of each structure in blinded fashion (no measurement visible) and submitted electronically.





The Newborn Cross-Sectional Study (NCSS):

The study aimed to produce birthweight, length and head circumference for gestational age standards describing fetal size at birth and to provide data for epidemiological studies of the different phenotypes of the impaired fetal growth and preterm delivery syndromes.

The study also examined the relationship of size at birth with neonatal morbidity and mortality.

The study population included all newborns delivered at the selected institutions occurring over a 12 month study period.

There were two subpopulations:

1. Population selected using the FGLS entry criteria to construct the prescriptive standards of size at birth.
2. Newborns from higher-risk pregnancies. (Villar et al., 2013; Villar et al., 2014)



The Preterm Postnatal Follow-up Study (PPFS):

The study aimed to develop postnatal growth charts for preterm newborns based on the INTERGROWTH-21st conceptual principles.

All preterm newborns ($\geq 26^{+0}$ but $< 37^{+0}$ weeks of gestation) from the FGLS cohort were followed for 8 months after delivery to evaluate postnatal growth.

The postnatal anthropometric measurements were weight, length and head circumference.

The three measurements (plus a standard clinical evaluation and records of morbidity and food intake) were taken every 2 weeks during the first 8 weeks, and then every 4 weeks until 8 postnatal months, using essentially the same methodology employed in MGRS. (Villar et al., 2013; Villar et al., 2015)

Anthropometric measurements at birth





Standardization

All centres followed the same, standardised, clinical care protocols as described in the following manuals:

- The [Correct Measurement of Fetal Crown Rump Length and Standardization of Ultrasonographers](#) manual: to standardize CRL measurement methodology for pregnancy **dating**. The same CRL regression formula was used across all study sites to interpret CRL.
- The [Ultrasound Operations Manual](#): to standardize the **ultrasound technique**.
- The [Anthropometry Handbook](#): to standardize **anthropometric measurements**.
- The [Basic Neonatal Care Manual](#): to standardised neonatal care protocols. Common definitions of neonatal morbidities were used across all participating institutions.



All anthropometric measurements in the INTERGROWTH-21st Project were performed on identical equipment using a highly standardised protocol. Please see the next modules for detailed instructions on measurement technique.



Seca Adult Scale 877



Head Circumference Tape



Seca Stadiometer



Seca Baby Scale 376



The Harpenden Infantometer



Data collection

All documentation and forms used were prepared by the Project Coordinating Unit, tested at the local level and introduced into the specially developed electronic data management system.

All forms were integrated and linked to reduce duplication in the data collection process and facilitate data quality control mechanisms.

Similarities among the populations of fetuses and newborns were assessed by following the same basic principles that were adopted in MGRS.

- The main fetal indicators were CRL and head circumference, complemented as a secondary parameter by femur length.
- For all newborns and preterm infants, length at birth and in the first 8 months were used as the main indicator for the comparisons.



Strategies for Statistical Analysis

In order to determine if the results of the measurements from the 8 sites were similar enough to combine in a standard, four approaches were used:

1. Comparing crude data
2. Sensitivity analysis
3. Standardised site difference
4. Variance component analysis

Results: the INTERGROWTH-21st populations



All pregnancies in 8 sites

Newborn Cross Sectional
Study NCSS

n = 59,137



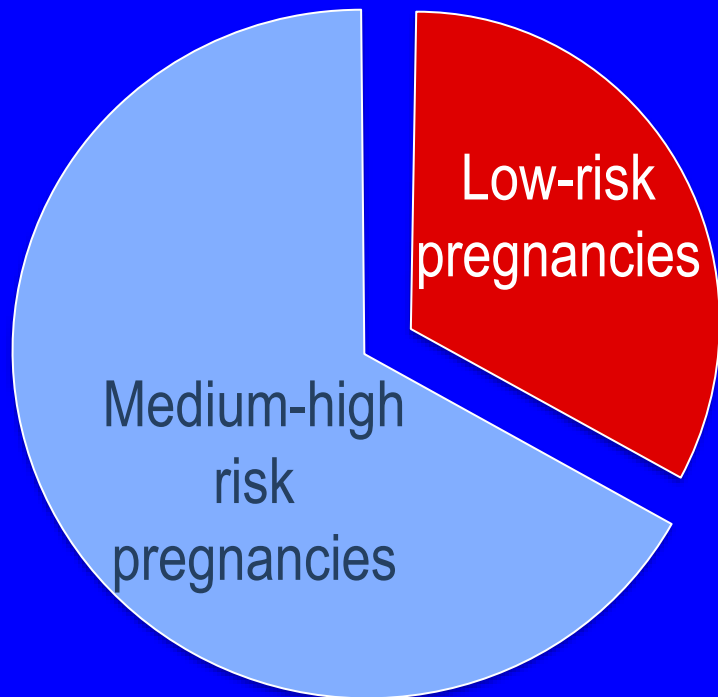
Total
population

Results: the INTERGROWTH-21st populations



Within the total population,
Low-risk pregnancies

n = 20,486

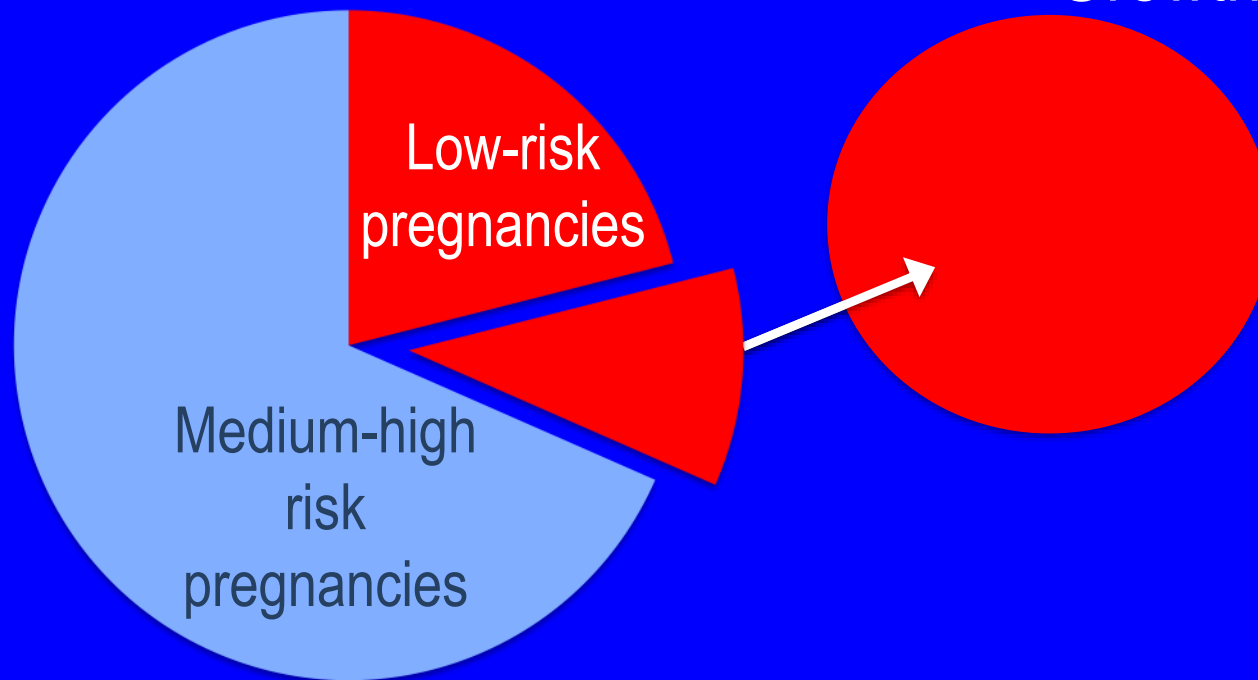


→ From the low-risk pregnancies in NCSS International Newborn Size at birth Standards have been produced

Results: the INTERGROWTH-21st populations



Low-risk pregnancies
n = 20,486



Within the low-risk
pregnancies, 4,607 women
Consented to be in the Fetal
Growth Longitudinal Study
(FGLS)

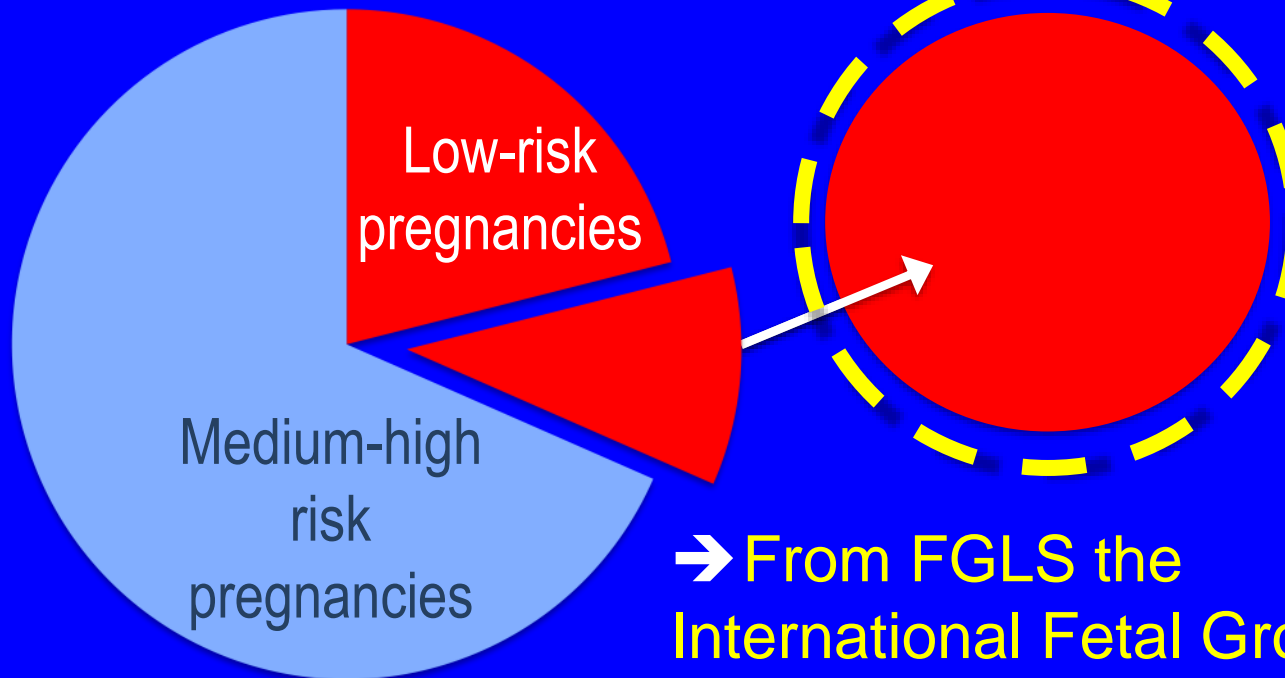
Results: the INTERGROWTH-21st populations



Low-risk pregnancies
n = 20,486

FGLS

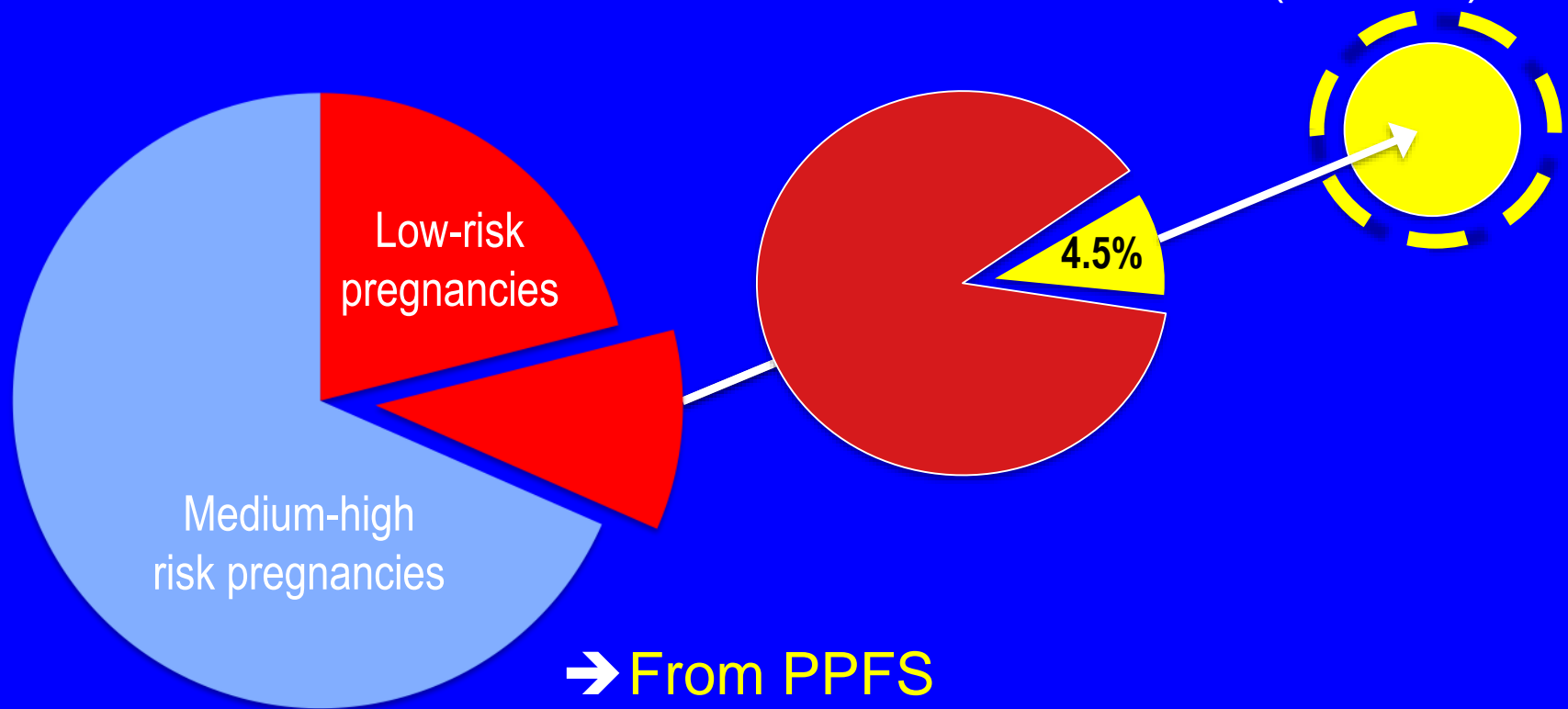
n = 4,607



→ From FGLS the International Fetal Growth Standards have been produced

Results: Preterm births in Fetal Growth Longitudinal Study

Preterm Postnatal
Follow-up Study PPFS
(n = 193)

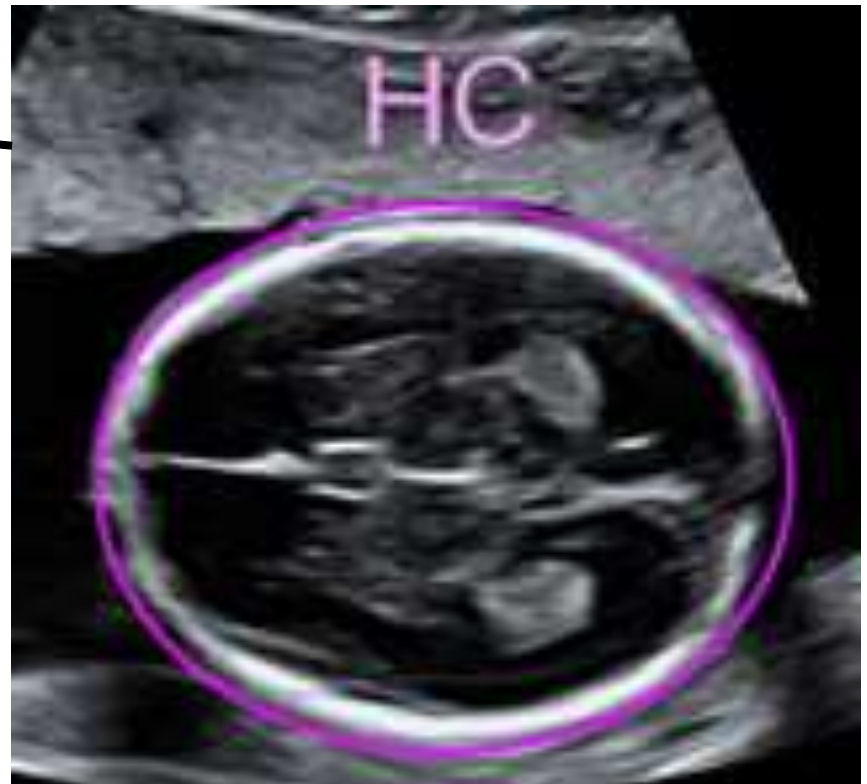
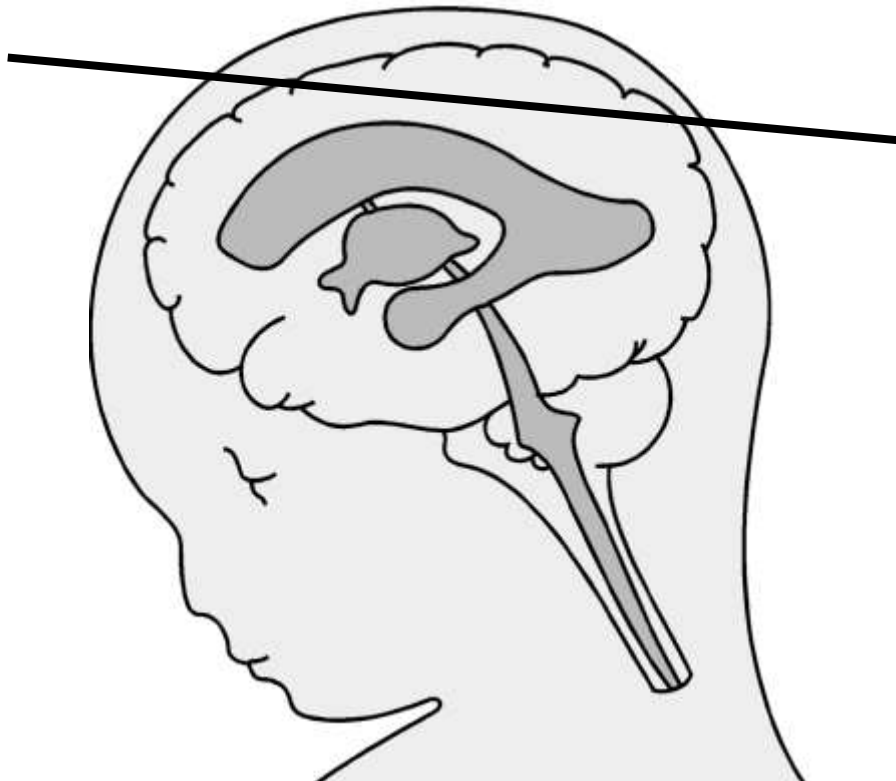


→ From PPFS
International Preterm Postnatal Growth
Standards have been produced

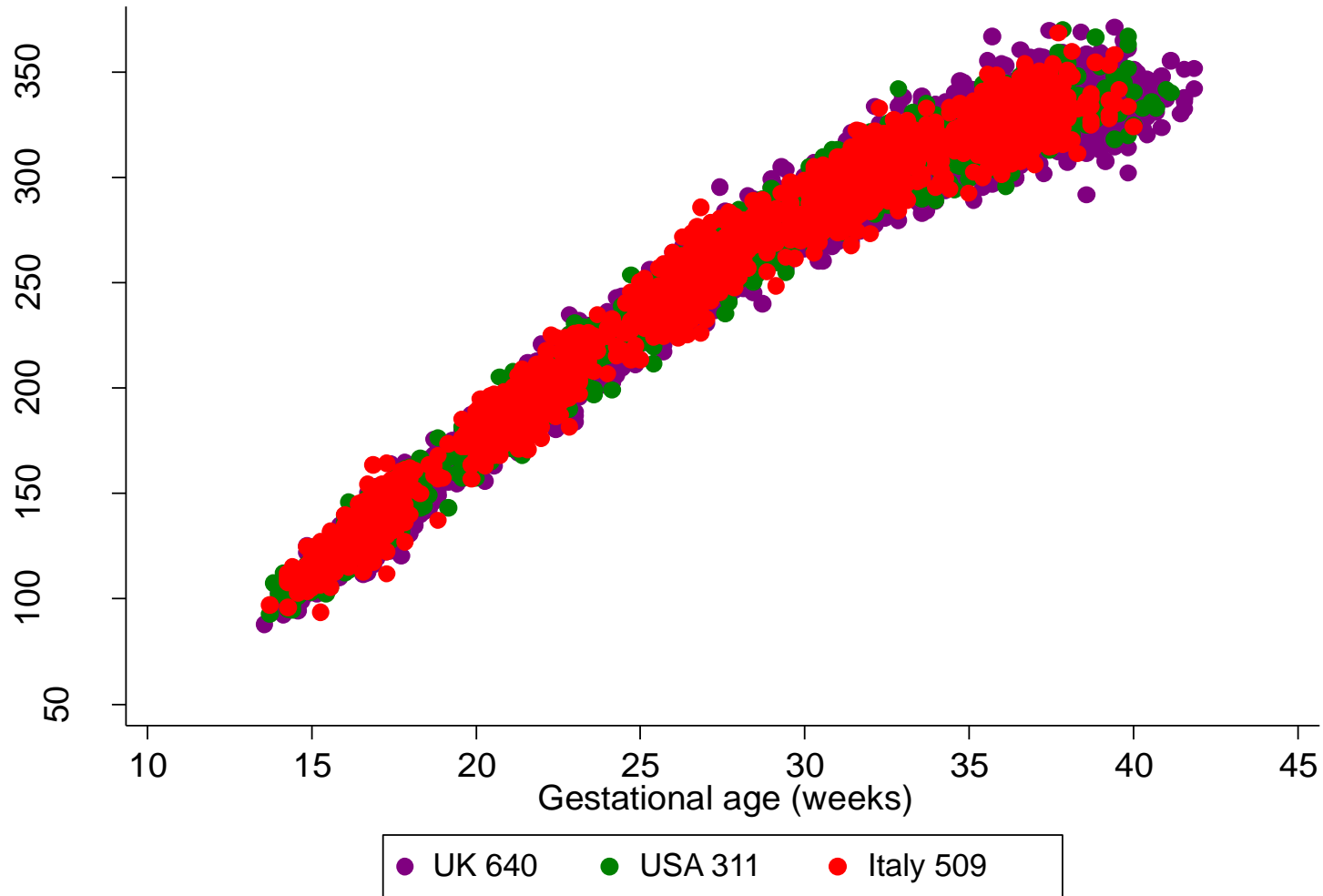


Results: Comparability of measurements

Taking the example of fetal head circumference, how did the results of all the sites compare?



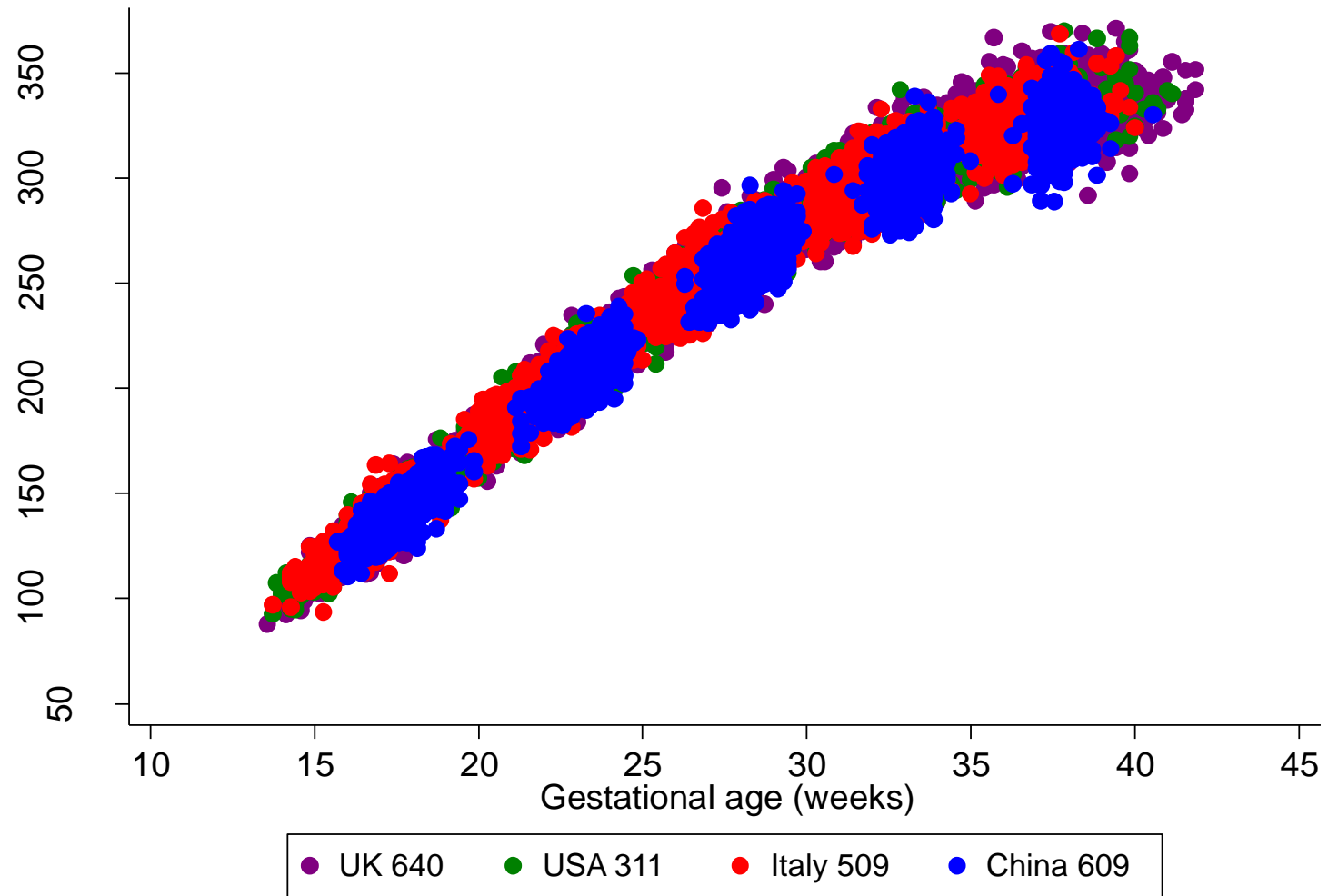
Fetal HC by gestational age for UK, USA & Italy



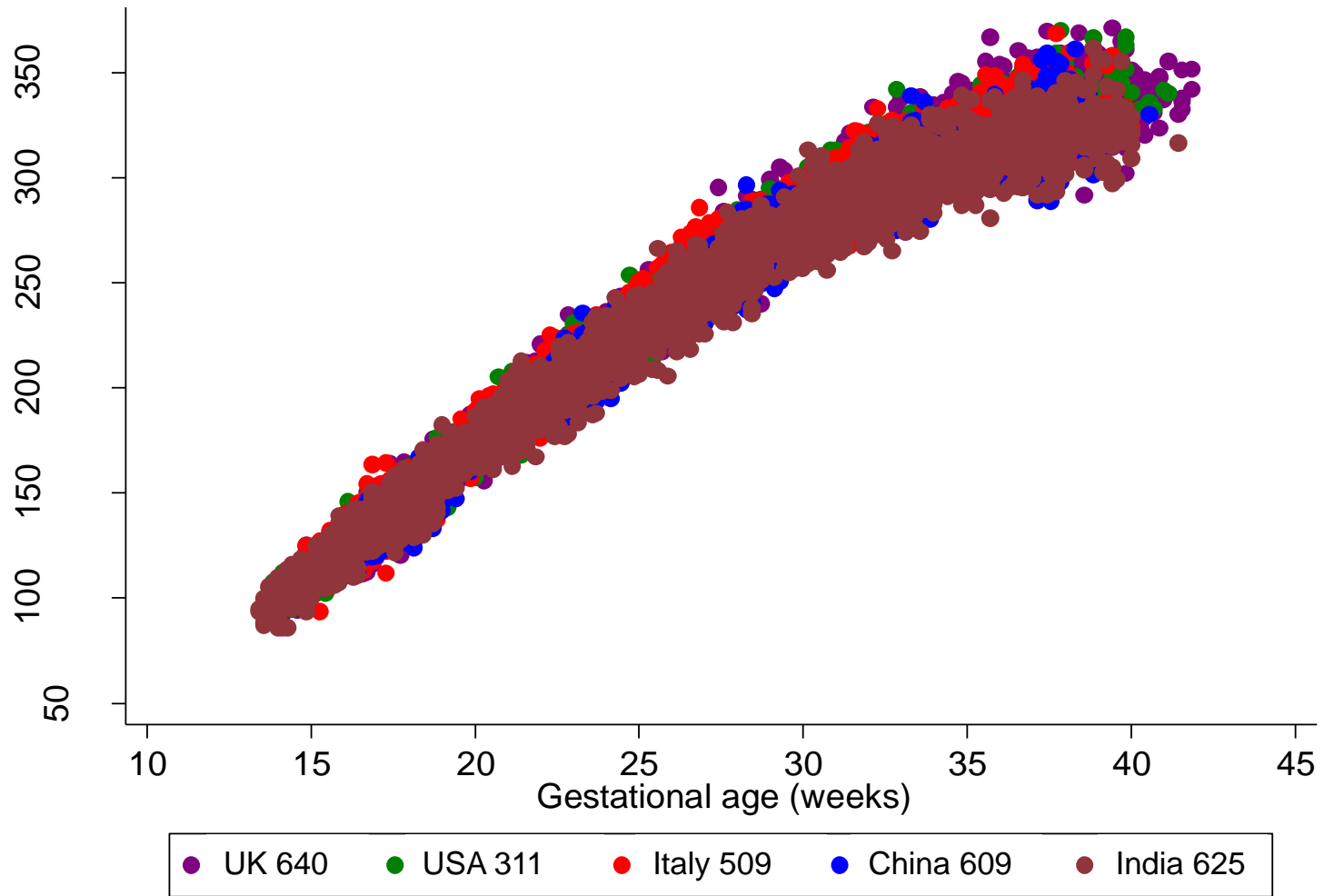
Each dot represents a measurement. You can see there is near perfect overlap between babies from these high-income countries.

Look at the next slides to see the measurements of babies from the other countries in INTERGROWTH-21st.

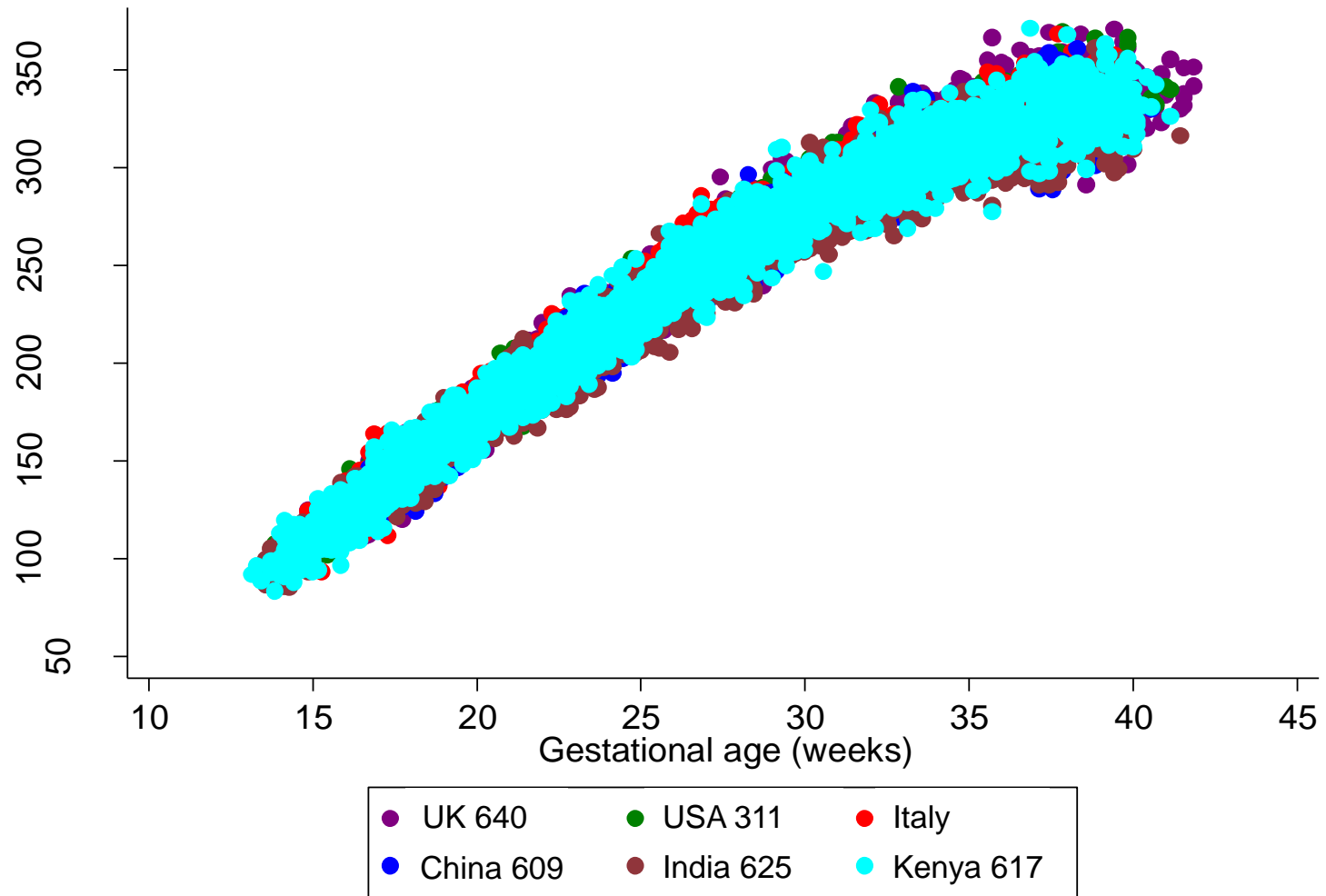
Fetal HC by gestational age for UK, USA, Italy & China



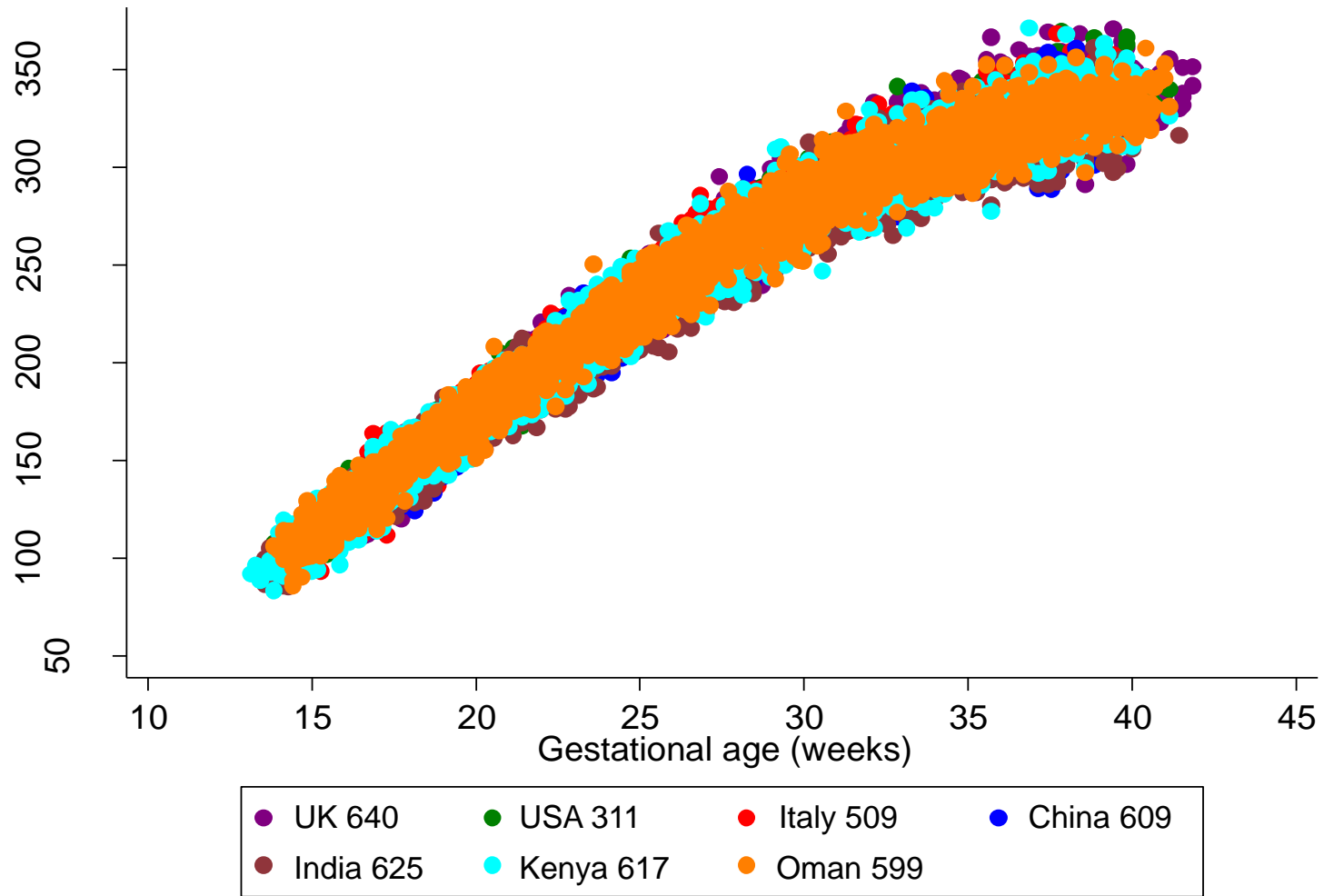
Fetal HC by gestational age for UK, USA, Italy, China & India



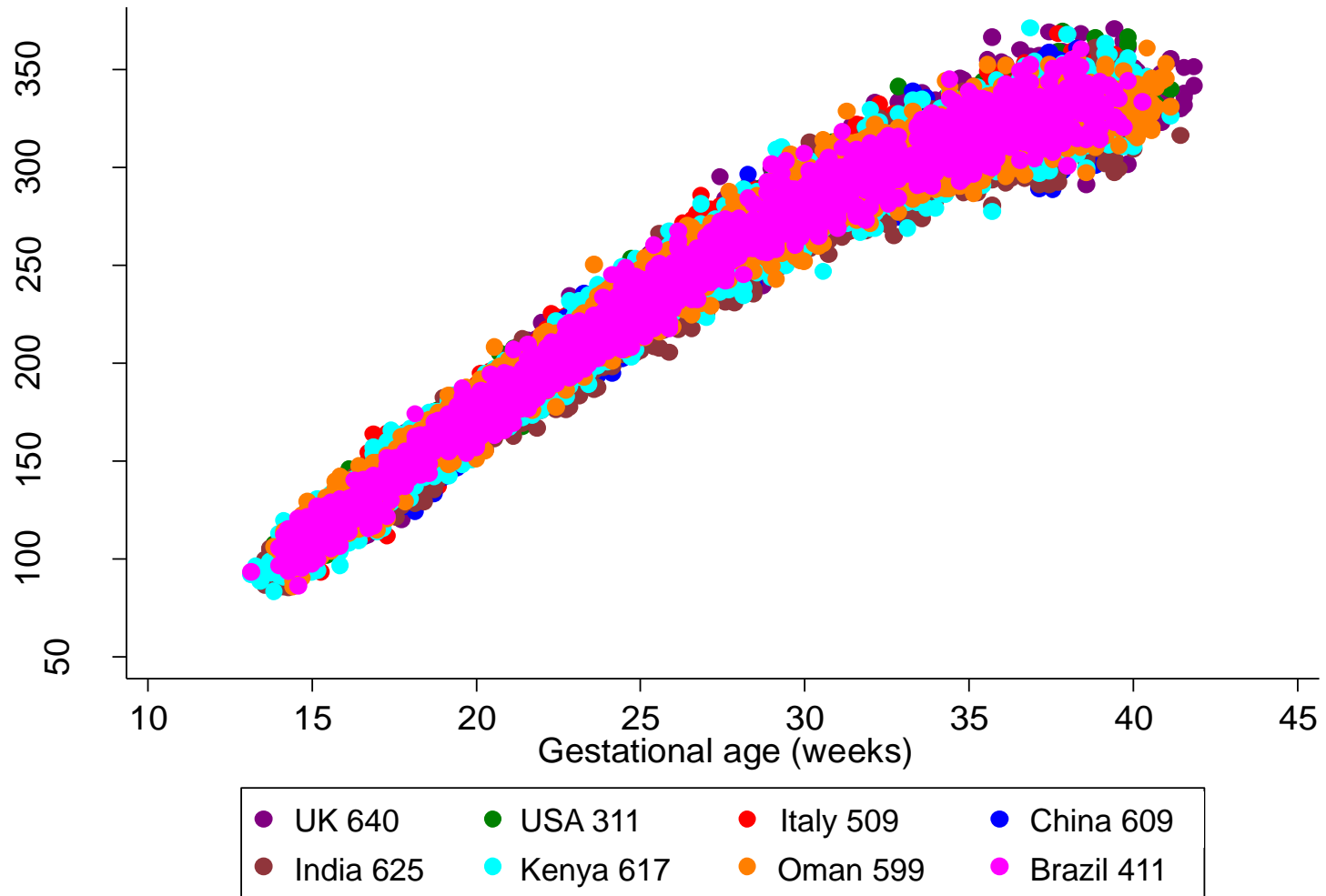
Fetal HC by gestational age for UK, USA, Italy, China, India & Kenya



Fetal HC by gestational age for UK, USA, Italy, China, India, Kenya & Oman

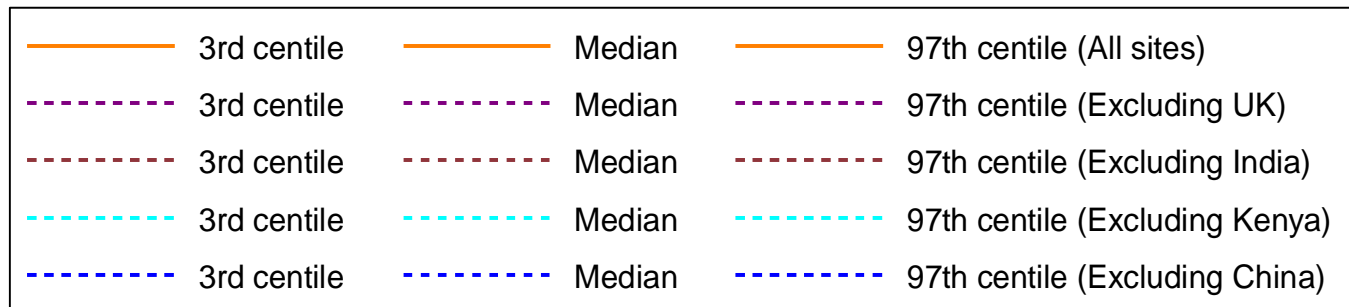
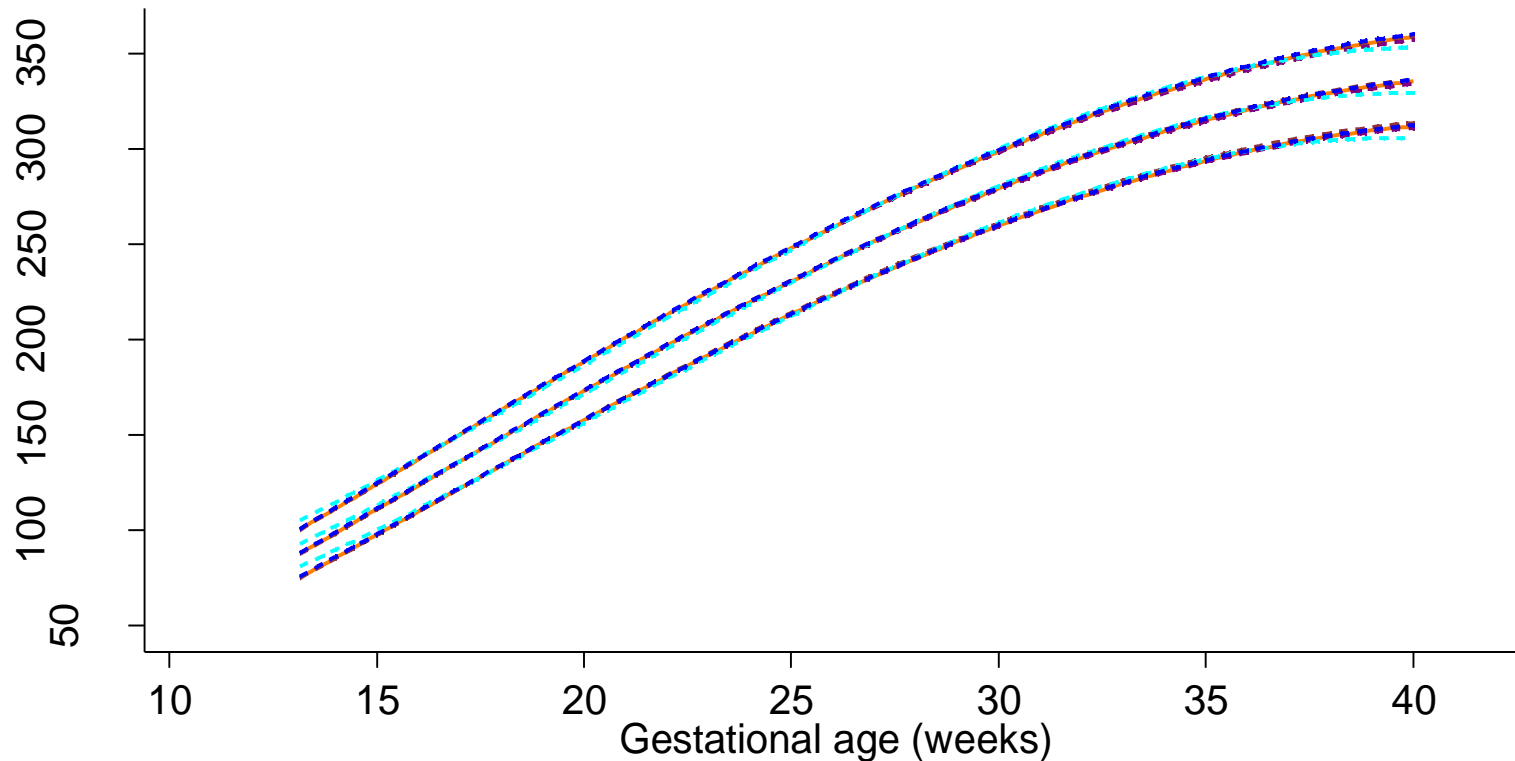


Fetal HC by gestational age for UK, USA, Italy, China, India, Kenya, Oman & Brazil



Thus, there was near perfect overlap of the distribution of head size in all sites.

Sensitivity analysis for fetal HC measures: The effect of excluding each country one by one



Variance component analysis for fetal CRL and HC, and newborn length

	FGLS		FGLS-like	WHO-MGRS (2006)	Habicht (1974)
	Fetal CRL	Fetal HC	Newborn length	Infant length	Child height
Variance among study sites	1.9%	2.6%	3.5%	3.4%	3.0%
Unexplained variance	98.1%	97.4%	96.5%	96.6%	-

Thus most of the variation (>96%) in the size of babies is due to between site differences

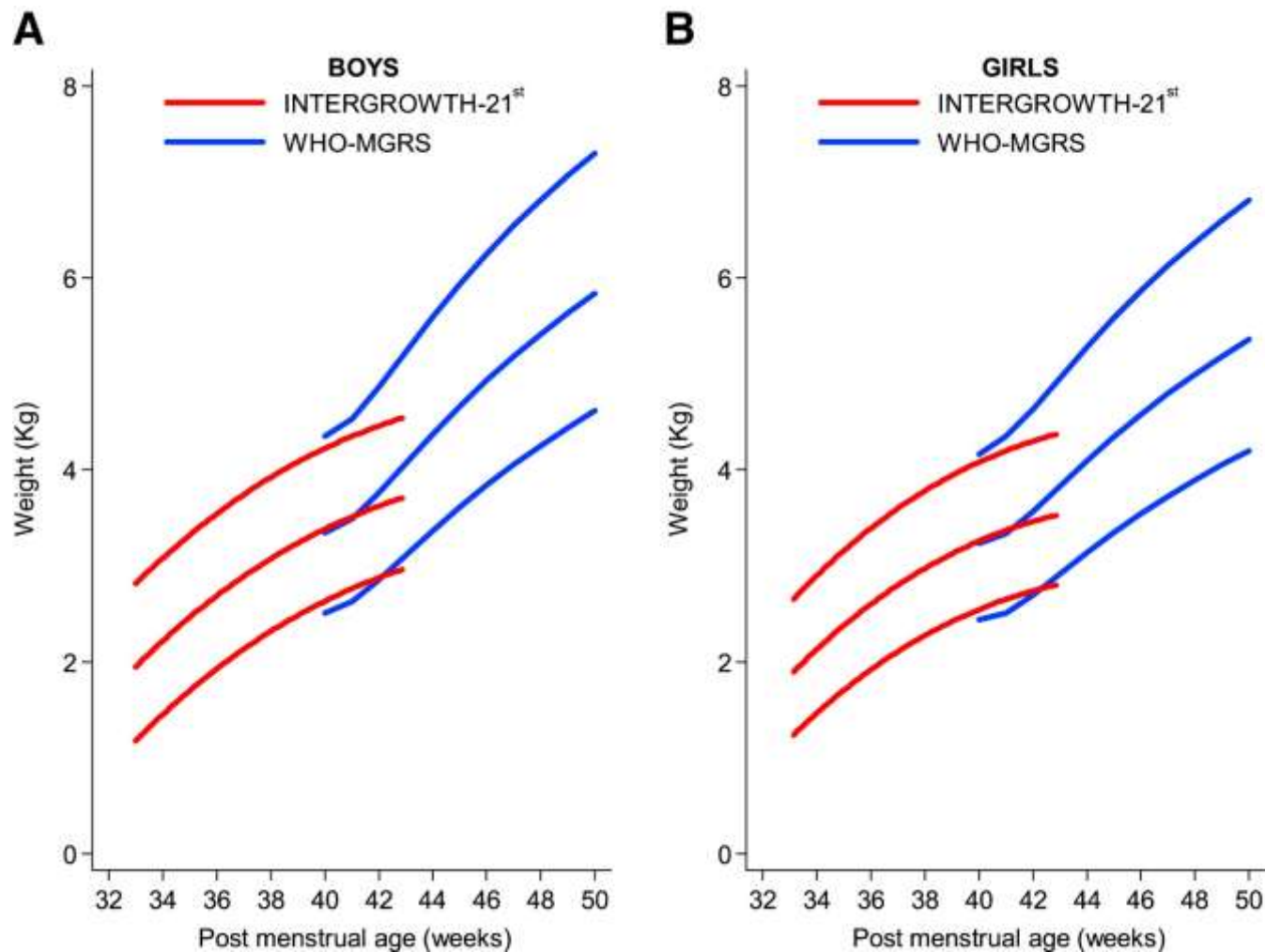
Comparison between INTERGROWTH-21st data and WHO Child Growth Standards at birth in term babies

	INTERGROWTH-21 st	WHO
Birth weight	3.3 (0.5) kg	3.3 (0.5) kg
Birth length	49.3 (1.8) cm	49.5 (1.9) cm

You can see that the mean size of babies born in the INTERGROWTH-21st Project at term was almost identical to the mean in the WHO MGRS study over 10 years earlier!



Thus the INTERGROWTH-21st Standards directly complement the WHO Child Growth Standards





INTERGROWTH - 21st international standards

From these findings, the INTERGROWTH - 21st Project produced international standards for:

- [Early pregnancy dating by Crown-Rump length](#)
- [Fetal growth from 14 weeks to 41 weeks](#)
- [Newborn weight, length, and head circumference by gestational age and sex](#)
- [Preterm postnatal growth standards](#)
- [Maternal gestational weight gain](#) (also references for overweight women)

An application tool, [the INTERGROWTH-21st Newborn Size Application Tool](#), was developed to facilitate the classification of birth weight, length and head circumference according to the international newborn size standards.

Watch a seminar on the Global Standards for Fetal and Newborn growth [here](#).



INTERGROWTH-21st Project conclusions

The use of prescriptive standards is justified by the extensive biologic, genetic, and epidemiologic evidence that skeletal growth is similar from conception to childhood across geographic populations, when health, nutrition, environmental, and health care needs are met.

The INTERGROWTH-21st Project produced international standards for gestational age estimation, first-trimester fetal size, fetal growth, newborn size for gestational age, and postnatal growth of preterm infants.

The INTERGROWTH - 21st International standards complement the World Health Organization Child Growth Standards conceptually, methodologically and analytically.

These prescriptive growth standards describe how all fetuses and newborns should grow, as opposed to traditional charts that describe how some have grown at a given place and time.



Challenges in standardising the measurement of fetuses and newborns around the world

Careful planning and implementation are required to implement the new fetal and neonatal standards on a sufficiently large scale, and use the information obtained from their implementation to evaluate and revise maternal and neonatal care programmes.

Health workers, at all levels, need to be trained to obtain the information correctly and, more importantly, to use it in clinical decision-making and actions.

Practices and norms may need to be revised and modified in accordance with the INTERGROWTH-21st standards.

Adequate planning time needs to be allocated to address issues to secure success in translating the new standards into better practices.

Meeting the challenge of achieving 'optimal' fetal growth would include addressing embryonic and placental growth and development.



This course overview has:

- Discussed some of the **conceptual issues** about fetal and newborn growth monitoring.
- Introduced the INTERGROWTH-21st Project: **rationale, aim, design and implementation.**
- Presented the **key findings** from INTERGROWTH-21st Project on the likeness of early human growth.
- Introduced the **INTERGROWTH-21st growth standards.**
- Highlighted challenges in standardising the measurement of fetuses and newborns around the world.



For more information on the INTERGROWTH-21st Project, please visit <https://intergrowth21.tghn.org/>.

Click here for an interactive e-learning module “[Assessing newborn size by anthropometry](#)”.

Click here for an interactive e-learning module “[Assessing Maternal Anthropometry and Weight Gain During Pregnancy](#)”

A similar module, “Monitoring of fetal growth by ultrasound” will be available shortly.



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