Euro-Peristat study on intrauterine growth references

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Fetal growth restriction (FGR)

- Fetal growth restriction (FGR) is a failure of the fetus to reach its full growth potential.
- Associated with risks of stillbirth, birth hypoxia, neonatal morbidity, neonatal death and neuro-developmental impairment
- No straightforward way to identify FGR infants.
  - Because growth potential is unknown
  - FGR is caused by multiple maternal and fetal conditions

Small for gestational age (SGA)

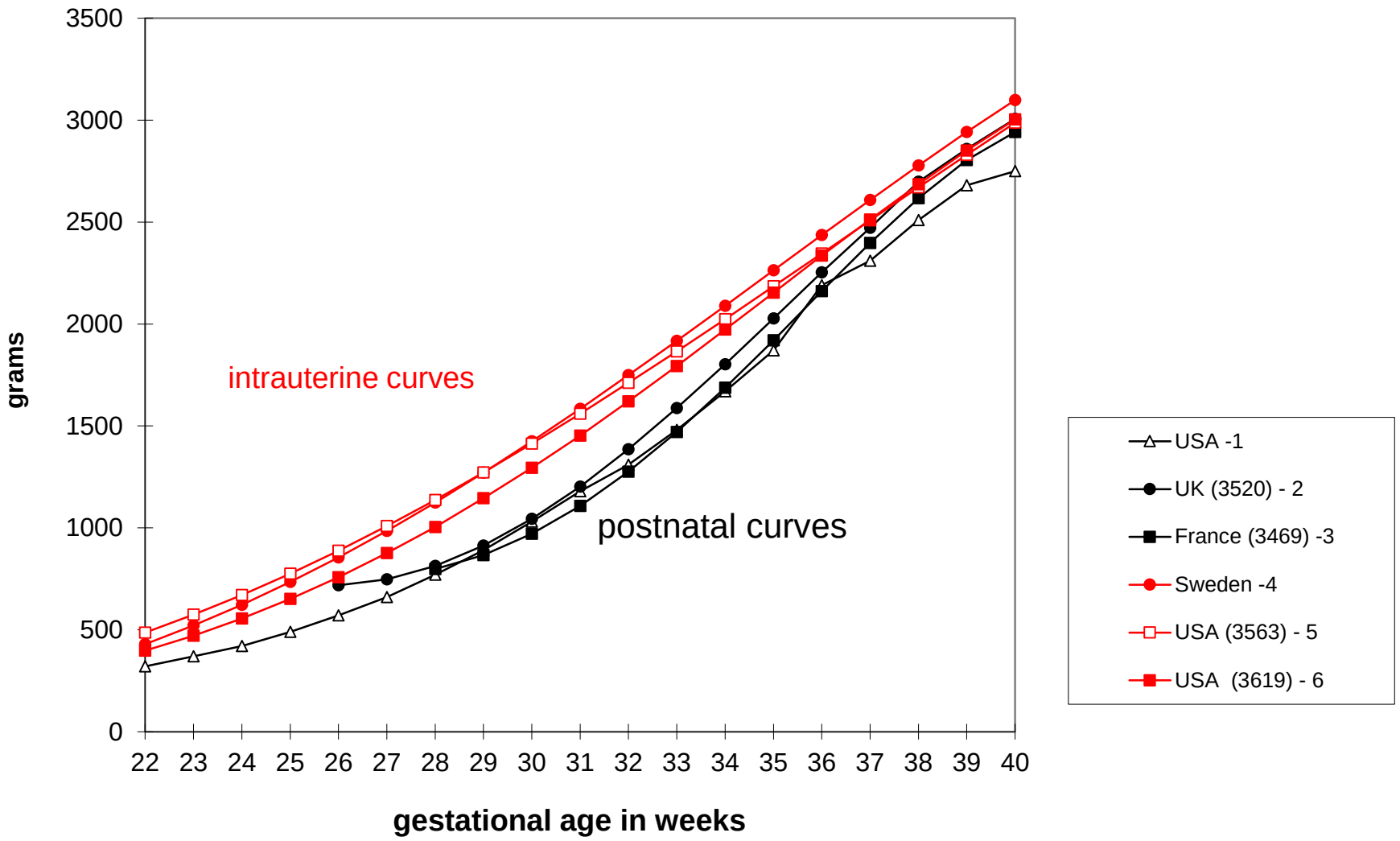
- FGR most often defined as estimated fetal weight or birthweight < 10^{th} percentile for gestational age or SGA
- The 10^{th} percentile is associated with higher mortality and morbidity in many studies.
- This definition is
  - recommended for screening purposes during pregnancy
  - used for epidemiological and clinical surveillance after birth.

Which growth references should be used to define the 10th percentile

- Growth references based on birthweight are not appropriate because of the association of growth restriction with prematurity
- However, most studies use neonatal growth references, with a few exceptions (ex. Sweden), no consensus on which intrauterine references should be used
- Problem of which references to use is compounded in multinational studies

Marsal K et al. *Acta Paediatr* 1996;85(7):843-8.

Comparison of intra-uterine and postnatal 10th percentile curves



Which growth references should be used?

- Gardosi's approach for customised references to generate country-specific references
  - Ego A et al. *Am J Obstet Gynecol*, 2006
  - Mikolajczyk et al. *Lancet*, 2011
- Common reference for all countries
  - Villar et al. *The lancet. Diabetes & endocrinology*, 2014

- Questions:
  - How does the Gardosi model fare for assessing growth restriction in a very preterm population?
  - Can one reference be used for European populations?

Aims

- To develop intrauterine growth references for adapted to European countries
- Use them to measure proportions of small for gestational age (SGA) infants
- To measure the impact of using country-specific versus common European references.

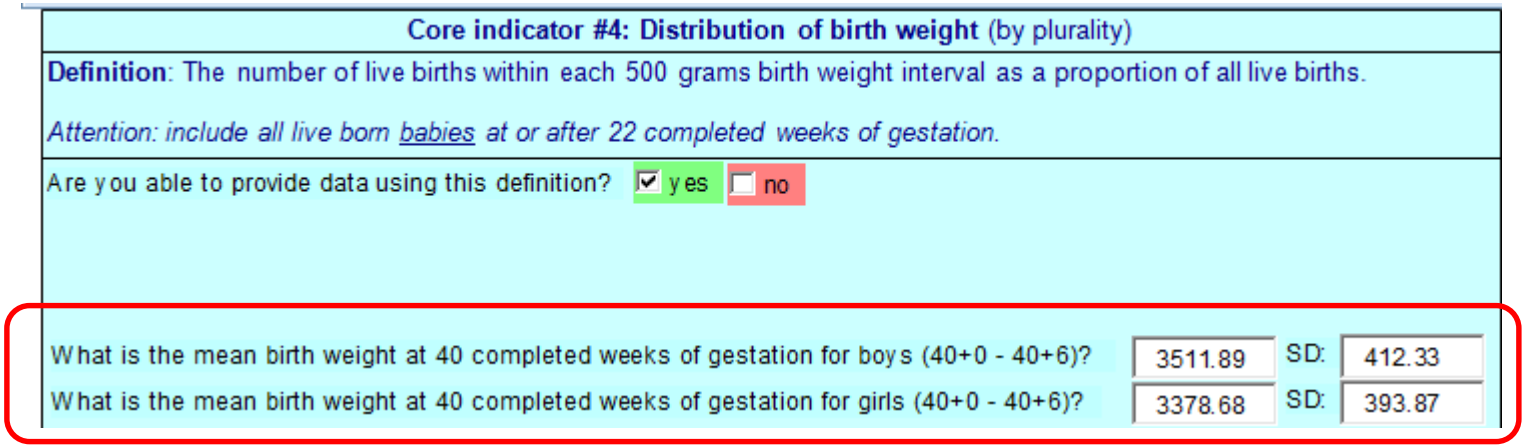
Methods – developing references

- We adapted the approach proposed by Gardosi et al. based on Hadlock's fetal growth equation
- Expected fetal weights at each GA are represented as a % of the expected weight at 40 weeks of gestation
- Percentiles are established by assuming a normal distribution using the coefficient of variation at term.

  - Country-specific references by sex for each country
  - Common European references by sex using the median values (boys (3597g), girls (3444g))
  - The median CV of 12% was used for all models

Data

- Euro-Peristat data collection in 2010
- Mean birthweights of girls and boys at 40 weeks in European countries



Core indicator #4: Distribution of birth weight (by plurality)

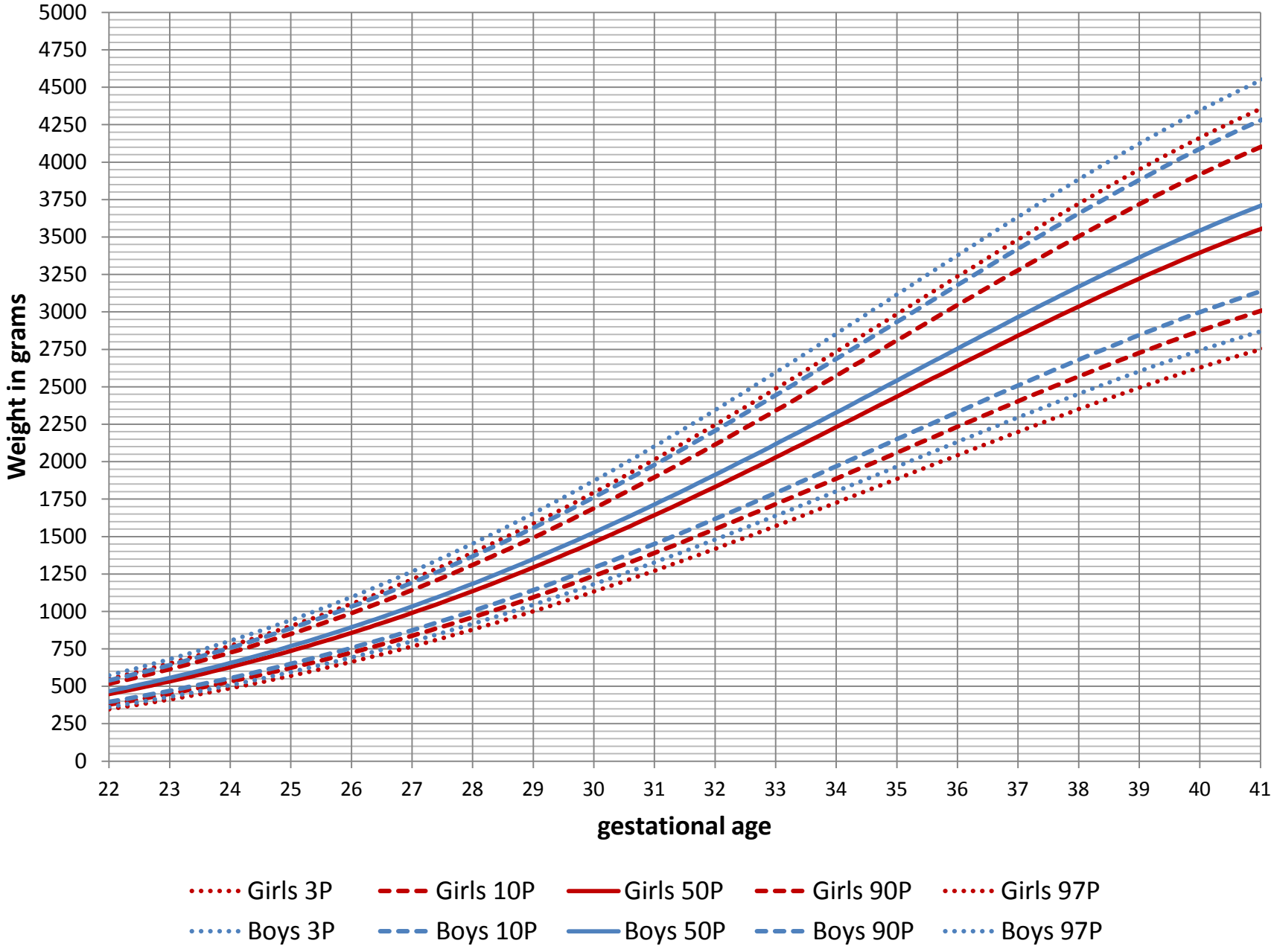
Definition: The number of live births within each 500 grams birth weight interval as a proportion of all live births.

Attention: include all live born babies at or after 22 completed weeks of gestation.

Are you able to provide data using this definition? ☑ yes ☐ no

What is the mean birth weight at 40 completed weeks of gestation for boys (40+0 - 40+6)?	3511.89	SD:	412.33
What is the mean birth weight at 40 completed weeks of gestation for girls (40+0 - 40+6)?	3378.68	SD:	393.87

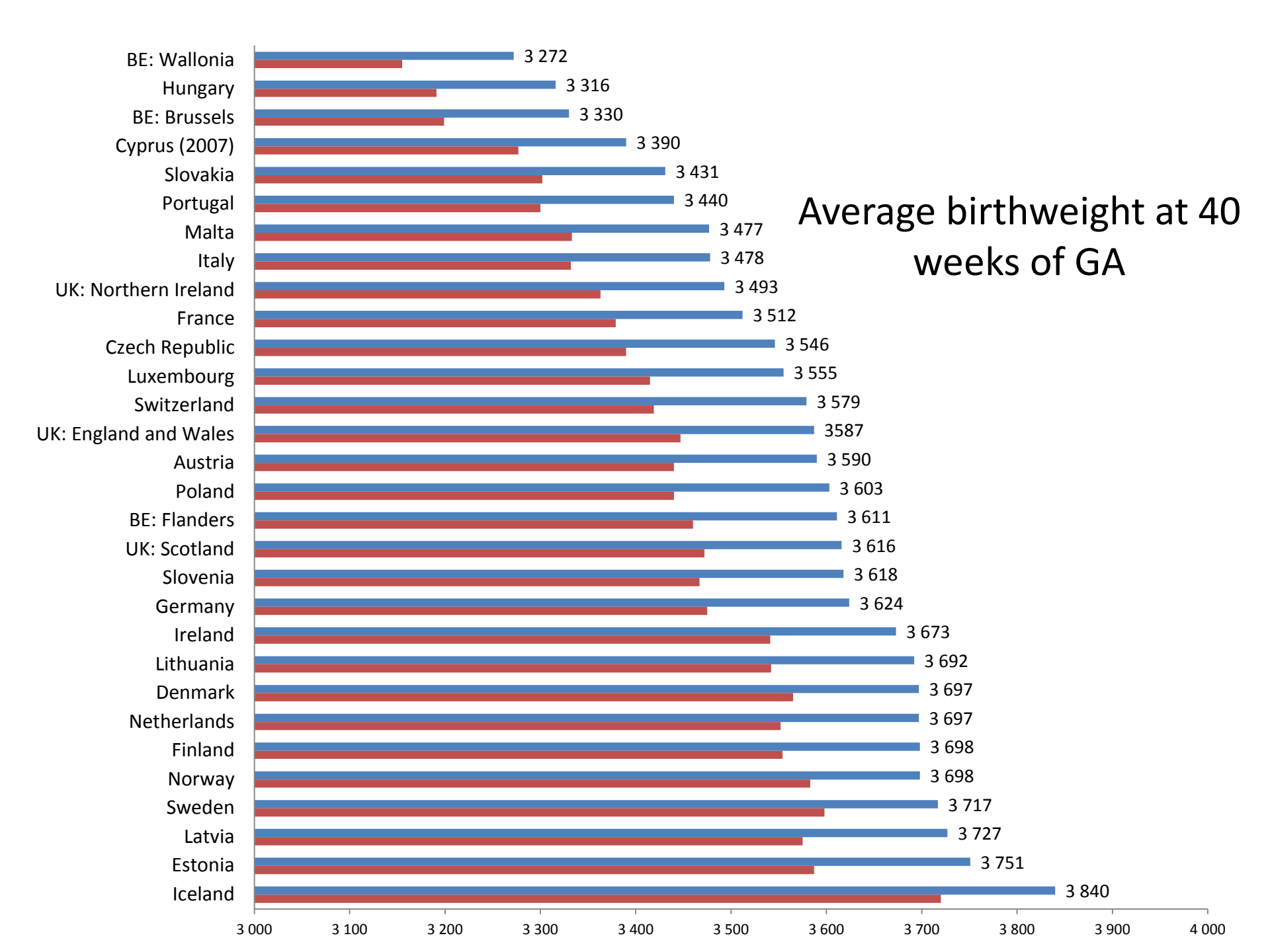
- Objective: Use these data to define
  - Country-specific intrauterine references
  - European references


Weight in grams
5000
4750
4500
4250
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
250
0
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
gestational age
Girls 3P
Girls 10P
Girls 50P
Girls 90P
Girls 97P
Boys 3P
Boys 10P
Boys 50P
Boys 90P
Boys 97P

Data requested

- If possible:
  - **individual data** on 5 variables for all SINGLETON births in 2010 and the most recent year
  - Gestational age, birthweight, Sex, vital status, neonatal death
  - **aggregated data** computing tables directly using a SAS or STATA macro to built tables directly
  - Waiting to finalize analysis strategy using individual level data to send programme

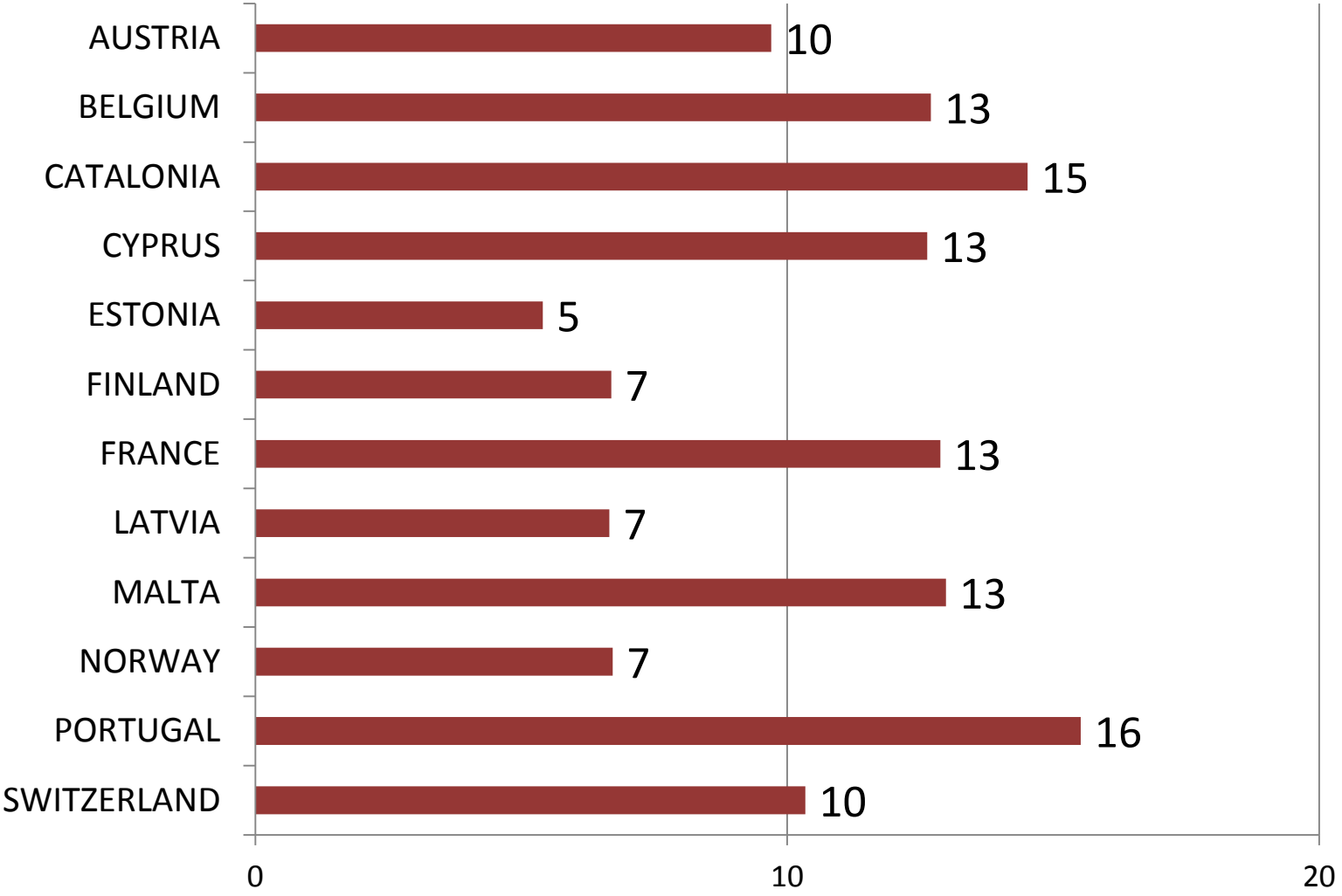
Results


Average birthweight at 40 weeks of GA
BE: Wallonia 3 272
Hungary 3 316
BE: Brussels 3 330
Cyprus (2007) 3 390
Slovakia 3 431
Portugal 3 440
Malta 3 477
Italy 3 478
UK: Northern Ireland 3 493
France 3 512
Czech Republic 3 546
Luxembourg 3 555
Switzerland 3 579
UK: England and Wales 3587
Austria 3 590
Poland 3 603
BE: Flanders 3 611
UK: Scotland 3 616
Slovenia 3 618
Germany 3 624
Ireland 3 673
Lithuania 3 692
Denmark 3 697
Netherlands 3 697
Finland 3 698
Norway 3 698
Sweden 3 717
Latvia 3 727
Estonia 3 751
Iceland 3 840
3 000
3 100
3 200
3 300
3 400
3 500
3 600
3 700
3 800
3 900
4 000

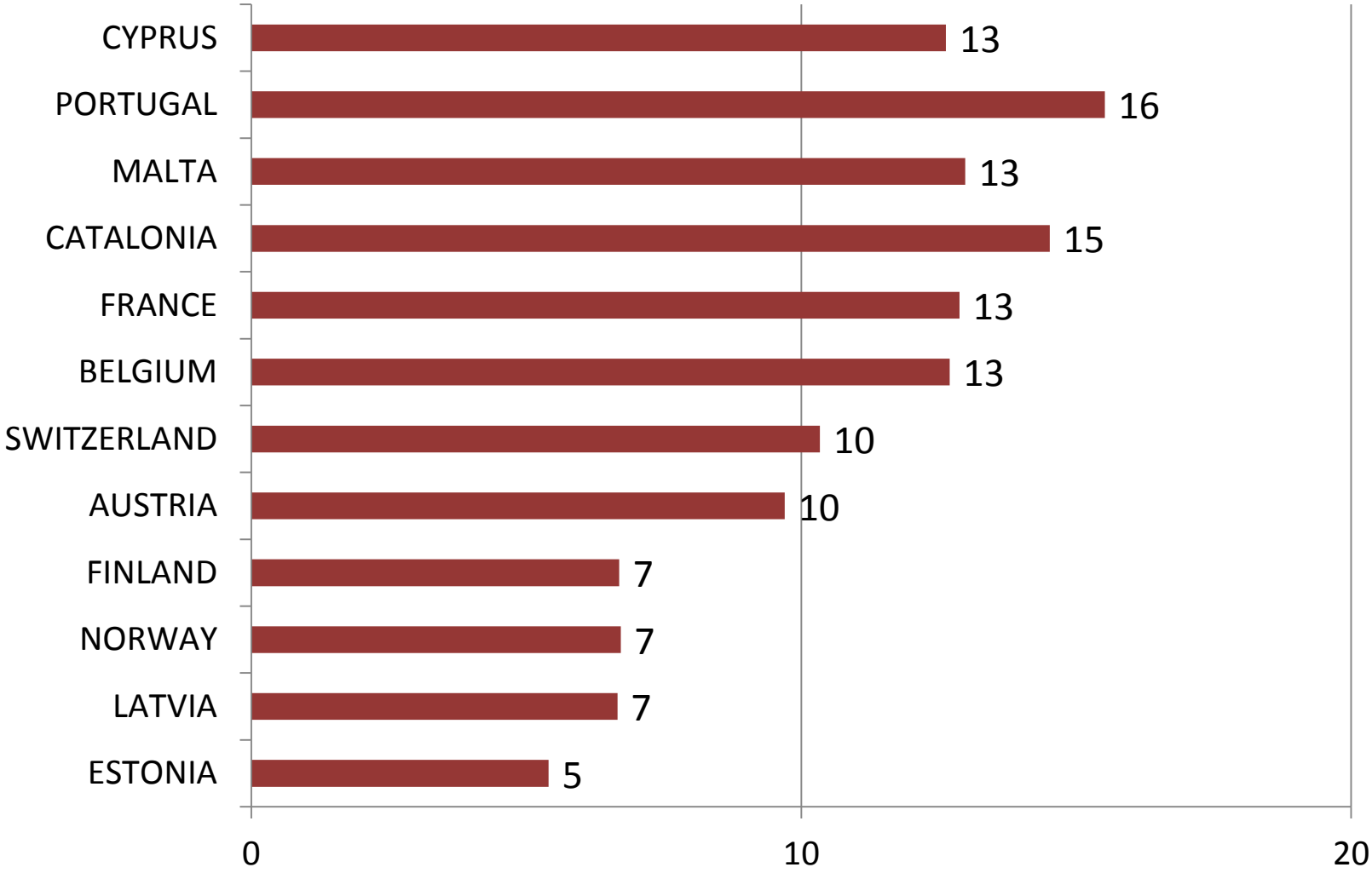
Preliminary data – 12 regions/countries

Country	years	Total live births
AUSTRIA	(2010/2104)	155,008
BELGIUM	(2010/2014)	72,721
CATALONIA	(2010)	80,312
CYPRUS	(2007-2013)	20,816
ESTONIA	(2010/2014)	30,714
FINLAND	(2010/2014)	115,407
FRANCE	(2010)	14,326
LATVIA	(2010/2014)	39,495
MALTA	(2010/2014)	8,049
NORWAY	(2010/2014)	118,165
PORTUGAL	(2010/2013)	179,048
SWITZERLAND	(2010/2013)	156,384

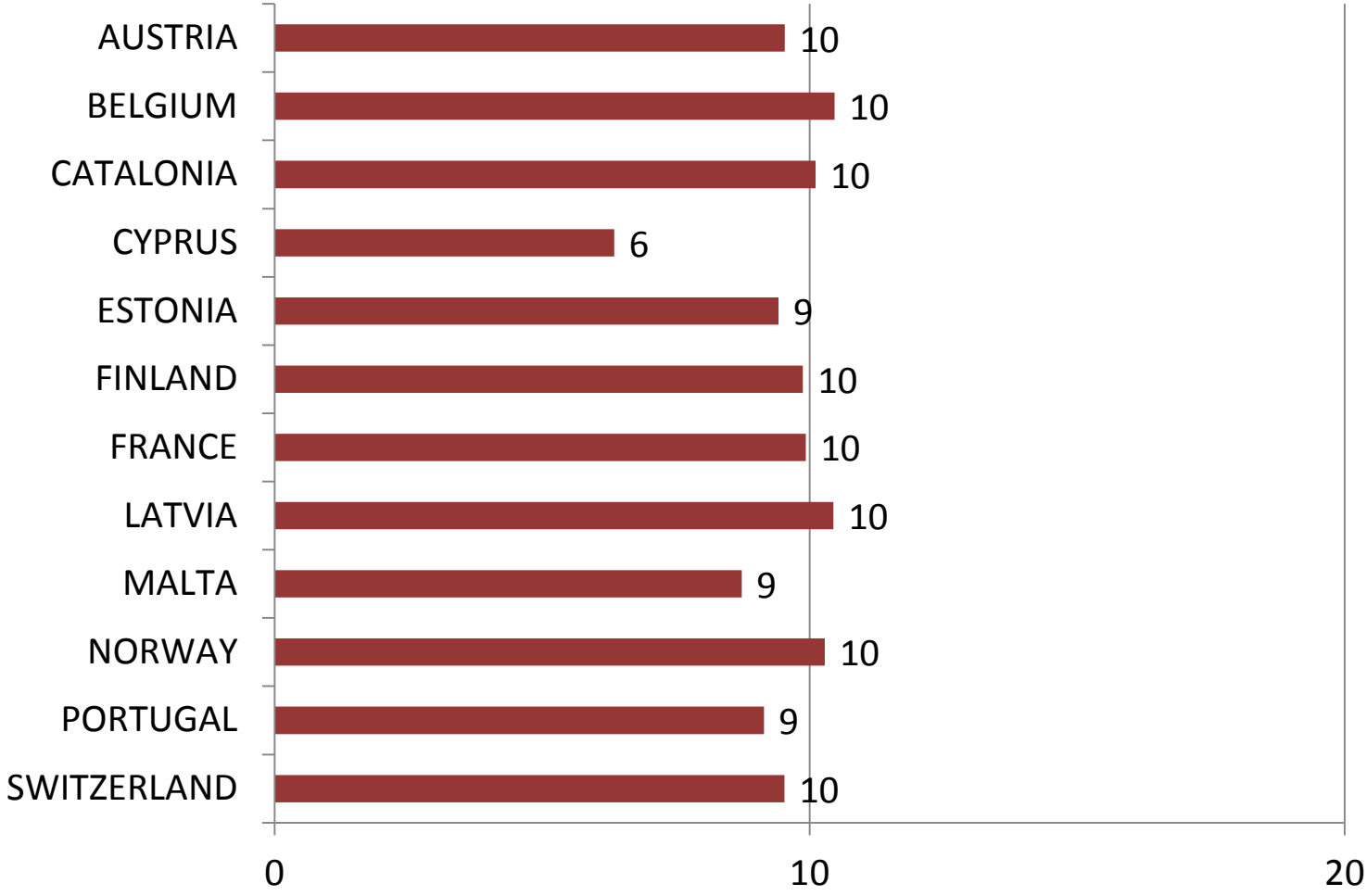
% SGA, using the European references (live singleton births)



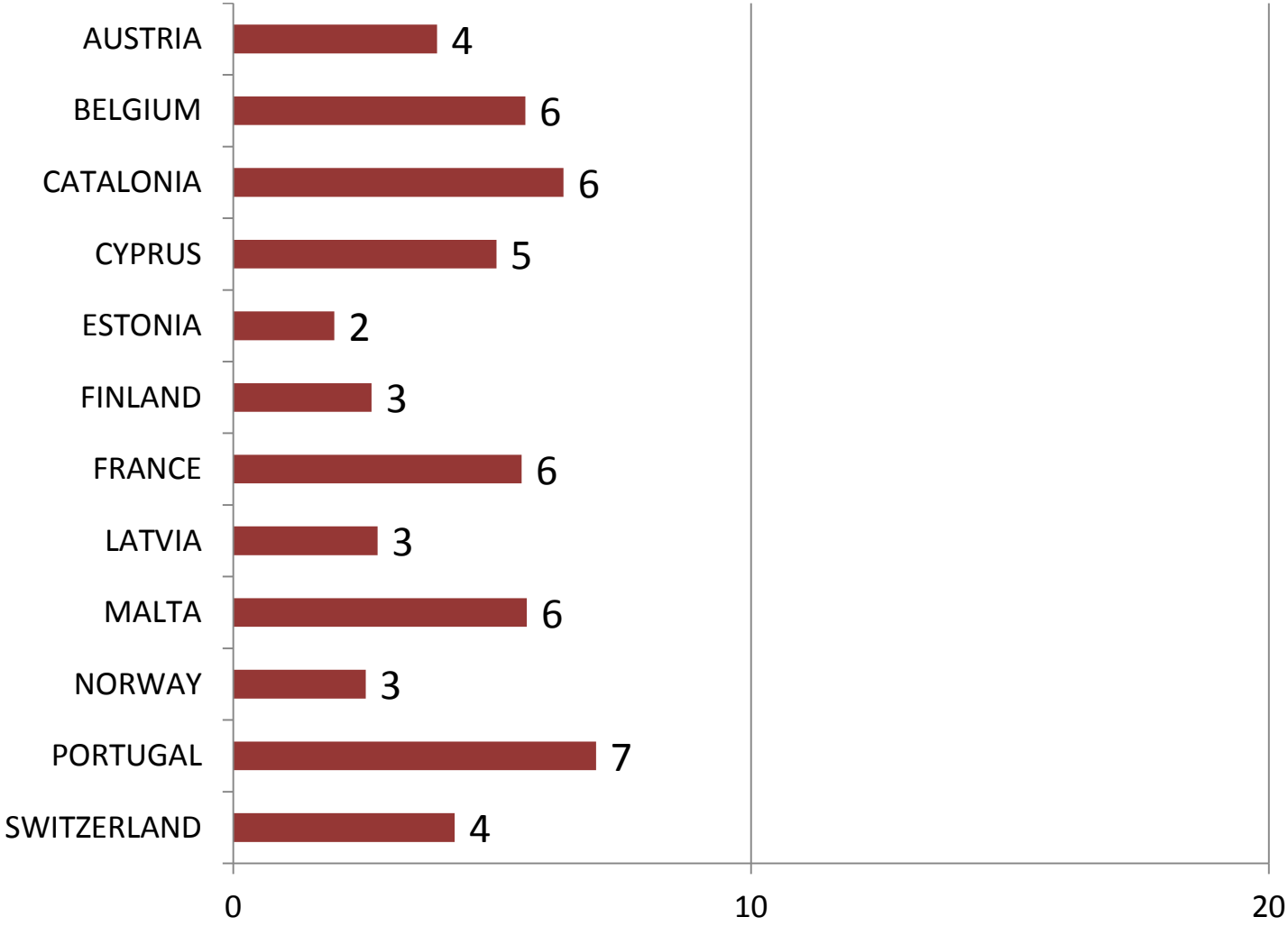
% SGA, using European references sorted by BW at 40 wks (live singletons)



% SGA, using country-specific references (live singleton births)



% SGA, using intergrowth newborn references (starting at 33 wks GA)



Villar J, Cheikh Ismail L, Victora CG, Ohuma EO, Bertino E, Altman DG, et al. International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. *Lancet* 2014;384(9946):857-68.

Summary

- European references give very different SGA rates from country to country
- Associated with birthweight at term
- Disappear when country-specific curves are used
- Intergrowth newborn references give very low estimates of SGA
- Consequences
  - Implications of having different % of babies under the 10th percentile (research, use of resources if used for screening)
  - Similar identification of infants at risks

Some next steps for analysis

- Study the mortality by birthweight percentile for both sets of references
  - <3rd, <10th
  - Stillbirths, neonatal deaths, perinatal deaths
- Explore percentile at which mortality is lowest
  - By gestational age group
  - By reference
  - By outcome (stillbirth vs neonatal death)

Addition of more countries

- Individual level data
  - UK: Scotland can participate: we have completed data access form
  - Add other PREBIC countries? US, Canada, Japan?

- Aggregate tables
  - Countries that cannot provide individual data
  - « meta-analysis approach » is less flexible, harder to pool data

How create aggregate tables using SAS macro program?

- Automatic program to create percentiles:

<3/3-9.99/10-89.99/90-96.99/>=97

- European curve: please enter in the macro program
  - Median BW for boys (3597g), Median BW for girls (3444g), and Coefficient of variation (12%)

- Country curve: please enter in the macro program
  - Mean BW at 40 weeks for boys and girls and Coefficient of variation for boys and girls
  - Correspond to data you provided inEuro-Peristat data collection in 2010 (C4)

How create aggregate tables using SAS macro program?

- **Output (example from Finland data)**
  - European common reference: SINGLETON STILLBIRTHS - BOYS

Table de GA par PERCENTILE_5cl_EC

PERCENTILE_5cl_EC(PERCENTILE <3/3-9.99/10-89.99/90-96.99/>=97 - European curve)

GA / *Fréquence*	*<3*	*3-9.99*	*10-89.99*	*90-96.99*	*>=97*	*Total*
22	1	0	3	0	1	5
23	1	0	0	0	0	1
24	1	0	2	0	0	3
25	1	2	2	0	0	5
26	1	0	0	0	0	1
27	3	0	2	0	0	5
28	3	0	0	0	1	4
29	3	0	2	0	0	5
30	3	0	0	0	0	3
31	1	2	0	0	1	4
32	1	0	1	1	0	3
33	0	0	3	0	1	4
34	1	1	3	0	0	5
36	1	0	2	0	0	3
37	0	0	4	0	0	4
38	1	1	5	0	0	7
39	1	0	2	0	0	3
40	0	1	6	1	0	8
41	0	0	4	1	0	5
Total	23	7	41	3	4	78

Valeur(s) manquante(s) = 3

- **You can develop a Stata program if we don't use SAS software**